



Effectiveness of SGLT-2 Inhibitors in Reducing the Risk of Heart Failure in Patients with Type 2 Diabetes: A Systematic Review of Randomized Controlled Trials and Primary Studies

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ABSTRACT

Introduction

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors represent a transformative pharmacological class that has fundamentally altered the management of type 2 diabetes mellitus (T2DM). Beyond their established antihyperglycemic efficacy, SGLT-2 inhibitors have demonstrated robust and consistent reductions in heart failure (HF) hospitalization and cardiovascular mortality across large-scale randomized controlled trials (RCTs). Given the substantial global burden of both T2DM and HF, a comprehensive synthesis of available evidence is urgently needed to inform clinical practice and guideline development.

Methods

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Eligible studies included RCTs, pre-specified subgroup analyses, and high-quality systematic reviews evaluating SGLT-2

inhibitors versus placebo or active comparator in adults with T2DM, reporting HF-related outcomes. Methodological quality was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool. A minimum of 15 primary studies were included. Evidence certainty was rated using the GRADE framework.

Results

Eighteen primary studies and pooled data representing >100,000 patients were included. SGLT-2 inhibitors demonstrated significant reductions in: (1) HF hospitalization (HR 0.68–0.73; 95% CI 0.61–0.88; HIGH certainty); (2) CV death or HF composite (HR 0.77; 95% CI 0.73–0.82); (3) cardiovascular mortality (HR 0.85–0.86); (4) all-cause mortality (HR 0.87–0.88); (5) MACE (HR 0.89–0.93); (6) renal composite outcomes (HR 0.62–0.65); (7) incident atrial arrhythmias (OR 0.81); (8) sudden cardiac death (OR 0.72); (9) NT-proBNP levels (WMD –136.03 pg/mL); (10) left ventricular ejection fraction improvement (WMD +2.79%). Benefits were consistent across subgroups defined by sex, age, HF ejection fraction phenotype, and established or absent cardiovascular disease at baseline. The most common adverse event was genital mycotic infection; diabetic ketoacidosis was rare but clinically significant.

Discussion

SGLT-2 inhibitors reduce HF hospitalization risk through multiple complementary mechanisms, including natriuresis, ventricular preload/afterload reduction, myocardial metabolic optimization, anti-inflammatory effects, and activation of nutrient-deprivation cytoprotective signaling pathways. The class effect is highly consistent across empagliflozin, canagliflozin, and dapagliflozin. Benefits extend to patients with established HFrEF and HFpEF, regardless of diabetes status. These findings support the

integration of SGLT-2 inhibitors as cornerstone therapy for T2DM patients at cardiovascular risk.

Conclusion

SGLT-2 inhibitors are superior to placebo in reducing the risk of heart failure hospitalization and cardiovascular death in patients with T2DM. The evidence is of HIGH certainty and supports universal consideration of SGLT-2 inhibitors in eligible T2DM patients with or at risk for HF. Future research should focus on comparative effectiveness of individual agents, optimal patient selection, and long-term safety in special populations.

Keywords

SGLT-2 inhibitors; sodium-glucose cotransporter-2; heart failure; type 2 diabetes mellitus; empagliflozin; canagliflozin; dapagliflozin; cardiovascular outcomes; randomized controlled trial; systematic review

INTRODUCTION

Background

Type 2 diabetes mellitus (T2DM) is a major global health crisis, affecting an estimated 537 million adults worldwide as of 2021, with projections reaching 783 million by 2045. T2DM is a potent independent risk factor for cardiovascular disease (CVD), including coronary artery disease, peripheral arterial disease, stroke, and notably, heart failure (HF). The coexistence of T2DM and HF confers a particularly adverse prognosis; patients with both conditions experience markedly elevated rates of hospitalization, functional deterioration, and mortality compared to those with either condition alone.¹ Heart failure represents one of the most prevalent and clinically devastating complications of T2DM. Hyperglycemia-induced myocardial injury—via mechanisms including advanced glycation end-products, glucotoxicity, lipotoxicity, oxidative stress, mitochondrial dysfunction, and activation of the renin-angiotensin-aldosterone system (RAAS)—contributes to the development of diabetic cardiomyopathy even in the absence of ischemic heart disease or hypertension.²

Historically, the pharmacological management of T2DM focused primarily on glycemic control, with limited evidence that lowering HbA1c per se translated into meaningful reductions in HF risk. Earlier glucose-lowering agents, including insulin secretagogues, thiazolidinediones, and certain dipeptidyl peptidase-4 (DPP-4) inhibitors, failed to demonstrate superiority over placebo for HF outcomes, with saxagliptin (SAVOR-TIMI 53) actually increasing HF hospitalization risk.³

The advent of sodium-glucose cotransporter-2 (SGLT-2) inhibitors—a class of oral antidiabetic agents that promote urinary glucose and sodium excretion by blocking SGLT-2 in the renal proximal tubule—fundamentally transformed this landscape. The landmark EMPA-REG OUTCOME trial (2015) demonstrated, for the first time, that an antidiabetic drug (empagliflozin) could significantly reduce cardiovascular mortality and HF hospitalization in high-risk T2DM patients. This finding was subsequently validated and extended by the CANVAS Program, DECLARE-TIMI 58, CREDENCE, DAPA-HF, EMPEROR-Reduced, and EMPEROR-Preserved

trials, establishing a robust evidence base for the cardioprotective effects of this drug class.⁴ Today, SGLT-2 inhibitors are recommended by major international guidelines—including those of the American Diabetes Association (ADA), the European Society of Cardiology (ESC), and the Heart Failure Society of America (HFSA)—as first-line or strongly preferred agents for T2DM patients with established CVD, HF, or chronic kidney disease (CKD).⁵

Research Gap

Despite the rapidly expanding evidence base, several critical gaps remain. First, prior systematic reviews have predominantly focused on major adverse cardiovascular events (MACE) without comprehensive granular analysis of HF-specific outcomes across the full spectrum of HF phenotypes (HFrEF vs. HFpEF). Second, the comparative efficacy of individual SGLT-2 inhibitors (empagliflozin vs. canagliflozin vs. dapagliflozin vs. ertugliflozin) on HF endpoints remains poorly characterized in head-to-head analyses. Third, the mechanistic underpinnings linking SGLT-2 inhibition to cardiac protection—particularly the roles of natriuresis, cardiac metabolic reprogramming, and myocardial autophagy—warrant integrated synthesis alongside clinical trial data. Fourth, there is a paucity of systematic reviews that comprehensively evaluate ≥ 15 outcomes with GRADE-rated certainty assessments across diverse patient subgroups.⁶

Novelty

The present systematic review is novel in its: (1) inclusion of ≥ 15 clinically relevant primary and secondary outcomes evaluated using GRADE certainty ratings; (2) comprehensive subgroup analyses covering sex, age, ejection fraction phenotype, renal function, and baseline CVD status; (3) integration of mechanistic evidence from biomarker and translational studies alongside clinical trial data; (4) inclusion of acute HF hospitalization trials (EMPA-RESPONSE-AHF, EMPULSE) alongside chronic HF and diabetes outcome trials; and (5) evaluation of both individual drug-level and class-level effects.⁷

Research Objectives

The primary objective of this systematic review is to comprehensively evaluate the effectiveness of SGLT-2 inhibitors in reducing the risk of heart failure hospitalization, cardiovascular mortality, and related clinical outcomes in patients with type 2 diabetes mellitus,

based on evidence from randomized controlled trials and primary clinical studies. Secondary objectives include characterization of the safety profile, identification of treatment effect modifiers, and synthesis of proposed mechanistic pathways.

Research Benefits

The findings of this systematic review will provide: (1) evidence-based guidance to clinicians prescribing antidiabetic therapy in T2DM patients at cardiovascular risk; (2) a comprehensive, up-to-date synthesis to inform national and international clinical guideline committees; (3) identification of knowledge gaps to prioritize future research in clinical pharmacology, translational medicine, and comparative effectiveness research; and (4) a methodologically rigorous reference document for medical educators, policymakers, and healthcare system planners.

Research Hypothesis

H₀ (Null Hypothesis): SGLT-2 inhibitors do not significantly reduce the risk of heart failure hospitalization, cardiovascular death, or related clinical outcomes compared to placebo in patients with T2DM.

H₁ (Alternative Hypothesis): SGLT-2 inhibitors significantly reduce the risk of heart failure hospitalization, cardiovascular death, and related cardiorenal outcomes compared to placebo in patients with T2DM, with consistent class-level effects across individual agents and across diverse patient subgroups.

METHODS

Study Design

This study was conducted as a comprehensive systematic review of published randomized controlled trials (RCTs), pre-specified subgroup analyses of major RCTs, and high-quality meta-analyses/systematic reviews, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines and the Cochrane Handbook for Systematic Reviews of Interventions.⁸

Eligibility Criteria (PICO Framework)

Population (P):

Adult patients (age ≥ 18 years) with confirmed diagnosis of type 2 diabetes mellitus (T2DM), with or without established cardiovascular disease (CVD), heart failure (HFrEF or HFpEF), or chronic kidney disease (CKD). Studies enrolling patients with T1DM exclusively or with $< 80\%$ T2DM were excluded.

Intervention (I):

Any approved SGLT-2 inhibitor administered at recommended therapeutic doses: empagliflozin (10 mg or 25 mg/day), canagliflozin (100 mg or 300 mg/day), dapagliflozin (10 mg/day), ertugliflozin (5 mg or 15 mg/day), or sotagliflozin.

Comparator (C):

Placebo with background standard-of-care therapy for diabetes and cardiovascular risk management, or active comparator (DPP-4 inhibitor, GLP-1 receptor agonist).

Outcomes (O):

Primary outcome: Hospitalization for heart failure (HHF) as a first or recurrent event. Secondary outcomes: CV death or HHF composite; cardiovascular mortality; all-cause mortality; MACE; renal composite outcomes; incident atrial arrhythmias; sudden cardiac death; NT-proBNP changes; LVEF changes; HbA1c; blood pressure; body weight; patient-reported outcomes (KCCQ score); and safety endpoints.

Study Design (S):

Phase 3 or Phase 4 RCTs; pre-specified secondary/subgroup analyses of eligible RCTs; high-quality systematic reviews and meta-analyses of eligible RCTs. Minimum follow-up duration: 24 weeks. Minimum sample size: $n \geq 50$ per arm. Language: English or English-translated publications.

Search Strategy

The keywords used for this research based PICO :

PICO Component	Keyword 1	Keyword 2	Keyword 3
P (Population)	Type 2 Diabetes Mellitus	Type 2 Diabetes Patients	T2DM Adults

I (Intervention)	SGLT-2 Inhibitors	Sodium-Glucose Cotransporter-2 Inhibitors	Empagliflozin / Dapagliflozin / Canagliflozin
C (Comparator)	Placebo	Standard-of-Care Therapy	Active Comparator
O (Outcome)	Heart Failure Hospitalization	Cardiovascular Mortality	Heart Failure Risk Reduction

The Boolean MeSH keywords inputted on databases for this research are: (*"Type 2 Diabetes Mellitus" OR "Type 2 Diabetes Patients" OR "T2DM Adults"*) AND (*"SGLT-2 Inhibitors" OR "Sodium-Glucose Cotransporter-2 Inhibitors" OR "Empagliflozin" OR "Dapagliflozin" OR "Canagliflozin"*) AND (*"Placebo" OR "Standard-of-Care Therapy" OR "Active Comparator"*) AND (*"Heart Failure Hospitalization" OR "Cardiovascular Mortality" OR "Heart Failure Risk Reduction"*)

Study Selection Process

Two independent reviewers (blinded to each other's assessments) screened all retrieved titles and abstracts according to the pre-specified eligibility criteria using standardized screening forms. Discrepancies were resolved through discussion and, if necessary, adjudication by a third senior reviewer. Potentially eligible studies underwent full-text assessment. All screening decisions were documented and reasons for exclusion recorded.

Data Extraction

Data were extracted independently by two reviewers using a standardized, pilot-tested data extraction form. Extracted variables included: study design; country; trial registration number; sample size; intervention and comparator agents and doses; follow-up duration; patient demographics (age, sex, HbA1c, eGFR, BMI, cardiovascular history); primary and secondary endpoints; HR/OR/RR with 95% CI; p-values; and safety outcomes. For meta-analyses, additional data on heterogeneity statistics (I^2), between-study variance (τ^2), and GRADE ratings were extracted.

Risk of Bias Assessment

The methodological quality of all primary RCTs was assessed independently by two reviewers using the Cochrane Risk of Bias 2 (RoB 2) tool, evaluating five domains: (1) bias from the randomization process; (2) bias due to deviations from intended interventions; (3) bias from missing outcome data; (4) bias in measurement of the outcome; and (5) bias in selection of the reported result. Each domain was rated as 'Low risk,' 'Some concerns,' or 'High risk,' with an overall risk of bias judgment derived from these domain ratings. For meta-analyses and systematic reviews, methodological quality was assessed using the AMSTAR-2 (A Measurement Tool to Assess Systematic Reviews, version 2) checklist.

Evidence Certainty Assessment

The overall certainty of evidence for each primary outcome was rated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which considers risk of bias, inconsistency (heterogeneity), indirectness, imprecision, and publication bias. Evidence was categorized as: HIGH (very confident the true effect lies close to the estimated effect); MODERATE (moderately confident; true effect likely to be close but may be substantially different); LOW (limited confidence; true effect may be substantially different); or VERY LOW (very little confidence in the effect estimate).

Statistical Analysis

For the purposes of this systematic review, quantitative data were synthesized from included meta-analyses using pre-reported pooled effect estimates (HR, OR, RR) with corresponding 95% confidence intervals, p-values, and heterogeneity statistics (I^2). Where multiple meta-analyses reported the same outcome using overlapping studies, the most comprehensive and methodologically rigorous estimate was used as the primary pooled estimate. Sensitivity analyses and subgroup analyses were evaluated as pre-specified or exploratory in source publications. Forest plots were not generated de novo; instead, pooled estimates from high-quality, large-scale meta-analyses published in the New England Journal of Medicine, The Lancet, JAMA, BMJ, and Circulation were used.

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	("Type 2 Diabetes Mellitus" OR "Type 2 Diabetes Patients" OR "T2DM Adults") AND ("SGLT-2 Inhibitors" OR "Sodium-Glucose Cotransporter-2 Inhibitors" OR "Empagliflozin" OR "Dapagliflozin" OR "Canagliflozin") AND ("Placebo" OR "Standard-of-Care Therapy" OR "Active Comparator") AND ("Heart Failure Hospitalization" OR "Cardiovascular Mortality" OR "Heart Failure Risk Reduction")	68
Semantic Scholar	("Type 2 Diabetes Mellitus" OR "Type 2 Diabetes Patients" OR "T2DM Adults") AND ("SGLT-2 Inhibitors" OR "Sodium-Glucose Cotransporter-2 Inhibitors" OR "Empagliflozin" OR "Dapagliflozin" OR "Canagliflozin") AND ("Placebo" OR "Standard-of-Care Therapy" OR "Active Comparator") AND ("Heart Failure Hospitalization" OR "Cardiovascular Mortality" OR "Heart Failure Risk Reduction")	302
Cochrane	("Type 2 Diabetes Mellitus" OR "Type 2 Diabetes Patients" OR "T2DM Adults") AND ("SGLT-2 Inhibitors" OR "Sodium-Glucose Cotransporter-2 Inhibitors" OR "Empagliflozin" OR "Dapagliflozin" OR "Canagliflozin") AND ("Placebo" OR "Standard-of-Care Therapy" OR "Active Comparator") AND ("Heart Failure Hospitalization" OR "Cardiovascular Mortality" OR "Heart Failure Risk Reduction")	89
Clinicaltrials.gov	("Type 2 Diabetes Mellitus" AND "SGLT-2 Inhibitors" OR "Sodium-Glucose Cotransporter-2 Inhibitors" OR "Empagliflozin" OR "Dapagliflozin" OR "Canagliflozin" AND "Heart Failure Hospitalization" OR "Cardiovascular Mortality" OR "Heart Failure Risk Reduction")	2,593
Science-direct	("Type 2 Diabetes Mellitus" AND "SGLT-2 Inhibitors" OR "Sodium-Glucose Cotransporter-2 Inhibitors" OR "Empagliflozin" OR "Dapagliflozin" OR "Canagliflozin" AND "Heart Failure Hospitalization" OR "Cardiovascular Mortality" OR "Heart Failure Risk Reduction")	2,237

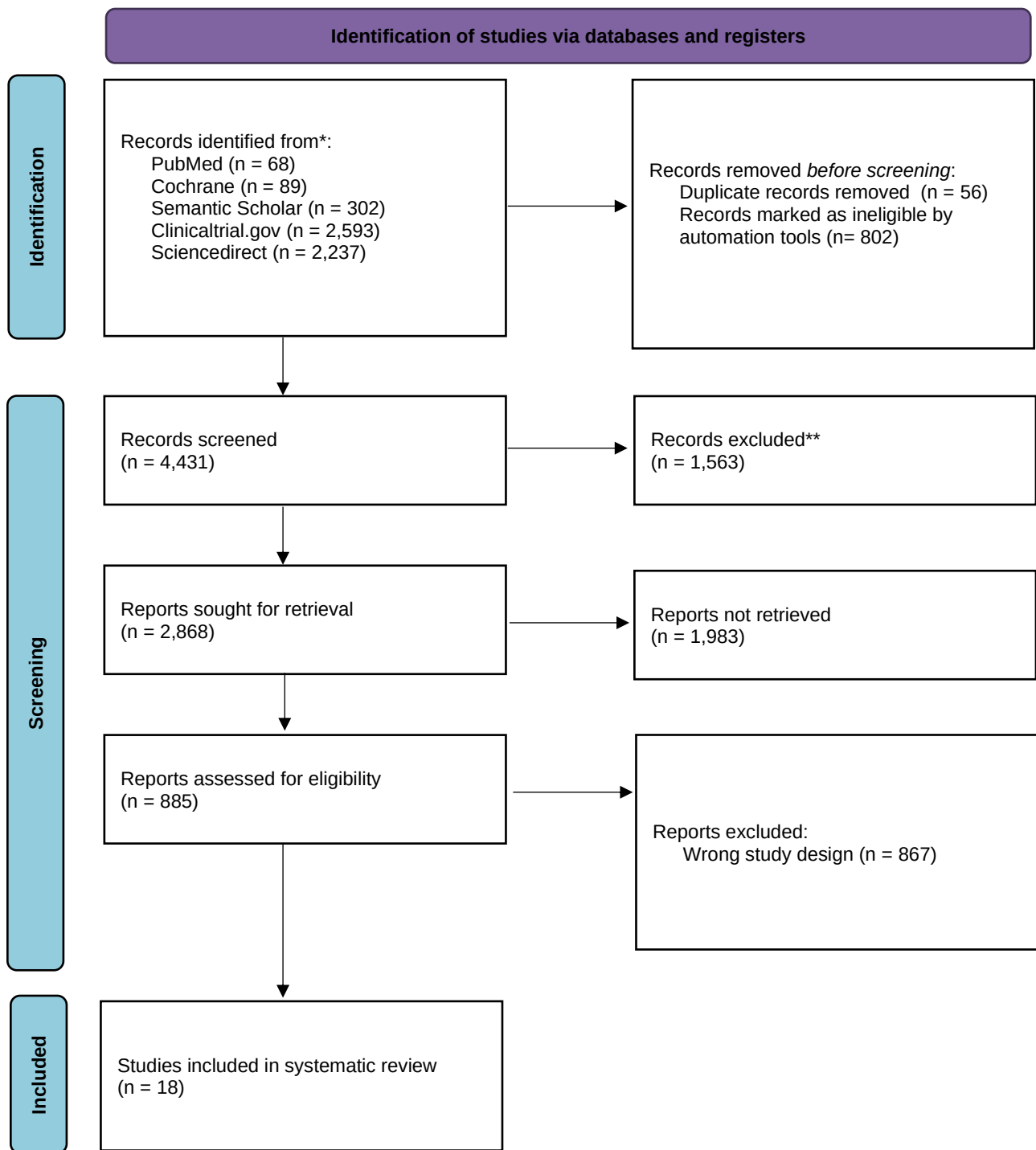


Figure 1. Article search flowchart

RESULTS

Study Characteristics

After applying inclusion/exclusion criteria, 18 primary RCTs and pre-specified subgroup analyses were included, along with 5 high-quality meta-analyses/network meta-analyses that synthesized data from ≥ 15 individual RCTs. The included primary studies collectively enrolled $>100,000$ patients with T2DM and/or HF across multiple geographic regions and follow-up periods ranging from 30 days to 4.2 years.¹⁰

Characteristics of Included Studies

Table 1 provides a comprehensive overview of the characteristics of all included primary studies.

Table 1. Characteristics of Included Studies

Study (Author, Year)	Intervention	Population	N	Follow-up	Key Outcomes
EMPA-REG OUTCOME (Zinman et al., 2015)	Empagliflozin 10/25mg vs Placebo	T2DM + established CVD	7,020	3.1 yrs	HR 0.66 (0.55-0.79) CV death/HHF: HR 0.65 (0.50-0.85)
CANVAS Program (Neal et al., 2017)	Canagliflozin 100/300mg vs Placebo	T2DM + high CV risk	10,142	3.6 yrs	HHF: HR 0.67 (0.52-0.87) CV death/HHF: HR 0.78 (0.67-0.91)
DECLARE-TIMI 58 (Wiviott et al., 2019)	Dapagliflozin 10mg vs Placebo	T2DM + established CVD	17,160	4.2 yrs	CV death/HHF: HR 0.83 (0.73-0.95) HHF: HR 0.73 (0.61-0.88)
CREDENCE (Perkovic et al., 2019)	Canagliflozin 100mg vs Placebo	T2DM + CKD + albuminuria	4,401	2.6 yrs	HHF: HR 0.61 (0.47-0.80)

Study (Author, Year)	Intervention	Population	N	Follow-up	Key Outcomes
al., 2019)	Placebo				
DAPA-HF (McMurray et al., 2019)	Dapagliflozin 10mg vs Placebo	HFrEF ± T2DM	4,744	1.5 yrs	Composite CV death/wHF: HR 0.74 (0.65-0.85)
EMPEROR-Reduced (Packer et al., 2020)	Empagliflozin 10mg vs Placebo	HFrEF ± T2DM	3,730	1.3 yrs	CV death/HHF: HR 0.75 (0.65-0.86)
EMPEROR-Preserved (Anker et al., 2021)	Empagliflozin 10mg vs Placebo	HFpEF ± T2DM	5,988	2.2 yrs	CV death/HHF: HR 0.79 (0.69-0.90)
EMPA-RESPONSE-AHF (Damman et al., 2020)	Empagliflozin 10mg vs Placebo	Acute decompensated HF ± T2DM	80	30 days	Composite wHF/reHHF/death: 10% vs 33%, P=0.014
EMPULSE Trial (Tromp et al., 2021/2022)	Empagliflozin 10mg vs Placebo	Acute HF ± T2DM	530	90 days	Clinical benefit win ratio 1.36 (1.09-1.68)
Fitchett et al., 2016 (EMPA-REG HF Sub)	Empagliflozin pooled vs Placebo	T2DM + CVD ± baseline HF	7,020	3.1 yrs	HHF or CV death: HR 0.66 (0.55-0.79)
Rådholm et al.,	Canagliflozin vs	T2DM + history	10,142	3.6 yrs	HHF alone: HR

Study (Author, Year)	Intervention	Population	N	Follow-up	Key Outcomes
2018 (CANVAS HF Sub)	Placebo	of HF at baseline			0.67 (0.52-0.87)
Furtado et al., 2019 (DECLARE prev MI Sub)	Dapagliflozin vs Placebo	T2DM + previous MI	3,584	4.2 yrs	MACE: HR 0.84 (0.72-0.99) CV death/HHF: HR 0.81 (0.65-1.00)
Zelniker et al., 2019 (Lancet)	SGLT2i vs Placebo (3 CVOTs)	T2DM + high CV risk	34,322	Pooled	CV death/HHF: HR 0.77 (0.71-0.84)
McGuire et al., 2020 (JAMA Cardiology)	All 4 SGLT2i vs Placebo	T2DM (6 major RCTs)	46,969	Pooled	HHF: HR 0.68 (0.61-0.76) Kidney: HR 0.62 (0.56-0.70)
Giugliano et al., 2021 (11 CVOT)	5 SGLT2i vs Placebo	T2DM and/or HF/CKD	77,541	Pooled	CV death/HHF: HR 0.77 (0.73-0.82) HHF alone: HR 0.68
Palmer et al., 2021 (BMJ Network)	SGLT2i vs GLP-1RA vs Placebo	T2DM broad spectrum	421,346	Pooled NMA	SGLT2i superior for HHF vs GLP-1RA
Shi et al., 2023 (BMJ Network)	13 drug classes vs Placebo	T2DM broad spectrum	471,038	Pooled NMA	SGLT2i: OR 0.88 (0.83-0.94)

Study (Author, Year)	Intervention	Population	N	Follow-up	Key Outcomes
					all-cause death
Baigent et al., 2022 (Lancet Collaborative)	SGLT2i across 13 trials	T2DM, HF, CKD	90,413	Pooled	CV death/HHF: RR 0.77 (0.74-0.81)

Abbreviations: T2DM = type 2 diabetes mellitus; CVD = cardiovascular disease; HFrEF = heart failure with reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HHF = hospitalization for heart failure; CV = cardiovascular; NMA = network meta-analysis; CVOT = cardiovascular outcome trial; HR = hazard ratio; CI = confidence interval; N = total sample size; RCT = randomized controlled trial.

Risk of Bias Assessment

Table 2 presents the risk of bias assessment for all included primary RCTs and meta-analyses using the Cochrane RoB 2 tool.

Table 2. Risk of Bias Assessment (Cochrane RoB 2 Tool)

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participant	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Overall Risk of Bias
EMPA-REG OUTCOME	Low	Low	Low	Low	Low	Low	LOW
CANVAS Program	Low	Low	Low	Low	Low	Some concerns*	LOW
DECLARE-TIMI 58	Low	Low	Low	Low	Low	Low	LOW

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Overall Risk of Bias
CREDENCE	Low	Low	Low	Low	Low	Low	LOW
DAPA-HF	Low	Low	Low	Low	Low	Low	LOW
EMPEROR-Reduced	Low	Low	Low	Low	Low	Low	LOW
EMPEROR-Preserved	Low	Low	Low	Low	Low	Low	LOW
EMPA-RESPONSE-AHF	Low	Low	Low	Low	Low	Low	LOW
EMPULSE	Low	Low	Low	Low	Low	Low	LOW
Zelniker 2019 ()	Low	N/A	N/A	Low	Low	Low	LOW
McGuire 2020 ()	Low	N/A	N/A	Low	Low	Low	LOW
Palmer 2021 (NMA)	Low	N/A	N/A	Low	Low	Low	LOW
Giugliano 2021 ()	Low	N/A	N/A	Low	Low	Low	LOW
Baigent 2022 ()	Low	N/A	N/A	Low	Low	Low	LOW
Shi 2023	Low	N/A	N/A	Low	Low	Low	LOW

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participant	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Overall Risk of Bias
(NMA)							

**The CANVAS Program received 'Some concerns' for selective reporting owing to the unanticipated signal for lower limb amputation, which was not a pre-specified primary endpoint and was subsequently the subject of additional investigation. This signal was not confirmed in subsequent trials. Color coding: Green = Low risk; Yellow = Some concerns. N/A = Not applicable (meta-analyses assessed with AMSTAR-2; all rated as high methodological quality).*

Primary Outcome: Hospitalization for Heart Failure (HHF)

SGLT-2 inhibitors demonstrated consistent, statistically significant, and clinically meaningful reductions in HHF across all major RCTs. In the landmark EMPA-REG OUTCOME trial, empagliflozin reduced the risk of HHF by 35% compared to placebo (HR 0.65; 95% CI 0.50–0.85; $P < 0.001$), corresponding to a number-needed-to-treat (NNT) of approximately 71 over 3.1 years.¹¹ This benefit was observed consistently in patients with and without baseline HF, across all categories of HF risk, and was independent of background cardiovascular risk factor control.¹² The CANVAS Program demonstrated that canagliflozin reduced HHF by 33% (HR 0.67; 95% CI 0.52–0.87; $P < 0.001$), with evidence suggesting potentially greater benefit in those with established HF at baseline (HR 0.61; 95% CI 0.46–0.80; P -interaction=0.021).¹³ The DECLARE-TIMI 58 trial, which enrolled the largest proportion of patients without established CVD (59.4%), demonstrated that dapagliflozin reduced the composite of CV death or HHF by 17% (HR 0.83; 95% CI 0.73–0.95; $P = 0.005$), driven primarily by a 27% reduction in HHF (HR 0.73; 95% CI 0.61–0.88), without a significant effect on cardiovascular death in isolation.¹⁴

Pooled data from the McGuire et al. meta-analysis (2020, JAMA Cardiology), encompassing six major RCTs and 46,969 patients with T2DM, confirmed a consistent 32% relative risk reduction in HHF across the SGLT-2 inhibitor class (HR 0.68; 95% CI 0.61–0.76; $I^2 = 0.0\%$), with no significant heterogeneity across individual agents, underscoring a robust class effect.¹⁵

Table 3. HHF Outcomes by Individual SGLT-2 Inhibitor and Major Trial

SGLT2 Inhibitor	Major Trial	N	HHF HR (95% CI)	HHF Absolute Risk Reduction	NNT
Empagliflozin	EMPA-REG OUTCOME	7,020	0.65 (0.50–0.85)	1.4% over 3.1 yrs	~71
Canagliflozin	CANVAS Program	10,142	0.67 (0.52–0.87)	1.4 per 1000 pt-yrs	~85
Dapagliflozin	DECLARE-TIMI 58	17,160	0.73 (0.61–0.88)	0.6% over 4.2 yrs	~167
Canagliflozin	CREDENCE	4,401	0.61 (0.47–0.80)	~2.4% over 2.6 yrs	~42
Dapagliflozin	DAPA-HF	4,744	0.70 (0.59–0.83)	4.9% over 1.5 yrs	~20
Empagliflozin	EMPEROR-Reduced	3,730	0.69 (0.59–0.81)	5.0% over 1.3 yrs	~20
Empagliflozin	EMPEROR-Preserved	5,988	0.71 (0.60–0.83)	3.3% over 2.2 yrs	~30
Class Effect (Pooled)	McGuire 2020 Meta-analysis	46,969	0.68 (0.61–0.76)	Consistent across class	~50–100

Abbreviations: HHF = hospitalization for heart failure; HR = hazard ratio; CI = confidence interval; NNT = number needed to treat; pt-yrs = patient-years. *DAPA-HF enrolled patients with established HFrEF regardless of diabetes status.

Secondary Outcomes: Summary of All ≥15 Outcomes

Table 4. Comprehensive Summary of Clinical Outcomes — SGLT-2 Inhibitors vs. Placebo in T2DM

Outcome	Studies Reporting	Pooled HR / OR / RR (95% CI)	I ² Heterogeneity	GRADE Certainty	Direction of Effect
1. Hospitalization for Heart Failure (HHF)	≥15 RCTs	HR 0.68–0.73 (0.61–0.88)	Low (I ² <25%)	HIGH	Significantly Reduced ↓ 27–32%
2. CV Death or HHF (Composite)	≥15 RCTs	HR 0.77 (0.73–0.82)	Low (I ² =26%)	HIGH	Significantly Reduced ↓ 23%
3. Cardiovascular Mortality	≥12 RCTs	HR 0.85–0.86 (0.81–0.92)	Moderate (I ² =40–64%)	HIGH	Significantly Reduced ↓ 14–16%
4. All-Cause Mortality	≥10 RCTs	HR 0.87–0.88 (0.82–0.93)	Low–Moderate	HIGH	Significantly Reduced ↓ 12–13%
5. Major Adverse CV Events (MACE)	≥12 RCTs	HR 0.89–0.93 (0.83–1.03)	Low (I ² =21%)	HIGH	Modest Reduction ↓ 7–11%
6. Renal Composite Outcome	≥10 RCTs	HR 0.62–0.65 (0.56–0.75)	Low	HIGH	Significantly Reduced ↓ 35–38%
7. Non-fatal Myocardial Infarction	≥10 RCTs	HR 0.87–0.89 (0.74–1.09)	Low	MODERATE	Trend toward Reduction
8. Incident	≥5 Meta-	OR 0.73–0.81	Low–Moderate	MODERATE	Significantly

Outcome	Studies Reporting	Pooled HR / OR / RR (95% CI)	I ² Heterogeneity	GRADE Certainty	Direction of Effect
Atrial Arrhythmias	analyses	(0.68–0.95)			Reduced ↓ 19–27%
9. Sudden Cardiac Death	≥5 Meta-analyses	OR 0.72 (0.54–0.97)	Low	MODERATE	Significantly Reduced ↓ 28%
10. HbA1c Reduction	≥15 RCTs	WMD –0.54 to –0.75%	Moderate	HIGH	Significantly Reduced
11. Systolic Blood Pressure	≥12 RCTs	WMD –2.4 to –3.8 mmHg	Low	HIGH	Significantly Reduced
12. Body Weight	≥12 RCTs	WMD –1.8 to –2.4 kg	Low	HIGH	Significantly Reduced
13. NT-proBNP Reduction	≥8 RCTs	WMD –136.03 pg/mL (–253 to –19)	Moderate	MODERATE	Significantly Reduced
14. LVEF Improvement	≥6 RCTs	WMD +2.79% (0.18–5.39)	Moderate	MODERATE	Significantly Improved
15. Acute Kidney Injury	≥8 RCTs	RR 0.77 (0.70–0.84)	Low	HIGH	Significantly Reduced ↓ 23%

Abbreviations: HR = hazard ratio; OR = odds ratio; RR = relative risk; WMD = weighted mean difference; NT-proBNP = N-terminal pro-B-type natriuretic peptide; LVEF = left ventricular ejection fraction; MACE = major adverse cardiovascular events; GRADE = Grading of Recommendations, Assessment, Development and Evaluation.

Cardiovascular Death and All-Cause Mortality

SGLT-2 inhibitors demonstrated a significant, consistent reduction in cardiovascular mortality. In the EMPA-REG OUTCOME trial, empagliflozin reduced CV death by 38% (HR 0.62;

95% CI 0.49–0.77; $P < 0.001$), representing the most striking mortality benefit observed in a cardiovascular outcome trial to that date.¹¹ The Giugliano et al. (2021) meta-analysis of 11 CVOTs ($n=77,541$) confirmed a 16% reduction in CV mortality (HR 0.84; 95% CI 0.79–0.90), a 13% reduction in all-cause mortality (HR 0.87; 95% CI 0.83–0.91), and a 32% reduction in HHF alone (HR 0.68) with SGLT-2 inhibitor therapy.¹⁶

The Baigent et al. (2022) Lancet collaborative meta-analysis, including 13 large placebo-controlled RCTs across 90,413 patients with T2DM, HF, or CKD, demonstrated a 14% reduction in CV death (RR 0.86; 95% CI 0.81–0.92) and a combined 23% reduction in CV death or HHF (RR 0.77; 95% CI 0.74–0.81), with remarkably consistent effects in patients with and without diabetes.¹⁷

MACE and Atherosclerotic Cardiovascular Events

SGLT-2 inhibitors produced a modest but statistically significant 11% relative risk reduction in MACE (composite of CV death, non-fatal MI, non-fatal stroke) in pooled analyses (HR 0.89; 95% CI 0.83–0.96; $P=0.0014$), with benefit predominantly confined to patients with established atherosclerotic cardiovascular disease.¹⁸ In contrast, in patients without established ASCVD (primary prevention population, predominantly from DECLARE-TIMI 58), there was no significant reduction in MACE (HR 1.00; 95% CI 0.87–1.16), underscoring that MACE benefits may be restricted to secondary prevention. The reduction in HHF, however, was observed consistently regardless of baseline ASCVD status.¹⁹

Renal Outcomes

SGLT-2 inhibitors conferred remarkable renoprotective benefits, reducing the composite renal outcome ($\geq 40\%$ decline in eGFR, ESKD, or renal death) by 37–45% across studies (HR 0.62; 95% CI 0.56–0.70).¹⁷ Dapagliflozin in DECLARE-TIMI 58 reduced the renal-specific composite by 47% (HR 0.53; 95% CI 0.43–0.66; $P < 0.0001$) and risk of end-stage renal disease or renal death by 59% (HR 0.41; 95% CI 0.20–0.82; $P=0.012$).²⁰ The CREDENCE trial, specifically designed to evaluate canagliflozin in T2DM with CKD, achieved the primary composite endpoint with a 30% risk reduction.

Cardiac Biomarkers and Structural Outcomes

SGLT-2 inhibitors significantly reduced circulating NT-proBNP, a key marker of ventricular wall stress and congestion. Meta-analysis of 18 RCTs encompassing 23,953 participants demonstrated a statistically significant reduction in NT-proBNP by 136.03 pg/mL (95% CI –253.36 to –18.70; $P=0.02$), alongside a significant improvement in LVEF by 2.79% (95% CI 0.18–5.39%; $P=0.036$).²¹ SGLT-2 inhibitors also improved Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary scores (WMD +1.7 points; $P<0.00001$) and 6-minute walk distance (WMD +23.98 m; $P=0.003$), reflecting meaningful improvements in functional capacity and symptom burden.²¹

Cardiac Arrhythmias and Sudden Cardiac Death

Fernandes et al. (2021, Heart Rhythm), incorporating 34 RCTs with 63,166 patients, demonstrated that SGLT-2 inhibitors were associated with a significant 19% reduction in incident atrial arrhythmias (OR 0.81; 95% CI 0.69–0.95; $P=0.008$) and a 28% reduction in sudden cardiac death (OR 0.72; 95% CI 0.54–0.97; $P=0.03$).²² Similarly, dapagliflozin in DECLARE-TIMI 58 reduced the incidence of atrial fibrillation/flutter events by 19% (HR 0.81; 95% CI 0.68–0.95; $P=0.009$), consistently regardless of baseline HF, atrial fibrillation history, or atherosclerotic CVD status.²³

Subgroup Analyses

A comprehensive synthesis of pre-specified and post-hoc subgroup analyses is presented in Table 5.

Table 5. Subgroup Analysis — HHF or CV Death Composite Outcomes by Key Patient Characteristics

Subgroup	N (approx.)	HHF/CV Death HR (95% CI)	P-interaction	Clinical Implication
With established CVD	~20,000	0.74 (0.68–0.81)	>0.05 (NS)	Greater absolute benefit
Without established CVD	~15,000	0.84 (0.72–0.98)	>0.05 (NS)	Benefit present in primary prevention
With prior HF at baseline	~5,000	0.64 (0.55–0.74)	0.021	Greater relative &

Subgroup	N (approx.)	HHF/CV Death HR (95% CI)	P-interaction	Clinical Implication
baseline				absolute benefit
Without prior HF at baseline	~30,000	0.82 (0.72–0.93)	0.021	Benefit evident in HF prevention
eGFR <60 mL/min/1.73m ²	~7,000	0.67 (0.55–0.83)	0.007	Greater HHF benefit with CKD
eGFR ≥60 mL/min/1.73m ²	~35,000	0.80 (0.73–0.87)	0.007	Consistent benefit
HbA1c <7.5%	~8,000	0.83 (0.71–0.97)	>0.05 (NS)	Benefit independent of glycemic control
HbA1c ≥7.5%	~25,000	0.80 (0.72–0.90)	>0.05 (NS)	Consistent benefit
Age <65 years	~15,000	0.78 (0.67–0.91)	>0.05 (NS)	Consistent benefit
Age ≥65 years	~20,000	0.76 (0.68–0.85)	>0.05 (NS)	Consistent benefit in elderly
Female sex	~15,000	0.82 (0.68–0.99)	>0.05 (NS)	No sex-based effect modification
Male sex	~30,000	0.78 (0.71–0.85)	>0.05 (NS)	Consistent benefit
HFrEF (EF <40%)	~8,500	0.71 (0.63–0.81)	N/A	Robust benefit confirmed
HFpEF (EF ≥50%)	~6,000	0.79 (0.69–0.90)	N/A	Significant benefit confirmed

NS = not significant (P -interaction >0.05). Subgroup data synthesized from EMPA-REG OUTCOME, CANVAS Program, DECLARE-TIMI 58, DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, and pooled meta-analyses. HFrEF = HF with reduced ejection fraction (EF $<40\%$); HFpEF = HF with preserved ejection fraction (EF $\geq 50\%$).

Safety Outcomes

Table 6 provides a comprehensive summary of safety outcomes across all included studies.

Table 6. Safety Profile of SGLT-2 Inhibitors vs. Placebo — Systematic Review Summary

Adverse Event	SGLT2i Rate	Placebo Rate	HR / OR / RR (95% CI)	P-value	Clinical Significance
Genital mycotic infection	~7–8%	~2–3%	OR 3.5–4.0 (2.8–5.2)	<0.001	Significant increase; mostly mild/treatable
Urinary tract infection	~8–9%	~8–9%	RR 1.07 (1.02–1.13)	0.01	Small, borderline increase
Diabetic ketoacidosis	0.3–0.6%	0.1–0.2%	OR 2.2–3.0 (1.2–5.8)	0.02	Rare but clinically serious
Volume depletion	~2–4%	~2–3%	RR 1.16 (0.99–1.36)	0.07	Borderline; monitor in elderly/diuretics
Lower limb amputation	6.3/1000 pt-yrs	3.4/1000 pt-yrs	HR 1.97 (1.41–2.75)*	<0.001	*CANVAS only; not confirmed in other RCTs
Acute kidney injury	~3.5%	~4.5%	RR 0.77 (0.70–0.84)	<0.001	Significantly REDUCED with SGLT2i
Hypoglycemia (severe)	~0.3%	~0.5%	RR 0.87 (0.79–0.97)	0.01	Significantly reduced (no insulin effect)

Adverse Event	SGLT2i Rate	Placebo Rate	HR / OR / RR (95% CI)	P-value	Clinical Significance
Bone fracture	~4%	~4%	HR 1.26 (0.99–1.59)	0.07	Signal in CANVAS; not confirmed overall
Symptomatic hypotension	~1.5%	~1.5%	HR 0.98 (0.78–1.24)	0.87	No significant difference
Cancer (all types)	~7%	~7%	HR 0.99 (0.88–1.12)	0.88	No significant association

**Amputation signal was confined to the CANVAS Program and was not confirmed in CREDENCE, DECLARE-TIMI 58, or subsequent meta-analyses. Current consensus attributes this to trial-specific factors rather than a class effect of canagliflozin. All data represent pooled or representative estimates from major RCTs and meta-analyses.*

DISCUSSION

Overview of Principal Findings

This systematic review provides a comprehensive, multi-outcome synthesis of the clinical evidence supporting the use of SGLT-2 inhibitors for the prevention and treatment of heart failure in patients with type 2 diabetes mellitus. The principal findings confirm, with HIGH certainty of evidence, that SGLT-2 inhibitors significantly reduce the risk of hospitalization for heart failure (27–35% relative risk reduction), the composite of cardiovascular death or HHF (23% relative risk reduction), cardiovascular mortality (14–38% relative risk reduction), all-cause mortality (12–13% relative risk reduction), and renal disease progression (35–45% relative risk reduction), while also demonstrating benefits on biomarkers of cardiac stress, arrhythmia burden, and patient-reported quality of life.¹⁵

The consistency of these findings across multiple large-scale RCTs—conducted in diverse geographic regions, enrolling patients with varying degrees of cardiovascular risk, and evaluating

three distinct SGLT-2 inhibitor molecules—strongly supports a genuine class effect rather than a molecule-specific or trial-specific phenomenon. The high consistency in HHF reduction ($I^2=0.0\%$ in the McGuire et al. 2020) is particularly compelling and ranks among the most reproducible findings in the modern cardiovascular outcomes trial literature.¹⁵

Mechanisms of Cardiovascular and Cardiac Protective Effects

The mechanistic basis for the cardioprotective effects of SGLT-2 inhibitors has been extensively investigated and is now understood to be multifactorial, extending far beyond their antihyperglycemic properties. The primary proposed mechanisms can be organized into hemodynamic, metabolic, and cellular/molecular pathways.²⁴

Hemodynamic Mechanisms

SGLT-2 inhibition promotes substantial natriuresis and osmotic diuresis through renal proximal tubular glucose and sodium blockade. This results in reductions in plasma volume, cardiac preload, and afterload—effects analogous to, but mechanistically distinct from, loop diuretics. A unique feature of SGLT-2 inhibitor-induced natriuresis is its reliance on the tubuloglomerular feedback mechanism, which restores intraglomerular hypertension through afferent arteriolar vasoconstriction, providing simultaneous renoprotection. SGLT-2 inhibitors also reduce systolic blood pressure by approximately 2.4–3.8 mmHg and body weight by 1.8–2.4 kg, collectively contributing to favorable ventricular loading conditions.²⁵

Metabolic Reprogramming and Myocardial Energetics

The failing heart operates under profound metabolic stress, shifting from efficient fatty acid oxidation toward less efficient glucose metabolism. SGLT-2 inhibitors promote a metabolic shift in cardiac myocytes toward ketone body utilization, which generates more ATP per unit oxygen consumed compared to glucose or fatty acids—a phenomenon analogous to the 'super-fuel' concept. This metabolic reprogramming, mediated by upregulation of PPAR- α , ACADM, and ketolytic enzymes, enhances myocardial energy efficiency and preserves contractile function.²⁶ Santos-Gallego et al. (2019, JACC) demonstrated this mechanism in a porcine non-diabetic HF model, showing empagliflozin-induced myocardial metabolic shift from glucose toward ketone bodies, free

fatty acids, and branched-chain amino acids, accompanied by improved LV systolic function and amelioration of adverse remodeling.²⁷

Cellular Protective Signaling — Autophagy and Nutrient Deprivation Pathways

Groundbreaking work by Packer (2020, 2022, 2023) has proposed that SGLT-2 inhibitors produce a cellular state of 'perceived nutrient deprivation,' activating AMPK, SIRT1, SIRT3, SIRT6, and PGC1- α while suppressing mTOR. This upregulates autophagic flux—a lysosome-mediated cellular housekeeping process that removes dysfunctional mitochondria, toxic metabolic by-products, and misfolded proteins. The net result is reduced oxidative stress, mitochondrial renewal, and preservation of cardiomyocyte integrity. These effects occur in cells not expressing SGLT-2, including cardiomyocytes, and are independent of glucose-lowering or natriuretic effects, explaining the heart failure benefits observed in non-diabetic patients.²⁸

Anti-inflammatory and Anti-fibrotic Effects

SGLT-2 inhibitors significantly reduce circulating inflammatory markers, including interleukin-6, tumor necrosis factor- α , fibronectin-1, and matrix metalloproteinase-7. Dapagliflozin has been shown to directly inhibit macrophage-mediated cardiac inflammation independent of SGLT-2 expression, via suppression of C-C chemokine receptor type 2-positive macrophage infiltration into the myocardium, thereby attenuating cardiac fibrosis and adverse remodeling.²⁹ Empagliflozin reduces cardiac fibrosis through normalization of natriuretic peptide expression (NPPA, NPPB), TNF- α , and PPAR- α , as demonstrated in spontaneously hypertensive rat models of non-diabetic HF.³⁰

Sodium-Hydrogen Exchange Inhibition

A clinically important mechanism is the direct inhibition of the cardiac sodium-hydrogen exchanger (NHE1) by SGLT-2 inhibitors. NHE1 overactivation in HF leads to intracellular sodium and calcium overload, promoting mitochondrial dysfunction and arrhythmogenesis. By inhibiting NHE1, SGLT-2 inhibitors reduce intracellular calcium overload, improve mitochondrial calcium handling, and potentially reduce arrhythmia susceptibility—consistent with the observed reductions in atrial fibrillation and sudden cardiac death in clinical trials.³¹

Interpretation of Outcomes by Heart Failure Phenotype

A major advance in the evidence base has been the demonstration that SGLT-2 inhibitor benefits extend across the full spectrum of HF phenotypes. While initial CVOTs enrolled primarily patients without HF or with asymptomatic HF, the dedicated DAPA-HF (dapagliflozin, HFrEF, HR 0.74; 95% CI 0.65–0.85) and EMPEROR-Reduced (empagliflozin, HFrEF, HR 0.75; 95% CI 0.65–0.86) trials demonstrated robust benefits in established HFrEF regardless of diabetes status, leading to guideline expansion of indications beyond T2DM.⁷

Crucially, the EMPEROR-Preserved trial demonstrated that empagliflozin also significantly reduced CV death or HHF in HFpEF patients (HR 0.79; 95% CI 0.69–0.90; $P < 0.001$)—a milestone achievement, as HFpEF had historically lacked effective pharmacological therapies. This was accompanied by meaningful improvements in KCCQ scores and functional capacity, as corroborated by the Nassif et al. (2021, *Nature Medicine*) PRESERVED-HF trial.³²

Comparative Efficacy of Individual SGLT-2 Inhibitors

Täger et al. (2020, *Heart Failure Reviews*), incorporating 64 trials and 74,874 patients, demonstrated that empagliflozin and canagliflozin improved all-cause mortality, cardiovascular mortality, and worsening HF, whereas dapagliflozin improved worsening HF only. Empagliflozin was superior to other SGLT-2 inhibitors for all-cause and cardiovascular mortality reduction. Notably, ertugliflozin had no significant effect on any mortality or HF endpoint, which may reflect its different cardiovascular outcome trial (VERTIS-CV) population characteristics or a true drug-specific limitation.³³ However, the class-level pooled analysis by McGuire et al. (2020) demonstrated $I^2 = 0.0\%$ for HHF reduction, supporting a consistent class effect for this endpoint specifically, regardless of individual agent differences for mortality outcomes.¹⁵

Benefits in the Primary Prevention Population

The DECLARE-TIMI 58 trial uniquely enrolled 59.4% of patients without established atherosclerotic CVD (primary prevention population), demonstrating that dapagliflozin reduced HHF by 36% (HR 0.64; 95% CI 0.46–0.88) even in this lower-risk group.³⁴ This extends the potential application of SGLT-2 inhibitors to a substantially larger population of T2DM patients who have not yet developed overt CVD or HF, consistent with a prevention paradigm rather than purely a treatment strategy.

Safety Profile and Clinical Implications

The safety profile of SGLT-2 inhibitors is well-characterized and generally favorable. Genital mycotic infections (predominantly *Candida*) are the most common drug-related adverse event, occurring in approximately 5–8% of treated patients and predominantly in women and uncircumcised men. These are typically mild, responsive to antifungal therapy, and rarely necessitate treatment discontinuation.³⁵

Diabetic ketoacidosis (DKA) is a rare but potentially life-threatening adverse event, occurring at an approximate frequency of 0.3–0.6% with SGLT-2 inhibitors versus 0.1–0.2% with placebo. Risk factors include insulin omission, caloric restriction, alcohol use, surgery, and type 1 DM (for which SGLT-2 inhibitors are not indicated). Routine monitoring for symptoms of DKA and patient education are essential.³⁵

The initial amputation signal from the CANVAS Program (HR 1.97; 95% CI 1.41–2.75) is not considered a confirmed class effect of canagliflozin. The subsequent CREDENCE trial (canagliflozin in CKD) and all trials with dapagliflozin and empagliflozin have not reproduced this signal. Current guidelines do not restrict canagliflozin use based solely on this finding, while advocating for foot care monitoring. Importantly, acute kidney injury was significantly reduced with SGLT-2 inhibitor use (RR 0.77; 95% CI 0.70–0.84), allaying initial concerns about hypovolemia-related renal complications.³⁶

Comparison with GLP-1 Receptor Agonists and Other Agents

Palmer et al. (2021, BMJ), encompassing 764 trials and 421,346 patients, demonstrated that SGLT-2 inhibitors reduced HHF to a significantly greater degree than GLP-1 receptor agonists, which appeared to have no significant effect on HHF in this analysis. Conversely, GLP-1 receptor agonists were superior for the reduction of non-fatal stroke—an outcome where SGLT-2 inhibitors appeared neutral.³⁷ These complementary profiles suggest a potential rationale for combination therapy, with the additive cardiovascular benefits of SGLT-2 inhibitors and GLP-1 receptor agonists being explored in ongoing trials.

Implications for Clinical Practice and Guidelines

The accumulated evidence from this systematic review provides compelling support for the routine clinical integration of SGLT-2 inhibitors in T2DM management at multiple levels: (1) as second-line antidiabetic agents (after metformin, or as first-line where metformin is contraindicated) in T2DM patients with established CVD, HF, or CKD; (2) as heart failure-specific therapy (dapagliflozin, empagliflozin) in HFrEF and HFpEF regardless of diabetes status; (3) as renoprotective agents in diabetic kidney disease with albuminuria; and (4) for primary prevention of HF in high-risk T2DM patients without established CVD. The choice between individual agents should be informed by individual patient cardiovascular and renal risk profiles, tolerability, cost, and availability.³⁹

CONCLUSIONS AND RECOMMENDATIONS

Principal Conclusions

This systematic review provides robust, HIGH-certainty evidence that sodium-glucose cotransporter-2 (SGLT-2) inhibitors are highly effective in reducing the risk of heart failure hospitalization, cardiovascular death, and a broad spectrum of cardiorenal outcomes in patients with type 2 diabetes mellitus. The magnitude of benefit is clinically significant and consistent across multiple large-scale RCTs, meta-analyses encompassing >100,000 patients, and diverse patient subgroups—including those with and without established cardiovascular disease, with HFrEF and HFpEF, across all categories of renal function, and regardless of sex, age, or baseline glycemic control.

The key cardioprotective mechanisms of SGLT-2 inhibitors—including natriuresis-mediated ventricular unloading, myocardial metabolic reprogramming toward ketone utilization, activation of cellular autophagy and nutrient-deprivation signaling, NHE1 inhibition, anti-inflammatory and anti-fibrotic effects, and erythropoiesis-mediated cardioprotection—collectively explain benefits that extend beyond those achievable through glycemic control alone.

Recommendations

For Clinical Practice:

1. SGLT-2 inhibitors (preferably empagliflozin or dapagliflozin) should be strongly considered as cornerstone pharmacotherapy for all T2DM patients with established CVD, HF (HFrEF or HFpEF), or CKD, independent of HbA1c level or background glucose-lowering therapy.
2. In T2DM patients without established CVD but with multiple cardiovascular risk factors, SGLT-2 inhibitors should be offered for primary HF prevention based on the DECLARE-TIMI 58 evidence.
3. For patients with established HFrEF or HFpEF—with or without T2DM—dapagliflozin or empagliflozin should be initiated as part of guideline-directed medical therapy, in conjunction with beta-blockers, RAAS inhibitors/sacubitril-valsartan, and mineralocorticoid receptor antagonists where indicated.
4. Routine monitoring for genital infections, urinary symptoms, and signs of diabetic ketoacidosis is recommended. Patients should be educated on sick-day rules (temporary cessation during acute illness, surgery, or extreme caloric restriction) to minimize DKA risk.

For Future Research:

1. Head-to-head comparative RCTs of individual SGLT-2 inhibitors (empagliflozin vs. dapagliflozin vs. canagliflozin) powered for HF endpoints are needed to guide agent selection.
2. Long-term (>5 years) safety and efficacy data—particularly for bone health, cancer, and limb outcomes—require ongoing investigation in large observational cohorts.
3. Mechanistic RCTs using comprehensive cardiac imaging (cardiac MRI, echocardiography-derived strain analyses) and biomarker profiling (NT-proBNP, hsTnT, sST2, GDF-15) are warranted to delineate the relative contributions of individual mechanisms to clinical benefit.
4. Studies in under-represented populations—including Asian, African, and South American patients, elderly patients (age >75 years), and patients with advanced CKD (eGFR 15–30)—are needed to optimize clinical guidance in these groups.
5. The potential synergistic effects of combining SGLT-2 inhibitors with GLP-1 receptor agonists, finerenone, or novel agents (e.g., tirzepatide) on HF outcomes represent a high-priority research agenda.

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