RESEARCH PAPER

THE ROLE OF SODIUM–GLUCOSE COTRANSPORTER-2 INHIBITORS IN PATIENTS WITH HEART FAILURE AND TYPE 2 DIABETES MELLITUS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMISED CONTROLLED TRIALS AND PRIMARY STUDIES

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ABSTRACT

Background: *Heart failure (HF) and type 2 diabetes mellitus (T2DM) coexist in approximately 30–40% of patients and confer a substantially worse prognosis than either condition alone. Sodium–glucose cotransporter-2 (SGLT2) inhibitors are now guideline-recommended across the HF spectrum, yet evidence specific to the dual-diagnosis population is dispersed across trial subgroups, cardiovascular outcome trials, mechanistic studies and real-world cohorts.* ***Objective:*** *To quantify the efficacy and safety of SGLT2 inhibitors in adults with coexisting HF and T2DM.* ***Methods:*** *Systematic review and meta-analysis reported according to PRISMA 2020. Literature published between January 2011 and October 2026 was searched through the Consensus academic engine (Semantic Scholar, OpenAlex, PubMed) and citation tracking. Randomised controlled trials (RCTs, including diabetic subgroups of HF trials and HF subgroups of cardiovascular/renal outcome trials), comparative cohort studies and case series were eligible. Hazard ratios (HRs), risk ratios (RRs) and mean differences (MDs) were pooled with DerSimonian–Laird random-effects models; risk of bias was appraised with RoB 2, ROBINS-I and the JBI checklist, and certainty of evidence with GRADE.* ***Results:*** *Twenty-one studies (14 randomised, 6 cohort, 1 case series; ≈170,000 participants) were included, 18 of which contributed to meta-analyses. Among randomised participants with HF and T2DM, SGLT2 inhibitors reduced the composite of cardiovascular death or HF hospitalisation (10 estimates, n = 16,111; HR 0.75, 95% CI 0.70–0.80; I^2 = 0%; 95% prediction interval 0.69–0.81), first HF hospitalisation (HR 0.68, 0.62–0.75), cardiovascular death (HR 0.83, 0.73–0.94) and all-cause death (HR 0.82, 0.70–0.96). Effects were consistent across HF phenotype (p-interaction = 0.36), trial setting (p = 0.52) and individual agents (p = 0.65). Cohort studies corroborated lower HF hospitalisation (HR 0.55, 0.44–0.67) and mortality (HR 0.70, 0.64–0.77). SGLT2 inhibitors improved Kansas City Cardiomyopathy Questionnaire scores (MD 3.12 points, 1.94–4.30) and reduced serious adverse events (RR 0.89, 0.85–0.94), but tripled genital infections (RR 3.02, 1.77–5.13); volume depletion, severe hypoglycaemia, amputation and kidney events were not significantly increased, and ketoacidosis was rare. No small-study effects were detected (Egger p = 0.30).* ***Conclusion:*** *In patients with HF and T2DM, SGLT2 inhibitors provide a robust, class-wide 25% relative reduction in cardiovascular death or HF hospitalisation (high-certainty evidence), irrespective of ejection fraction, with additional reductions in mortality and improved health status, and a favourable safety profile dominated by genital mycotic infections.*

Keywords: *Sodium–Glucose Cotransporter-2 Inhibitors, Heart Failure, Type 2 Diabetes Mellitus, Heart Failure Hospitalisation, Cardiovascular Mortality, Meta-Analysis*

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INTRODUCTION

Heart failure (HF) and type 2 diabetes mellitus (T2DM) are among the most prevalent and closely interlinked chronic cardiometabolic disorders worldwide. T2DM is present in approximately 30–40% of patients with HF, both with reduced (HFrEF) and preserved ejection fraction (HFpEF), and its coexistence is associated with a higher risk of HF hospitalisation (HHF), cardiovascular (CV) death and all-cause mortality. Conversely, HF is frequently the first cardiovascular manifestation of T2DM and remains under-recognised in diabetic populations.[1–3]

Sodium–glucose cotransporter-2 (SGLT2) inhibitors were originally developed as glucose-lowering agents that block proximal tubular glucose and sodium reabsorption. Cardiovascular outcome trials (CVOTs) in T2DM — EMPA-REG OUTCOME, the CANVAS Program, DECLARE-TIMI 58 and VERTIS CV — consistently reduced HHF by approximately 30%, and a meta-analysis of these trials demonstrated a 23% reduction in CV death or HHF that was similar in patients with and without a history of HF.[4–8]

Dedicated HF trials subsequently established SGLT2 inhibitors as disease-modifying therapy: dapagliflozin and empagliflozin reduced CV death or worsening HF in HFrEF (DAPA-HF, EMPEROR-Reduced) and in HF with mildly reduced or preserved ejection fraction (DELIVER, EMPEROR-Preserved), while sotagliflozin reduced total CV deaths and HF events when initiated around a worsening-HF hospitalisation in patients with T2DM (SOLOIST-WHF). Pooled analyses confirmed a 23–26% reduction in CV death or HHF, and the 2023 European Society of Cardiology (ESC) guidelines now recommend SGLT2 inhibitors for all patients with HF and T2DM, irrespective of ejection fraction.[3,9–16]

Despite this body of evidence, diabetes-specific estimates remain scattered across prespecified subgroup analyses of HF trials, HF subgroups of CVOTs, small mechanistic randomised trials and real-world registries, and diabetes-specific safety concerns — euglycaemic diabetic ketoacidosis (DKA), hypoglycaemia during concomitant insulin or sulfonylurea therapy, genital mycotic infections and amputation — are concentrated in this population. A dedicated, contemporary synthesis restricted to patients who simultaneously have HF and T2DM is therefore warranted.[17–20]

A. Objectives of the Study

The general objective was to evaluate the efficacy and safety of SGLT2 inhibitors in adults with coexisting HF and T2DM. The specific objectives were (1) to quantify the effect of SGLT2 inhibitors on the composite of CV death or HHF, first HHF, CV death, all-cause mortality, health status and natriuretic peptides; (2) to evaluate the consistency of benefit across HF phenotype, trial setting and individual agents; (3) to integrate evidence from comparative cohort studies and case series; and (4) to characterise safety outcomes, using only studies published within the last 15 years.[21]

B. Research Hypothesis

The research hypothesis (H_1) was that, in adults with HF and T2DM, SGLT2 inhibitors reduce the risk of the composite of CV death or HHF compared with placebo or standard care, whereas the null hypothesis (H_0) stated that no difference exists. Secondary hypotheses postulated that the benefit is consistent across ejection-fraction phenotypes and agents and is not accompanied by an excess of serious adverse events.[14,15]

C. Significance of the Study

Theoretically, this review provides a quantitative synthesis of the dual cardiometabolic role of SGLT2 inhibitors restricted to the dual-diagnosis population, integrating randomised, observational and case-series evidence. Clinically, it delivers absolute effect estimates and diabetes-specific safety data that may support treatment decisions, health-system strategies to reduce HF hospitalisations and the implementation of guideline-directed therapy in settings with a rising burden of both conditions, including Indonesia.[3,16]

LITERATURE REVIEW

A. Heart Failure in Type 2 Diabetes Mellitus: Epidemiology and Pathophysiology

The incremental risk conferred by diabetes is clearly visible in contemporary HF trials. In EMPEROR-Reduced, placebo-treated patients with diabetes had an approximately 40% higher incidence of CV death or HHF than those without diabetes (24.6 versus 17.6 per 100 patient-years) and an almost two-fold faster decline in estimated glomerular filtration rate (eGFR); in EMPEROR-Preserved the corresponding event rates were 10.25 versus 7.21 per 100 patient-years, and in DELIVER the incidence rose from 6.9 per 100 patient-years in normoglycaemia to 10.1 per 100 patient-years in T2DM.[22–24]

Insulin resistance, myocardial lipotoxicity, accumulation of advanced glycation end-products, coronary microvascular dysfunction, interstitial fibrosis, neurohormonal activation and diabetic kidney disease are thought to underlie this excess risk. Both HFrEF and HFpEF are common in T2DM, HFpEF is frequently undiagnosed, and HF therapies that are effective in the general HF population are equally effective in patients with T2DM, whereas several glucose-lowering drugs are neutral or harmful with respect to HF.[1,2]

B. SGLT2 Inhibitors: Pharmacology and Cardioprotective Mechanisms

SGLT2 inhibitors (gliflozins) inhibit the high-capacity sodium–glucose cotransporter in the proximal tubule, producing glycosuria and natriuresis. Sotagliflozin additionally inhibits intestinal SGLT1. The agents and doses evaluated in the programmes included in this review are summarised in Table 1.[13,25]

Table 1. SGLT2 Inhibitors Evaluated in Heart Failure and Type 2 Diabetes Programmes

Agent	Doses in included trials	Key programmes	Main HF-related finding
Dapagliflozin	10 mg once daily (5 mg in one case series)	DECLARE-TIMI 58, DAPA-HF, DELIVER, REFORM[24,26–28]	↓ Worsening HF or CV death across the EF spectrum
Empagliflozin	10 mg (10/25 mg in EMPA-REG OUTCOME)	EMPA-REG OUTCOME, EMPEROR-Reduced, EMPEROR-Preserved, SUGAR-DM-HF[8,22,23,29]	↓ CV death or HHF in HFrEF and HFpEF; reverse remodelling
Canagliflozin	100 mg (100/300 mg in CANVAS)	CANVAS Program, CREDENCE, CANDLE[30–32]	↓ HHF in T2DM with high CV risk or CKD
Ertugliflozin	5/15 mg	VERTIS CV[33]	↓ First and total HHF
Sotagliflozin (SGLT1/2)	200 mg, up to 400 mg	SOLOIST-WHF[13]	↓ Total CV deaths and HF events after worsening HF

↓, reduction; CKD, chronic kidney disease; CV, cardiovascular; EF, ejection fraction; HF, heart failure; HHF, hospitalisation for heart failure; T2DM, type 2 diabetes mellitus.

The benefits of SGLT2 inhibition extend well beyond glycaemic control. Proposed mechanisms include natriuresis and decongestion with limited neurohormonal activation, haemoconcentration and stimulation of erythropoiesis, reduction of preload and afterload, a shift of myocardial substrate utilisation toward ketone bodies with improved energetic efficiency, attenuation of inflammation, oxidative stress and fibrosis, and nephroprotection. Mediation analyses of CVOTs indicate that changes in haematocrit, haemoglobin,

serum urate and albuminuria — rather than glycated haemoglobin (HbA1c) — account for most of the effect on HF events.[25,34–36]

The conceptual framework of this review is summarised in Figure 1. T2DM and HF share pathophysiological pathways that culminate in CV death, HHF and impaired health status; SGLT2 inhibitors act on several of these pathways, and their effects on clinical, functional and safety outcomes, together with potential effect modifiers, were examined.[1,25]

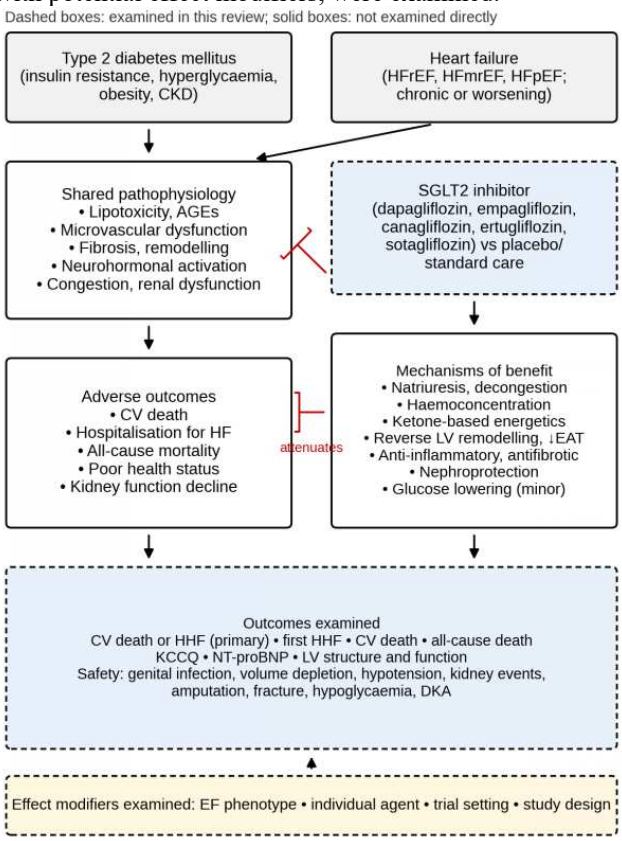


Figure 1: Conceptual framework of the review. Dashed boxes, examined; solid boxes, not examined directly. AGEs, advanced glycation end-products; CKD, chronic kidney disease; DKA, diabetic ketoacidosis; EAT, epicardial adipose tissue; KCCQ, Kansas City Cardiomyopathy Questionnaire; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

C. Previous Studies

Previous meta-analyses relevant to this question are summarised in Table 2. Trial-level analyses of CVOTs demonstrated a 23% reduction in CV death or HHF irrespective of HF history, pooled analyses of dedicated HF trials reported 23–26% reductions irrespective of diabetes status, and observational meta-analyses confirmed lower HHF in routine practice. These reviews, however, pooled entire HF or T2DM populations, were restricted to RCTs or did not pool diabetes-specific safety outcomes.[4,14,15,18–20,37,38]

Table 2. Summary of Previous Systematic Reviews and Meta-Analyses

Review	Evidence base; population	Main findings; added value of the present review
Zelniker et al. 2019[4]	3 CVOTs; 34,322 patients; T2DM ± HF	CV death/HHF HR 0.77 (0.71–0.84), consistent by HF history. Added value: HF + T2DM only; adds HF trials and cohorts
Zannad et al. 2020[14]	DAPA-HF + EMPEROR-Reduced; 8474; HFrEF ± T2DM	CV death/first HHF HR 0.74 (0.68–0.82), consistent by diabetes. Added value: HFmrEF/HFpEF and worsening HF
Li et al. 2021[20]	7 RCTs; 14,113; HF ± DM (58.9% DM)	CV death/HHF RR 0.77; volume depletion RR 1.18; SAE RR 0.87. Added value: diabetes-specific safety
Vaduganathan et al. 2022[15]	5 HF RCTs; 21,947; HF ± T2DM	CV death/HHF HR 0.77 (0.72–0.82); all-cause death 0.92 (0.86–0.99). Added value: diabetes-specific estimates; CVOT HF subgroups
Hinton et al. 2022[18]	43 observational studies; T2DM	HHF HR 0.65 (0.59–0.72). Added value: restricted to established HF
Chen et al. 2024[37]	18 RCTs; 23,953; chronic HF ± T2DM	NT-proBNP −136 pg/mL; KCCQ and 6MWD improved. Added value: diabetes-specific KCCQ
Yao et al. 2025[19]	12 studies; 9509; HF + T2DM	CV death/HHF reduced by 23%; improved remodelling and KCCQ. Added value: larger evidence base, cohorts, GRADE
Bodea et al. 2026[38]	11 RCTs; 23,812; HF ± T2DM	CV death/HHF HR 0.77 (0.72–0.82); KCCQ-CSS +4.6. Added value: diabetes-restricted with real-world data

6MWD, 6-minute walk distance; CVOT, cardiovascular outcome trial; DM, diabetes mellitus; HFmrEF/HFpEF/HFrEF, heart failure with mildly reduced/preserved/reduced ejection fraction; KCCQ(-CSS), Kansas City Cardiomyopathy Questionnaire (clinical summary score); RCT, randomised controlled trial; RR, risk ratio; SAE, serious adverse event.

D. Research Gap

Several gaps therefore persist. First, no previous synthesis has combined diabetic subgroups of dedicated HF trials with HF

subgroups of CVOTs and renal outcome trials to estimate the effect specifically in patients with both conditions. Second, real-world cohorts and case series in HF with T2DM have not been integrated with randomised evidence. Third, diabetes-specific safety outcomes, including ketoacidosis, hypoglycaemia and genital infection, have not been pooled within this population, and the consistency of benefit across agents and ejection-fraction phenotypes remains incompletely characterised.[15,18–20]

E. Novelty

The novelty of this review lies in its strict restriction to patients who simultaneously have HF and T2DM, its integration of randomised subgroup estimates, real-world cohorts and a prospective case series within a 15-year window, its pooling of diabetes-specific safety data extracted directly from full texts and figures, and its translation of relative effects into absolute benefits and harms using GRADE.[21,39]

METHODS

A. Research Design

This study was a systematic review and meta-analysis of randomised controlled trials (RCTs), comparative cohort studies and case series, conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The PICOS framework, outcome hierarchy and statistical analysis plan were prespecified before data extraction; the protocol is to be registered in PROSPERO (registration number to be inserted).[21]

B. Eligibility Criteria

Eligibility criteria are summarised in Table 3. Adults with HF of any phenotype and coexisting T2DM were eligible, as were broader populations if estimates for patients with HF and T2DM were reported separately. Systematic reviews, meta-analyses and narrative reviews were excluded from data synthesis but retained for discussion; case reports, conference abstracts without a full report, animal studies and publications before January 2011 were excluded. When several reports derived from the same dataset, the most comprehensive report for each outcome was used.[21,40]

Table 3. Eligibility Criteria According to the PICOS Framework

Domain	Inclusion criteria (exclusion criteria)
Population	Adults (≥18 years) with HF of any phenotype (HFrEF, HFmrEF, HFpEF; chronic, worsening or recently hospitalised) and T2DM (history or HbA1c ≥6.5%); broader populations only if HF + T2DM estimates were reported separately. (Excluded: type 1 diabetes; non-diabetic populations without diabetes-specific estimates; paediatric populations.)
Intervention	Any SGLT2 inhibitor (dapagliflozin, empagliflozin, canagliflozin, ertugliflozin, sotagliflozin) at licensed doses added to background therapy. (Excluded: combinations without a separable SGLT2 inhibitor effect.)
Comparator	Placebo, usual care, non-SGLT2 inhibitor glucose-lowering therapy (e.g., DPP-4 inhibitor, sulfonylurea) or non-use; none for case series.
Outcomes	Primary: CV death or HHF/worsening HF event. Secondary: first HHF, CV death, all-cause death, KCCQ, NT-proBNP, cardiac structure/function. Safety: SAE, AE-related discontinuation, volume depletion, hypotension, kidney AE, genital infection, UTI, amputation, fracture, severe hypoglycaemia, DKA.
Study design	RCTs (including subgroup analyses), comparative cohort studies, case series (≥5 patients). (Excluded from synthesis: systematic reviews/meta-analyses [discussion only], narrative reviews, case reports, editorials, abstracts without full report, animal or in-vitro studies.)
Time frame; language	Published 1 January 2011 to 18 October 2026 (≤15 years); English.

AE, adverse event; DKA, diabetic ketoacidosis; DPP-4, dipeptidyl peptidase-4; HbA1c, glycated haemoglobin; HHF, hospitalisation for heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SGLT2, sodium–glucose cotransporter-2; UTI, urinary tract infection.

C. Information Sources and Search Strategy

The literature was searched through the Consensus academic search engine, which indexes more than 400 million scholarly records from Semantic Scholar, OpenAlex and PubMed, using its medical mode. Twelve structured search runs were performed, with the last search on 18 October 2026, supplemented by backward and forward citation tracking, retrieval of full texts and supplementary material through PubMed Central, and cross-checking of trial registration numbers to identify overlapping reports. The queries and an equivalent Boolean string are reported in Table 4.[21]

Table 4. Search Strategy (Consensus Engine, Medical Mode; Last Search 18 October 2026)

Run	Search query → target evidence
1	dapagliflozin heart failure reduced ejection fraction with and without diabetes DAPA-HF → diabetic subgroup of DAPA-HF
2	empagliflozin cardiovascular and renal outcomes heart failure by baseline diabetes status EMPEROR-Reduced → diabetic subgroups of EMPEROR trials
3	dapagliflozin heart failure mildly reduced or preserved ejection fraction by baseline glycaemic status DELIVER type 2 diabetes → DELIVER diabetic subgroup
4	sotagliflozin patients with diabetes and recent worsening heart failure SOLOIST-WHF → SOLOIST-WHF

Run	Search query → target evidence
5	canagliflozin cardiovascular outcomes in type 2 diabetes with and without history of heart failure CANVAS Program → CANVAS/CREDENCE HF subgroups
6	dapagliflozin effect on heart failure and mortality in type 2 diabetes by baseline ejection fraction DECLARE-TIMI 58 → DECLARE HF subgroups
7	ertugliflozin heart failure outcomes in type 2 diabetes and atherosclerotic cardiovascular disease VERTIS CV history of heart failure → VERTIS CV HF subgroup
8	SGLT2 inhibitor use in patients with heart failure and type 2 diabetes registry cohort mortality heart failure hospitalisation propensity score → cohort studies
9	randomised trial SGLT2 inhibitor in type 2 diabetes and chronic heart failure NT-proBNP left ventricular mass canagliflozin glimepiride CANDLE dapagliflozin REFORM → mechanistic RCTs
10	dapagliflozin versus placebo left ventricular remodeling patients with diabetes and heart failure REFORM trial results → remodelling RCTs
11	case series euglycemic diabetic ketoacidosis SGLT2 inhibitor patients with heart failure → case series and safety
12	empagliflozin acute heart failure hospitalised patients clinical benefit win ratio diabetes subgroup EMPULSE → acute HF trials
Boolean	("sodium-glucose cotransporter 2 inhibitor*" OR SGLT2* OR gliflozin* OR dapagliflozin OR empagliflozin OR canagliflozin OR ertugliflozin OR sotagliflozin) AND ("heart failure" OR "cardiac failure" OR HFrEF OR HFpEF OR HFmrEF OR "ventricular dysfunction") AND ("type 2 diabetes" OR "diabetes mellitus" OR T2DM OR diabetic); limits: humans, 2011/01/01–2026/10/18 → reproduction in MEDLINE, Embase, CENTRAL

Queries reproduced verbatim (American spelling as entered). Up to 20 ranked records per run were screened; records from citation tracking and PubMed Central full texts were added as 'other methods' in the PRISMA flow diagram.

D. Study Selection and Data Extraction

Two reviewers independently screened titles and abstracts and then full texts against the eligibility criteria; disagreements were resolved by consensus or by a third reviewer. Data were extracted with a standardised, piloted form capturing study identifier, design, country and setting, population, definition of T2DM, HF phenotype, sample size, SGLT2 inhibitor and dose, comparator, follow-up, outcome definitions, effect estimates (HR with 95% CI and event counts), adjustment methods for observational studies and funding. Diabetes-specific estimates were preferentially extracted from HF trials, and HF-subgroup estimates from CVOTs and renal trials (in which all participants had T2DM). HF-subgroup estimates for CREDENCE were obtained from a secondary tabulation and were examined in a sensitivity analysis.[22,23,27,31]

E. Outcomes and Operational Definitions

The primary outcome was the time to first CV death or HHF. Trial-specific definitions were accepted: DAPA-HF and DELIVER included urgent HF visits requiring intravenous therapy, and SOLOIST-WHF reported total (first and recurrent) CV deaths, HHF and urgent HF visits. Operational definitions of all variables are summarised in Table 5.[13,24,27]

Table 5. Operational Definitions of Study Variables

Variable	Definition	Effect measure / scale
SGLT2 inhibitor exposure	Randomised allocation to, or initiation/use of, any SGLT2 inhibitor	Dichotomous (yes/no)
Heart failure	Trial- or registry-defined HF (NYHA II–IV, EF criteria, natriuretic peptides, history of HF)	Nominal (phenotype by EF)
Type 2 diabetes	History of T2DM or HbA1c ≥6.5% at baseline	Dichotomous
CV death or HHF	Time to first CV death or HF hospitalisation (± urgent HF visit)	HR (time-to-event)
First HHF	Time to first hospitalisation for HF	HR
CV death; all-cause death	Adjudicated or registry-defined death	HR
KCCQ	Placebo-adjusted change in KCCQ score	MD (points)
NT-proBNP	Change relative to control	Ratio of geometric means
Safety outcomes	Trial-defined SAE, AE-related discontinuation, volume depletion, hypotension, kidney AE, genital infection, UTI, amputation, fracture, severe hypoglycaemia, DKA	RR; Peto OR (DKA)

AE, adverse event; EF, ejection fraction; HR, hazard ratio; MD, mean difference; NYHA, New York Heart Association; OR, odds ratio; RR, risk ratio; UTI, urinary tract infection.

F. Risk-of-Bias and Quality Assessment

Randomised evidence was appraised with the revised Cochrane risk-of-bias tool (RoB 2) across five domains. Because randomisation in DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved and DELIVER was stratified by diabetes status, diabetic subgroups were considered to preserve randomisation, whereas HF subgroups of CVOTs, which were not stratification factors and were often analysed

post hoc, were rated at least 'some concerns' for selective reporting. Cohort studies were appraised with ROBINS-I across seven domains, and the case series with the 10-item JBI critical appraisal checklist.[40–42]

G. Statistical Analysis

For time-to-event outcomes, log-transformed HRs and standard errors derived from the reported 95% CIs as [ln(upper limit) − ln(lower limit)]/3.92 were pooled with the inverse-variance method under a DerSimonian–Laird random-effects model. Dichotomous safety outcomes were pooled as risk ratios (RRs; 0.5 continuity correction for zero cells), DKA was summarised with the Peto odds ratio, KCCQ changes as mean differences (MDs) and NT-proBNP as ratios of geometric means. Heterogeneity was quantified with Cochran's Q ($p < 0.10$ significant), I^2 and τ^2, and 95% prediction intervals were calculated; Hartung–Knapp–Sidik–Jonkman (HKSJ) and fixed-effect models were applied as sensitivity analyses.[15,38]

Prespecified subgroup analyses examined HF phenotype, trial setting, individual agent and study design using the Q-test for subgroup differences. The two non-overlapping HF subgroups of DECLARE-TIMI 58 were entered separately, with a sensitivity analysis retaining one estimate per trial. Robustness was examined by leave-one-out and cumulative meta-analysis and by excluding studies with secondary-source data, total-event endpoints or a risk of bias other than low. Small-study effects were explored with contour-enhanced funnel plots and Egger's regression test ($k \geq 10$), complemented by Galbraith and L'Abbé plots. Analyses were performed in Python 3 (NumPy, SciPy and Matplotlib) using the standard formulas implemented in Review Manager; a two-sided $p < 0.05$ was considered statistically significant.[21,41]

H. Certainty of Evidence

The certainty of evidence for each outcome was rated with the GRADE approach, considering risk of bias, inconsistency, indirectness, imprecision and publication bias. Randomised evidence started at high certainty, and observational evidence assessed with ROBINS-I was integrated according to GRADE guidance. Absolute effects were estimated by applying the pooled relative effect to the median control-group risk in the included diabetic subgroups.[39,42]

I. Ethical Considerations

Ethical approval was not required because this review synthesized published, de-identified aggregate data. All included studies reported approval by their respective ethics committees and informed consent of participants.[21]

RESULTS

A. Study Selection

The search identified 240 records from database runs and 6 records from other methods. After removal of 84 duplicates, 162 records were screened and 109 were excluded on title and abstract. All 53 full-text reports were retrieved and assessed; 32 were excluded, most commonly because estimates for patients with HF and T2DM were not extractable (n = 12) or because the population was non-diabetic or mixed without diabetes-specific data (n = 6). Twenty-one studies were included in the systematic review (14 randomised, 6 cohort studies and 1 case series), and 18 contributed to at least one meta-analysis (Figure 2).[21]

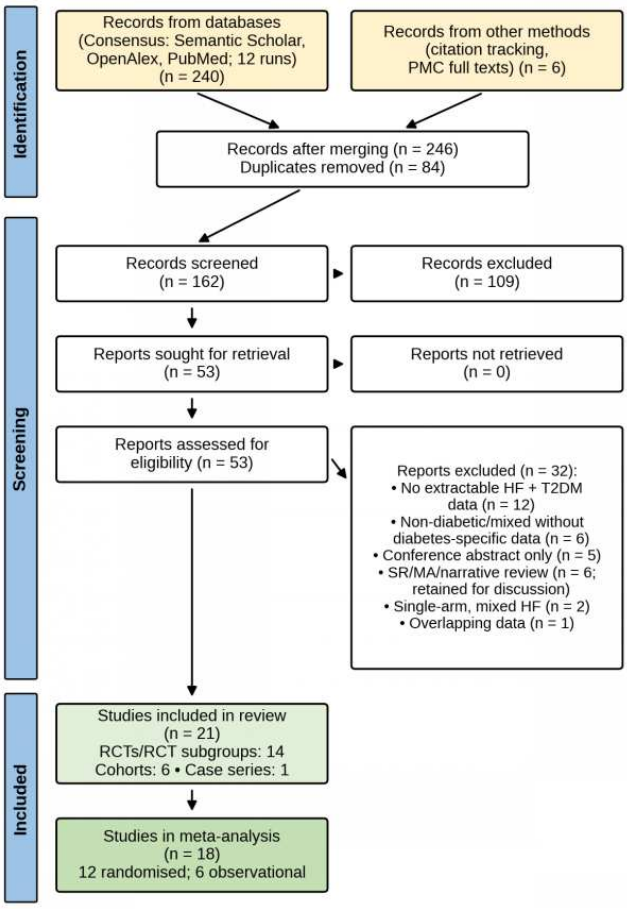


Figure 2: PRISMA 2020 flow diagram of study identification, screening, eligibility and inclusion.

B. Characteristics of Included Studies

The 14 randomised reports comprised four prespecified diabetic subgroup analyses of dedicated HF trials, one HF trial restricted to patients with T2DM (SOLOIST-WHF), HF subgroups of four CVOTs and one renal outcome trial, and four smaller mechanistic or biomarker trials. Randomised participants with HF and T2DM numbered 18,533; follow-up ranged from 12 weeks to a median of 4.2 years, and the comparator was placebo in 12 trials, glimepiride in one and usual care in one (Table 6).[8,13,22–24,26–33,43]

The six cohort studies were conducted in Sweden, Japan, Korea, the United States, Thailand and Denmark and together included more than 150,000 patients; two used active comparators (sitagliptin or a dipeptidyl peptidase-4 inhibitor), and four compared SGLT2 inhibitor use with non-use using propensity-score matching or inverse-probability weighting. The case series was a prospective multicentre series of 58 patients with T2DM and stable HF treated with dapagliflozin (Table 7). Extracted effect estimates are presented in Table 8.[44–50]

Table 6. Characteristics of the Included Randomised Controlled Trials and RCT Subgroup Analyses (HF + T2DM)

Study (trial)	Design; HF + T2DM population; N (SGLT2i/control)	Intervention vs comparator; follow-up; outcomes
Petrie et al. 2020 (DAPA-HF)[27]	Phase 3 double-blind RCT, 410 sites, 20 countries; prespecified subgroup. NYHA II–IV, LVEF ≤40%, elevated NT-proBNP; T2DM by history or HbA1c ≥6.5%. N = 1075/1064	Dapagliflozin 10 mg vs placebo; median 18.2 mo. Composite, HHF, CV death, ACM, KCCQ-TSS, safety
Anker et al. 2021 (EMPEROR-Reduced)[22]	Double-blind RCT, 520 centres, 20 countries; prespecified subgroup. NYHA II–IV, LVEF ≤40%. N = 927/929	Empagliflozin 10 mg vs placebo; median 16 mo. Composite, first/total HHF, CV death, renal, eGFR slope, KCCQ-CSS, safety
Filippatos et al. 2022 (EMPEROR-Preserved)[23]	Multinational double-blind RCT; prespecified subgroup. NYHA II–IV, LVEF >40% (mean 53.9%; HbA1c 7.26%). N = 1466/1472	Empagliflozin 10 mg vs placebo; median 26.2 mo. Composite, HHF, CV death, ACM, renal, safety
Inzucchi et al. 2022 (DELIVER)[24]	Double-blind RCT, 350 centres, 20 countries; prespecified subgroup. Age ≥40 y, NYHA II–IV, LVEF >40%, elevated NT-proBNP. N = 3150 (≈1:1)	Dapagliflozin 10 mg vs placebo; median 2.3 y. Worsening HF or CV death
Bhatt et al. 2021 (SOLOIST-WHF)[13]	Double-blind RCT, 306 sites, 32 countries (terminated early). T2DM hospitalised for worsening HF, any LVEF. N = 608/614	Sotagliflozin 200 mg (to 400 mg) vs placebo; median 9.0 mo. Total CV death/HHF/urgent visits, CV death, ACM, safety
Fitchett et al. 2016 (EMPA-REG OUTCOME)[8]	CVOT; HF subgroup. T2DM + established CVD with HF at baseline (10.1%). N = 462/244	Empagliflozin 10/25 mg vs placebo; median ≈3.1 y. Composite, HHF, CV death, ACM
Rådholm et al. 2018 (CANVAS)[30]	CVOT, 667 centres, 30 countries; HF subgroup. T2DM at high CV risk with history of HF (14.4%). N = 803/658	Canagliflozin 100/300 mg vs placebo; mean 188 wk. Composite, HHF, CV death, ACM, MACE
Kato et al. 2019 (DECLARE-TIMI 58)[26]	CVOT; HF subgroups by EF. HFrEF (EF <45%; n = 671) or HF without known reduced EF (n = 1316). N = 1987 (1:1)	Dapagliflozin 10 mg vs placebo; median 4.2 y. Composite, HHF, CV death, ACM
Cosentino et al. 2020 (VERTIS CV)[33]	CVOT, 567 centres, 34 countries; prespecified HF analyses. T2DM + ASCVD with history of HF (23.7%). N = 1286/672	Ertugliflozin 5/15 mg vs placebo; mean 3.5 y. First HHF
Sarraju et al. 2021 (CREDENCE)[31]	Renal outcome trial; HF subgroup. T2DM + albuminuric CKD with history of HF (15%). N = 329/323	Canagliflozin 100 mg vs placebo; median 2.6 y. Composite, HHF, ACM
Lee et al. 2021 (SUGAR-DM-HF)[29]	Multicentre double-blind RCT, UK. NYHA II–IV, LVEF ≤40%; T2DM 78.1% (remainder prediabetes). N = 105 (1:1)	Empagliflozin 10 mg vs placebo; 36 wk. CMR LV volumes, GLS, NT-proBNP, KCCQ
Singh et al. 2020 (REFORM)[28]	Double-blind RCT, UK. T2DM + HF with LV systolic dysfunction. N = 56 (1:1)	Dapagliflozin 10 mg vs placebo; 1 y. CMR remodelling, BP, diuretic need
Kusunose et al. 2021 (CANDLE)[32]	Multicentre open-label RCT, Japan (post hoc). T2DM + chronic HF (NYHA I–III; ≈70% LVEF ≥50%). N = 113/120	Canagliflozin 100 mg vs glimepiride; 24 wk. NT-proBNP by diastolic function

Study (trial)	Design; HF + T2DM population; N (SGLT2i/control)	Intervention vs comparator; follow-up; outcomes
Ovchinnikov et al. 2025[43]	Single-centre open-label RCT. T2DM + HFpEF (LVEF ≥50%, elevated filling pressure). N = 35/35	Empagliflozin 10 mg vs usual care; 6 mo. 6MWD, E/e′, LAVI, cardiac reserves, NT-proBNP, sST2

ACM, all-cause mortality; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CMR, cardiac magnetic resonance; E/e′, ratio of early mitral inflow to annular velocity; GLS, global longitudinal strain; KCCQ-CSS/TSS, KCCQ clinical summary/total symptom score; LAVI, left atrial volume index; LV(EF), left ventricular (ejection fraction); MACE, major adverse cardiovascular events; NYHA, New York Heart Association; sST2, soluble suppression of tumorigenicity-2.

Table 7. Characteristics of the Included Comparative Cohort Studies and Case Series (HF + T2DM)

Study; setting	Design; population; N; comparator	Main findings (adjusted HR, 95% CI)
Becher et al. 2021[44]; Sweden, Swedish HF Registry, 2016–2018	Registry cohort, 1:3 propensity-score matching; HF + T2DM (all EF); 6805 eligible (376 users); vs no SGLT2i; median 256 days	CV death/first HHF 0.70 (0.52–0.95); lower ACM and CV death
Nakai et al. 2022[45]; Japan, national claims database, 2014–2019	Propensity-score matching (2101 pairs); first acute HF hospitalisation with T2DM; 2277 vs 41,410; vs DPP-4 inhibitor; 1 y	Mortality 0.70 (0.56–0.89); HF readmission 0.52 (0.45–0.61)
Park et al. 2023[46]; Korea, HIRA database, 2015–2020	IPTW cohort; T2DM hospitalised for HF; 818 vs 28,472; vs no initiation; 1 y	HF readmission or CV death 0.90 (0.87–0.93)
Fu et al. 2023[47]; USA, Medicare, 2013–2019	New-user active-comparator cohort, propensity-score weighting; age ≥65 y with HF + T2DM; 16,253 vs 43,352; vs sitagliptin	ACM/HHF/urgent visit 0.72 (0.67–0.77); ACM 0.70 (0.63–0.78); HHF 0.64 (0.58–0.70)
Kongmalai et al. 2024[48]; Thailand, 2 tertiary hospitals, 2010–2022	Retrospective IPTW cohort (SGLT2i ≥3 months); T2DM and HF; 11,758; vs no SGLT2i; median 2.44 y	HHF 0.41 (0.28–0.61); in-hospital ACM 0.24 (0.14–0.42)
Svanström et al. 2024[49]; Denmark, national registers, 2020–2023	Linked database IPTW cohort; HFrEF (20% of users with T2DM); 6776 vs 14,686; vs no SGLT2i	ACM in T2DM subgroup 0.73 (0.58–0.91)
Soga et al. 2018[50] (case series); Japan, 5 institutions, 2016–2017	Prospective single-arm series; T2DM + stable HF; n = 58; dapagliflozin; 6 mo	E/e′ 9.3→8.5 (p = 0.020); LAVI 31→26 mL/m²; LVMI 75.0→67.0 g/m²

DPP-4, dipeptidyl peptidase-4; HIRA, Health Insurance Review and Assessment Service; IPTW, inverse-probability-of-treatment weighting; LVMI, left ventricular mass index.

Table 8. Effect Estimates Extracted From Randomised Studies (Hazard Ratio, 95% CI)

Study (subgroup)	CV death or HHF	First HHF	CV death	All-cause death
DAPA-HF, T2DM[27]	0.75 (0.63–0.90)	0.76 (0.61–0.95)	0.79 (0.63–1.01)	0.78 (0.63–0.97)
EMPEROR-Reduced, T2DM[22]	0.72 (0.60–0.87)	0.67 (0.54–0.83)	0.92 (0.71–1.20)	NR
EMPEROR-Preserved, T2DM[23]	0.79 (0.67–0.94)	0.69 (0.56–0.85)	0.99 (0.77–1.27)	1.05 (0.88–1.26)
DELIVER, T2DM[24]	0.81 (0.69–0.95)	NR	NR	NR
SOLOIST-WHF[13]	0.67[a] (0.52–0.85)	0.64[a] (0.49–0.83)	0.84 (0.58–1.22)	0.82 (0.59–1.14)
EMPA-REG OUTCOME, HF[8]	0.72 (0.50–1.04)	0.75 (0.48–1.19)	0.71 (0.43–1.16)	0.79 (0.52–1.20)
CANVAS Program, HF[30]	0.61 (0.46–0.80)	0.51 (0.33–0.78)	0.72 (0.51–1.02)	0.70 (0.51–0.96)
DECLARE-TIMI 58, HFrEF[26]	0.62 (0.45–0.86)	0.64 (0.43–0.95)	0.55 (0.34–0.90)	0.59 (0.40–0.88)
DECLARE-TIMI 58, HF non-rEF[26]	0.88 (0.66–1.17)	NR	NR	NR
VERTIS CV, HF[33]	NR	0.63 (0.44–0.90)	NR	NR
CREDENCE, HF[31]	0.81[b] (0.57–1.17)	0.76[b] (0.47–1.22)	NR	0.93[b] (0.61–1.41)

[a] Total (first and recurrent) events. [b] From a secondary tabulation of the CREDENCE HF-subgroup analysis. Event counts (SGLT2i vs control) for the composite: DAPA-HF 215/1075 vs 271/1064; EMPEROR-Reduced 200/927 vs 265/929; EMPEROR-Preserved 239/1466 vs 291/1472; EMPA-REG OUTCOME 75/462 vs 49/244; VERTIS CV first HHF 69/1286 vs 55/672. Other diabetic-subgroup outcomes: EMPEROR-Reduced renal composite 0.53 (0.31–0.90) and eGFR slope difference +2.21 mL/min/1.73 m²/year; CANVAS MACE 0.80 (0.61–1.05). NR, not reported.

C. Risk of Bias and Methodological Quality

Among the 14 randomised studies, six (42.9%) were at low risk of bias, seven (50.0%) raised some concerns and one (7.1%) was at high risk (Figures 3 and 4; Table 9). Concerns arose mainly in the domain of selection of the reported result for post hoc HF subgroups of CVOTs, from the early termination, changed primary endpoint and investigator-reported events of SOLOIST-WHF, and from the open-label design of two smaller trials.[8,13,26,30,41,43]



Figure 3: Risk-of-bias traffic-light plot of the randomised evidence (RoB 2). Green, low risk; yellow, some concerns; red, high risk.

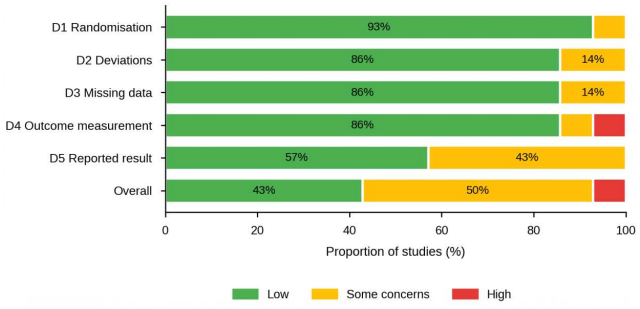


Figure 4: Risk-of-bias summary plot (RoB 2): proportion of randomised studies with each judgement across domains.

Table 9. Risk-of-Bias Judgements for Randomised Studies (RoB 2)[41]

Study	D1	D2	D3	D4	D5	Overall
Petrie 2020 (DAPA-HF)	L	L	L	L	L	Low
Anker 2021 (EMPEROR-Reduced)	L	L	L	L	L	Low
Filippatos 2022 (EMPEROR-Preserved)	L	L	L	L	L	Low
Inzucchi 2022 (DELIVER)	L	L	L	L	L	Low
Bhatt 2021 (SOLOIST-WHF)	L	L	SC	SC	SC	SC
Fitchett 2016 (EMPA-REG OUTCOME)	L	L	L	L	SC	SC
Rådholm 2018 (CANVAS)	L	L	L	L	SC	SC
Kato 2019 (DECLARE-TIMI 58)	L	L	L	L	SC	SC
Cosentino 2020 (VERTIS CV)	L	L	L	L	L	Low
Sarraju 2021 (CREDENCE)	L	L	L	L	SC	SC
Lee 2021 (SUGAR-DM-HF)	L	L	L	L	L	Low
Singh 2020 (REFORM)	L	L	SC	L	L	SC
Kusunose 2021 (CANDLE)	L	SC	L	L	SC	SC
Ovchinnikov 2025	SC	SC	L	H	L	High

D1, randomisation process; D2, deviations from intended interventions; D3, missing outcome data; D4, measurement of the outcome; D5, selection of the reported result; L, low risk; SC, some concerns; H, high risk. Principal reasons: post hoc HF subgroups of CVOTs/renal trials (D5); SOLOIST-WHF early termination, changed primary endpoint and investigator-reported events; small sample/imaging attrition (REFORM); open-label design (CANDLE, Ovchinnikov 2025) with unblinded effort-dependent primary outcome (Ovchinnikov 2025).

Of the six cohort studies, four were at moderate and two at serious overall risk of bias according to ROBINS-I (Figure 5; Table 10). Confounding by indication was the dominant concern; the two studies at serious risk compared users with non-users, and one required at least three months of exposure, a potential source of immortal-time bias, and reported in-hospital mortality. The case series fulfilled 8 of 10 JBI criteria, with uncertainty regarding consecutive and complete inclusion.[40,42,46,48,50]

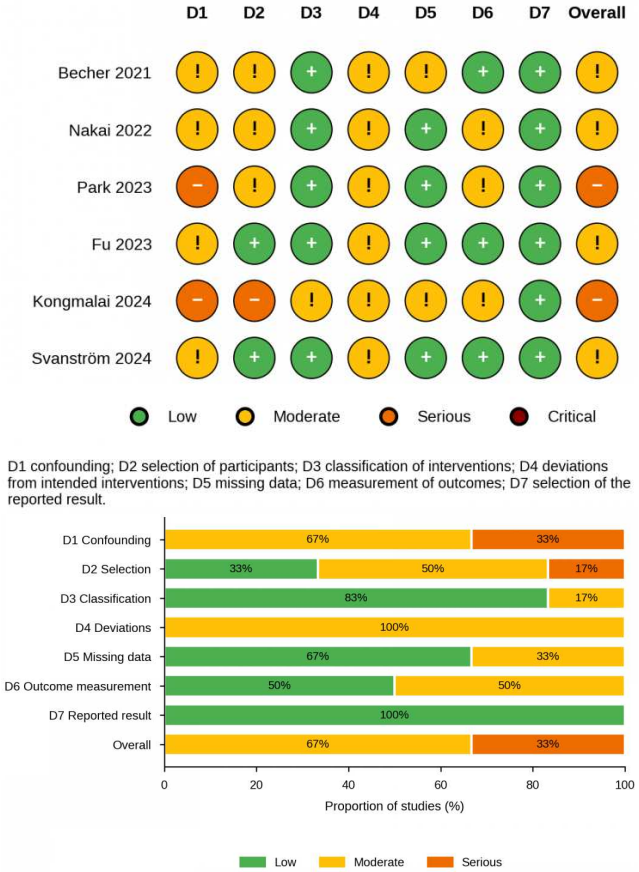


Figure 5: Risk of bias of the observational cohort studies (ROBINS-I): (A) traffic-light plot and (B) summary plot. Green, low; yellow, moderate; orange, serious.

Table 10. Risk-of-Bias Judgements for Cohort Studies (ROBINS-I)[42]

Study	D1	D2	D3	D4	D5	D6	D7	Overall
Becher 2021	M	M	L	M	M	L	L	Moderate
Nakai 2022	M	M	L	M	L	M	L	Moderate
Park 2023	S	M	L	M	L	M	L	Serious
Fu 2023	M	L	L	M	L	L	L	Moderate
Kongmalai 2024	S	S	M	M	M	M	L	Serious
Svanström 2024	M	L	L	M	L	L	L	Moderate

D1, confounding; D2, selection of participants; D3, classification of interventions; D4, deviations from intended interventions; D5, missing data; D6, measurement of outcomes; D7, selection of the reported result; L, low; M, moderate; S, serious. JBI appraisal of the case series (Soga 2018): 8/10 criteria met (Q4 consecutive and Q5 complete inclusion unclear) — acceptable quality.

D. Primary Outcome: Cardiovascular Death or Hospitalisation for Heart Failure

Ten randomised estimates (16,111 participants) contributed to the primary outcome. SGLT2 inhibitors reduced the risk of CV death or HHF by 25% (HR 0.75, 95% CI 0.70–0.80; Z = 8.06, p < 0.001), without heterogeneity ($\tau^2 = 0.000$; $\chi^2 = 7.13$, df = 9, p = 0.62; $I^2 = 0\%$); the 95% prediction interval (0.69–0.81) lay entirely below unity (Figure 6). Fixed-effect and HKSJ-adjusted estimates were identical (0.70–0.80). Control-arm event rates ranged from 19.8% to 28.5%, and the L'Abbé plot showed a uniform relative reduction across this range of baseline risk (Figure 7).[8,13,22–24,26,27,30,31]

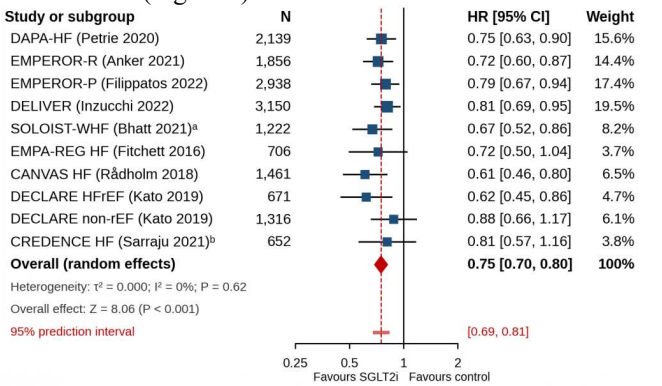


Figure 6: Forest plot of the composite of cardiovascular death or hospitalisation for heart failure in randomised participants with HF and T2DM (random-effects model). Squares are proportional to study weight; the red diamond and dashed line show the pooled estimate, and the red bar the 95% prediction interval. N, participants with HF and T2DM. [a] Total (first and recurrent) events (SOLOIST-WHF). [b] HF-subgroup estimates from a secondary tabulation (CREDENCE).

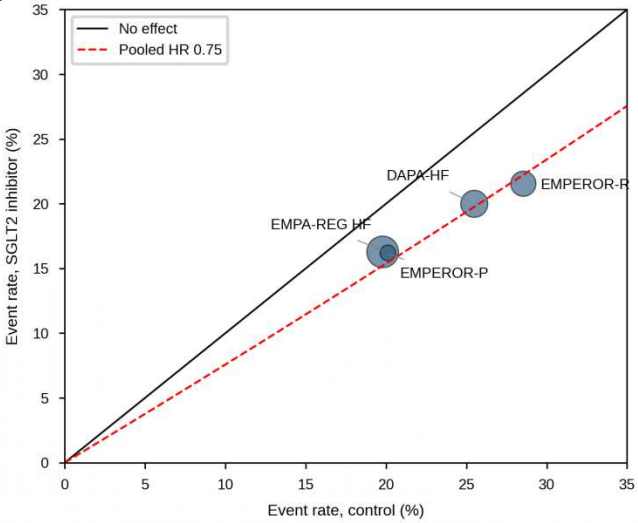


Figure 7: L'Abbé plot of the composite outcome in trials reporting event counts; bubble size proportional to sample size; dashed red curve, pooled HR 0.75.

E. Hospitalisation for Heart Failure

Nine randomised estimates (13,603 participants) reported first HHF. SGLT2 inhibitors reduced HHF by 32% (HR 0.68, 95% CI 0.62–0.75; p < 0.001; $I^2 = 0\%$; $\chi^2 = 3.58$, p = 0.89; 95%

prediction interval 0.60–0.76), with every point estimate favouring treatment (Figure 8). The effect was unchanged after exclusion of SOLOIST-WHF and CREDENCE (HR 0.68, 0.61–0.76).[8,13,22,23,26,27,30,31,33]

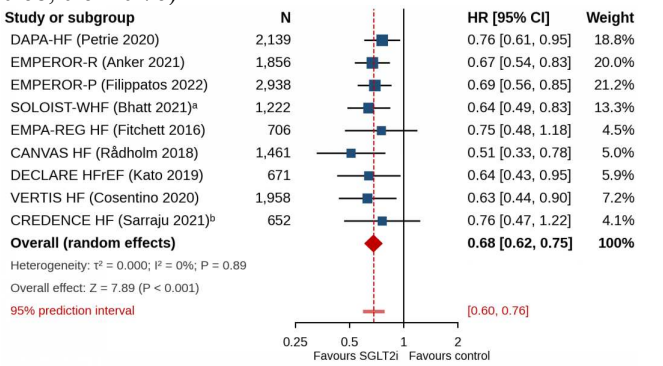


Figure 8: Forest plot of first hospitalisation for heart failure in randomised participants with HF and T2DM (random-effects model). [a] Total (first and recurrent) events (SOLOIST-WHF). [b] HF-subgroup estimates from a secondary tabulation (CREDENCE).

F. Cardiovascular Death

Seven randomised estimates (10,993 participants) reported CV death. SGLT2 inhibitors reduced CV death by 17% (HR 0.83, 95% CI 0.73–0.94; p = 0.002) with low heterogeneity (τ^2 = 0.002; I^2 = 7%; p = 0.38); the HKSJ-adjusted interval (0.71–0.96) remained significant, whereas the prediction interval (0.68–1.01) marginally crossed unity (Figure 9). The largest effect was observed in DECLARE-TIMI 58 patients with HFrEF (HR 0.55) and the smallest in EMPEROR-Preserved (HR 0.99).[8,13,22,23,26,27,30]

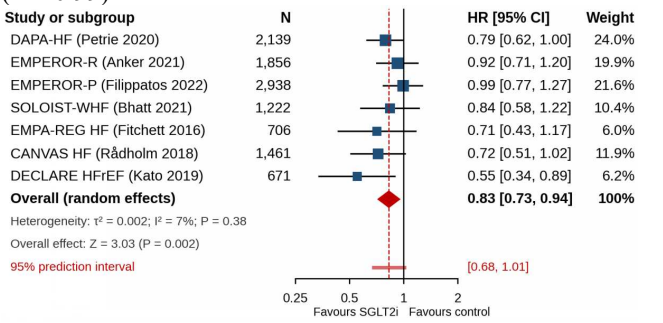


Figure 9: Forest plot of cardiovascular death in randomised participants with HF and T2DM (random-effects model).

G. All-Cause Mortality

Seven randomised estimates (9,789 participants) reported all-cause death. SGLT2 inhibitors reduced all-cause mortality by 18% (HR 0.82, 95% CI 0.70–0.96; p = 0.01; HKSJ 0.69–0.98) with moderate heterogeneity (τ^2 = 0.019; χ^2 = 11.02, p = 0.09; I^2 = 46%; prediction interval 0.55–1.23) (Figure 10). Heterogeneity was attributable to the neutral EMPEROR-Preserved estimate (HR 1.05); its exclusion yielded HR 0.76 (0.67–0.87) with I^2 = 0%. Pooled efficacy estimates are summarised in Figure 11 and Table 11.[8,13,23,26,27,30,31]

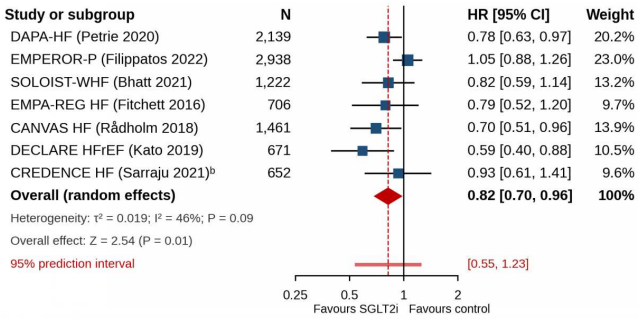


Figure 10: Forest plot of all-cause mortality in randomised participants with HF and T2DM (random-effects model). [b] HF-subgroup estimates from a secondary tabulation (CREDENCE).

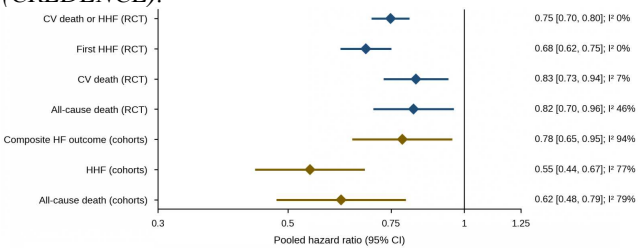


Figure 11: Summary of pooled efficacy estimates from randomised (blue) and observational (brown) evidence, with number of estimates (k) and I^2.

Table 11. Summary of Pooled Estimates for All Meta-Analysed Efficacy Outcomes

Outcome	k (n)	Pooled estimate (95% CI)	I^2 (%)	95% PI
CV death or HHF (RCT)	10 (16,111)	HR 0.75 (0.70–0.80)	0	0.69–0.81
First HHF (RCT)	9 (13,603)	HR 0.68 (0.62–0.75)	0	0.60–0.76
CV death (RCT)	7 (10,993)	HR 0.83 (0.73–0.94)	7	0.68–1.01
All-cause death (RCT)	7 (9,789)	HR 0.82 (0.70–0.96)	46	0.55–1.23
Composite HF outcome (cohorts)	3 (95,700)	HR 0.78 (0.65–0.95)	94	0.08–7.91
HHF (cohorts)	3 (115,050)	HR 0.55 (0.44–0.67)	77	0.05–6.11
All-cause death (cohorts)	4 (>115,050)	HR 0.62 (0.48–0.79)	79	0.21–1.81
All-cause death (cohorts; excl. in-hospital)	3 (>103,292)	HR 0.70 (0.64–0.77)	0	0.40–1.26
HHF (RCT + cohorts)	12 (128,653)	HR 0.63 (0.57–0.69)	34	0.51–0.78
KCCQ change (RCT), points	3 (5,108)	MD 3.12 (1.94–4.30)	0	—
NT-proBNP (RCT), ratio of means	2 (338)	0.85 (0.67–1.08)	56	—

All pooled estimates except NT-proBNP were statistically significant ($p \leq 0.01$). HKSJ-adjusted 95% CIs: CV death or HHF 0.70–0.80; first HHF 0.63–0.73; CV death 0.71–0.96; all-cause death 0.69–0.98. HKSJ, Hartung–Knapp–Sidik–Jonkman; k, number of estimates; MD, mean difference; PI, prediction interval (not calculable for $k < 3$).

H. Subgroup Analyses

The relative reduction in CV death or HHF was consistent across HF phenotypes — HFrEF (HR 0.72, 0.64–0.81), HFmrEF/HFpEF (HR 0.80, 0.71–0.90) and mixed or unspecified ejection fraction (HR 0.72, 0.63–0.82; $\chi^2 = 2.06$, df = 2, p = 0.36) (Figure 12). Estimates from dedicated HF trials (HR 0.76, 0.70–0.82) and HF subgroups of CVOT/renal trials (HR 0.72, 0.62–0.83) were similar (p = 0.52) (Figure 13), as were estimates for dapagliflozin (HR 0.78), empagliflozin (HR 0.75), canagliflozin (HR 0.69) and sotagliflozin (HR 0.67) (p = 0.65), supporting a class effect (Figure 14).[13,22–24,26,27,30,31]

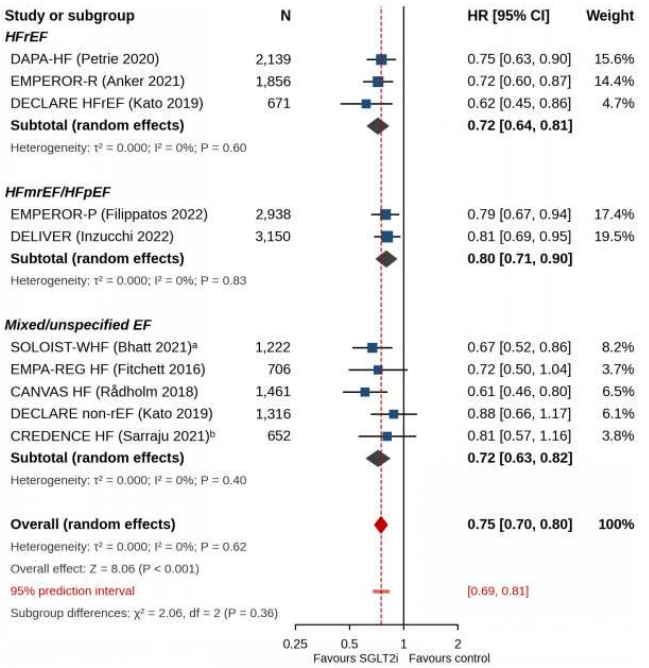


Figure 12: Subgroup forest plot of the composite outcome by heart-failure phenotype. [a] Total (first and recurrent) events (SOLOIST-WHF). [b] HF-subgroup estimates from a secondary tabulation (CREDENCE).

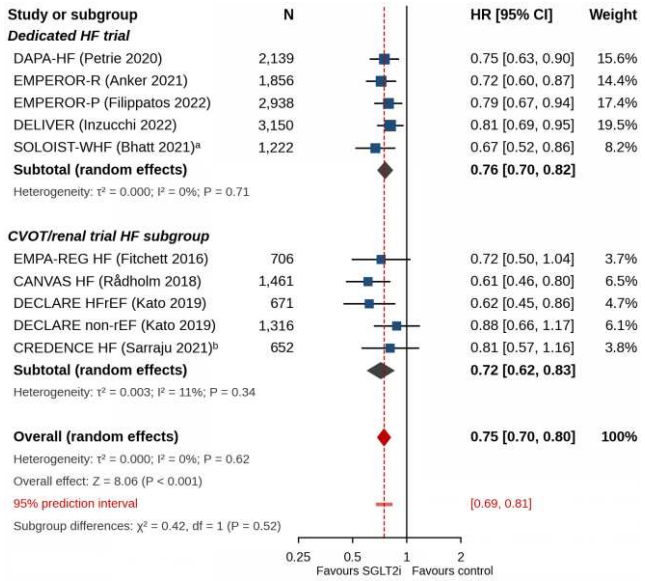


Figure 13: Subgroup forest plot of the composite outcome by trial setting (dedicated HF trials versus HF subgroups of cardiovascular or renal outcome trials). [a] Total (first and recurrent) events (SOLOIST-WHF). [b] HF-subgroup estimates from a secondary tabulation (CREDENCE).

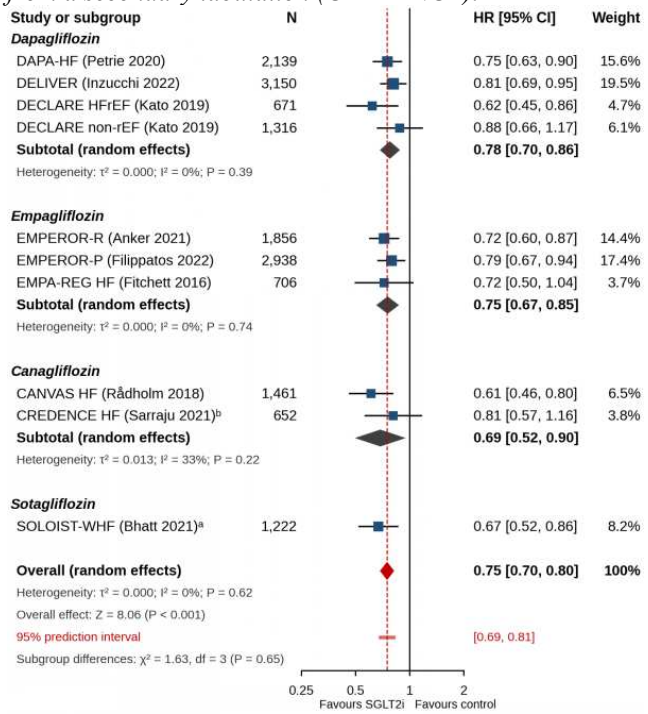


Figure 14: Subgroup forest plot of the composite outcome by individual SGLT2 inhibitor. [a] Total (first and recurrent) events (SOLOIST-WHF). [b] HF-subgroup estimates from a secondary tabulation (CREDENCE).

I. Evidence From Observational Cohort Studies

In real-world cohorts, SGLT2 inhibitor use was associated with lower risks of the composite HF outcome (HR 0.78, 0.65–0.95; $I^2 = 94\%$), HHF or readmission (HR 0.55, 0.44–0.67; $I^2 = 77\%$) and all-cause mortality (HR 0.62, 0.48–0.79; $I^2 = 79\%$) (Figure 15). After exclusion of the in-hospital mortality estimate, the mortality association was homogeneous (HR 0.70, 0.64–0.77; $I^2 = 0\%$). When

randomised and observational HHF estimates were combined (k = 12), the pooled HR was 0.63 (0.57–0.69; I^2 = 34%); observational estimates tended to be larger than randomised estimates (HR 0.55 vs 0.68; p for subgroup difference = 0.06), consistent with residual confounding (Figure 16).[44–49]

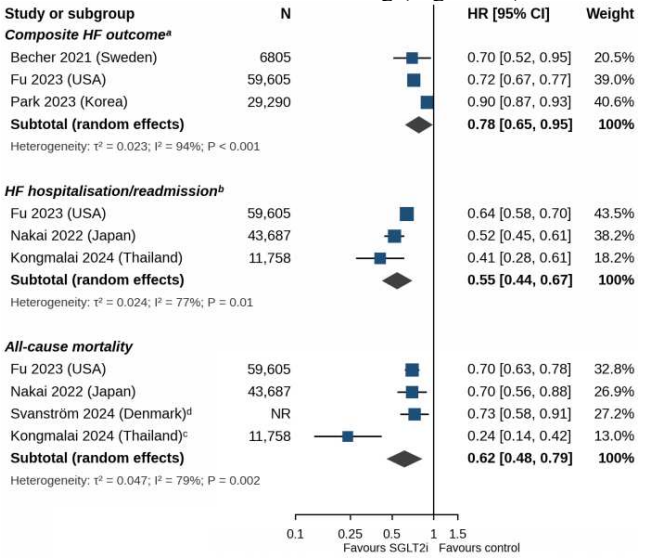


Figure 15: Forest plot of adjusted hazard ratios from observational cohort studies of patients with HF and T2DM, stratified by outcome (random-effects model within outcome). [a] Becher: CV death/HHF; Fu: all-cause death/HHF/urgent visit; Park: HF readmission/CV death. [b] Nakai: HF readmission. [c] In-hospital mortality (excluded in sensitivity analysis). [d] T2DM subgroup of an HFrEF cohort. NR, not reported.

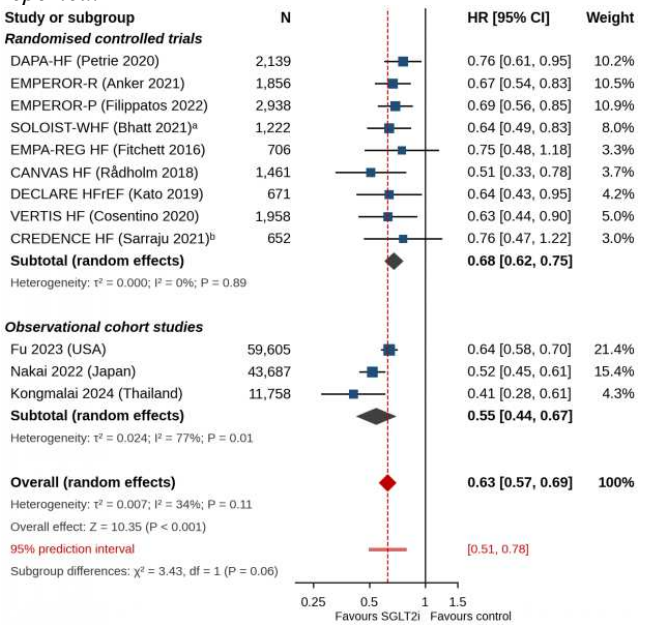


Figure 16: Forest plot of hospitalisation for heart failure stratified by study design (randomised controlled trials versus observational cohorts). [a] Total (first and recurrent) events (SOLOIST-WHF). [b] HF-subgroup estimates from a secondary tabulation (CREDENCE).

J. Health Status, Natriuretic Peptides and Cardiac Structure

Three randomised estimates (5,108 participants) reported placebo-adjusted changes in KCCQ scores; SGLT2 inhibitors improved health status by 3.12 points (95% CI 1.94–4.30; p < 0.001; I^2 = 0%) (Figure 17). SGLT2 inhibitors reduced NT-proBNP by 28% relative to placebo in SUGAR-DM-HF and non-significantly relative to glimepiride in CANDLE; the pooled ratio of geometric means was 0.85 (0.67–1.08; I^2 = 56%) (Figure 18).[22,27,29,32,51]

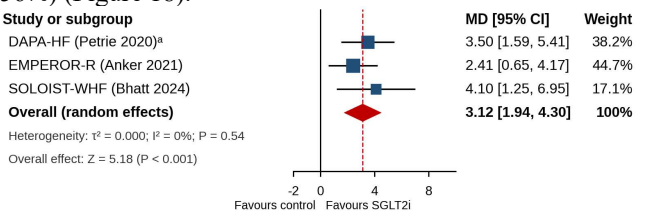


Figure 17: Forest plot of placebo-adjusted change in Kansas City Cardiomyopathy Questionnaire scores (mean difference, points). Instruments: KCCQ-TSS at 8 months (DAPA-HF), KCCQ-CSS at 52 weeks (EMPEROR-Reduced) and KCCQ-12 at 4 months (SOLOIST-WHF). [a] Derived from group-specific mean changes and 95% CIs.

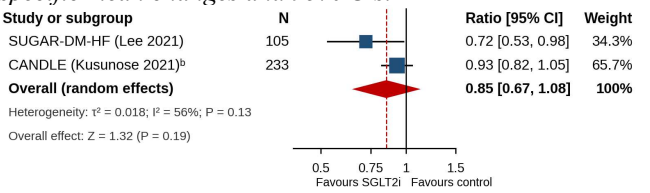


Figure 18: Forest plot of the effect of SGLT2 inhibitors on NT-proBNP (ratio of geometric means; exploratory analysis). [b] Glimepiride comparator (24 weeks); SUGAR-DM-HF placebo-controlled (36 weeks).

Mechanistic findings are summarised in Table 12. Empagliflozin reduced left ventricular end-systolic and end-diastolic volume indices by 6.0 and 8.2 mL/m² in HFrEF with T2DM or prediabetes, improved exercise capacity, diastolic function and left atrial and chronotropic reserves in HFpEF with T2DM, and dapagliflozin improved E/e′, left atrial volume and left ventricular mass in the prospective case series, whereas REFORM did not demonstrate an effect on left ventricular volumes.[28,29,32,43,50,52]

Table 12. Functional, Structural and Biomarker Findings From Mechanistic RCTs and the Case Series

Study	Design; population	Key findings (SGLT2 inhibitor vs control or baseline)
Lee et al. 2021 (SUGAR-DM-HF)[29]	RCT; HFrEF + T2DM/ prediabetes; 36 wk	LVESVi −6.0 mL/m² (−10.8 to −1.2); LVEDVi −8.2 mL/m² (−13.7 to −2.6); NT-proBNP −28% (−2% to −47%); no difference in GLS, KCCQ-TSS or 6MWD
Singh et al. 2020 (REFORM)[28]	RCT; T2DM + HF with LV systolic dysfunction; 1 y	No effect on LVESV or other CMR indices; reduced diastolic BP and loop-diuretic requirement; increased haemoglobin, haematocrit and ketones

Study	Design; population	Key findings (SGLT2 inhibitor vs control or baseline)
Kusunose et al. 2021 (CANDLE)[32]	Open-label RCT vs glimepiride; 24 wk	NT-proBNP ratio 0.93 (0.82–1.05); trend to greater reduction when septal e′ <4.7 cm/s (0.83, 0.66–1.04)
Ovchinnikov et al. 2025[43]	Open-label RCT; T2DM + HFpEF; 6 mo	Increased 6MWD; reduced LAVI and E/e′ at rest and exercise; improved diastolic, LA and chronotropic reserves; lower NT-proBNP and sST2 (all p < 0.05)
Soga et al. 2018; Tanaka et al. 2020[50,52]	Prospective single-arm; T2DM + stable HF; 6 mo	E/e′ 9.3→8.5 (p = 0.020); LAVI 31→26 mL/m²; LVMI 75.0→67.0 g/m²; GLS 15.5%→16.9% (p < 0.01), greatest in HFpEF

LA, left atrial; LVEDVi/LVESVi, left ventricular end-diastolic/end-systolic volume index.

K. Safety

Safety data from the diabetic subgroups of DAPA-HF, EMPEROR-Reduced and EMPEROR-Preserved (up to 6,925 participants) are shown in Figures 19 and 20 and Table 13. SGLT2 inhibitors reduced serious adverse events by 11% (RR 0.89, 0.85–0.94) and did not increase discontinuation due to adverse events (RR 0.98). Genital infections were tripled (RR 3.02, 1.77–5.13), whereas volume depletion (RR 1.14, 0.99–1.33) and hypotension (RR 1.18, 0.98–1.41) showed non-significant trends. Kidney adverse events, urinary tract infections, amputation, fracture and severe hypoglycaemia were not increased. DKA occurred in 3 of 2,000 patients receiving an SGLT2 inhibitor versus none of 1,989 controls (Peto OR 7.33, 0.76–70.58), and severe hypoglycaemia was more frequent with sotagliflozin in SOLOIST-WHF (1.5% vs 0.3%).[13,22,23,27]

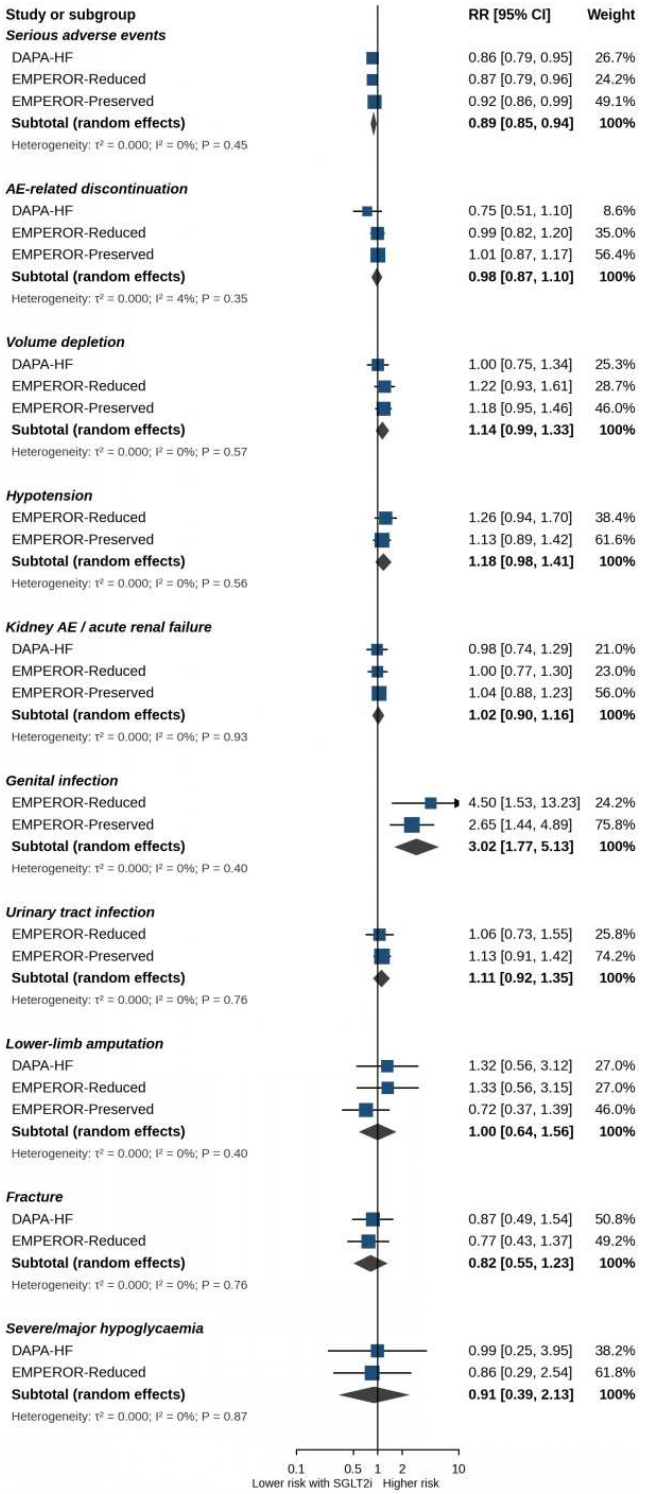


Figure 19: Forest plot of safety outcomes in diabetic HF subgroups (risk ratio, random-effects model within outcome).

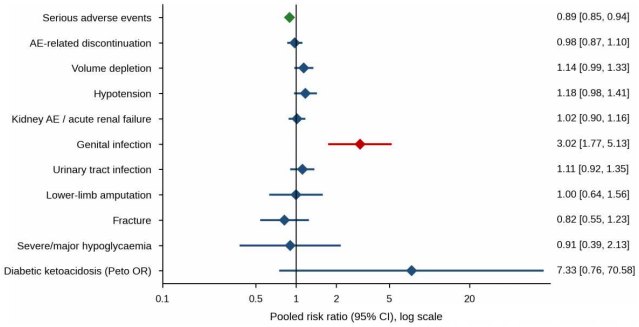


Figure 20: Summary of pooled safety estimates; green, significantly reduced risk; red, significantly increased risk with SGLT2 inhibitors.

Table 13. Pooled Safety Outcomes in Patients With HF and T2DM

Safety outcome	k	SGLT2i n/N	Control n/N	RR (95% CI); p	I² (%)
Serious adverse events	3	1576/3465	1768/3460	0.89 (0.85–0.94); <0.001	0
AE-related discontinuation	3	508/3465	521/3460	0.98 (0.87–1.10); 0.71	4
Volume depletion	3	348/3465	304/3460	1.14 (0.99–1.33); 0.07	0
Hypotension	2	228/2392	194/2397	1.18 (0.98–1.41); 0.08	0
Kidney AE / acute renal failure	3	419/3465	412/3460	1.02 (0.90–1.16); 0.79	0
Genital infection	2	55/2392	18/2397	3.02 (1.77–5.13); <0.001	0
Urinary tract infection	2	200/2392	180/2397	1.11 (0.92–1.35); 0.27	0
Lower-limb amputation	3	39/3465	39/3460	1.00 (0.64–1.56); 1.00	0
Fracture	2	42/2000	51/1989	0.82 (0.55–1.23); 0.33	0
Severe/major hypoglycaemia	2	10/2000	11/1989	0.91 (0.39–2.13); 0.82	0
Diabetic ketoacidosis	2[a]	3/2000	0/1989	Peto OR 7.33 (0.76–70.58); 0.09	—

[a] One study estimable (zero events in both arms of EMPEROR-Reduced). Data from diabetic subgroups of DAPA-HF, EMPEROR-Reduced and EMPEROR-Preserved (safety populations). AE, adverse event; OR, odds ratio; RR, risk ratio.

L. Small-Study Effects and Sensitivity Analyses

The contour-enhanced funnel plot of the primary outcome was symmetrical, and Egger's test showed no evidence of small-study effects (intercept −1.08, SE 0.96; p = 0.30) (Figure 21). All estimates lay within the ±2 band of the Galbraith plot (Figure 22). In leave-one-out analyses the pooled HR ranged from 0.73 to 0.76 with I² = 0% throughout (Figure 23), and cumulative meta-analysis showed that the benefit became statistically significant once the CANVAS HF subgroup was added in 2018 and has remained stable since (Figure 24). Other sensitivity analyses did not materially change the results (Table 14).[13,26,30,31]

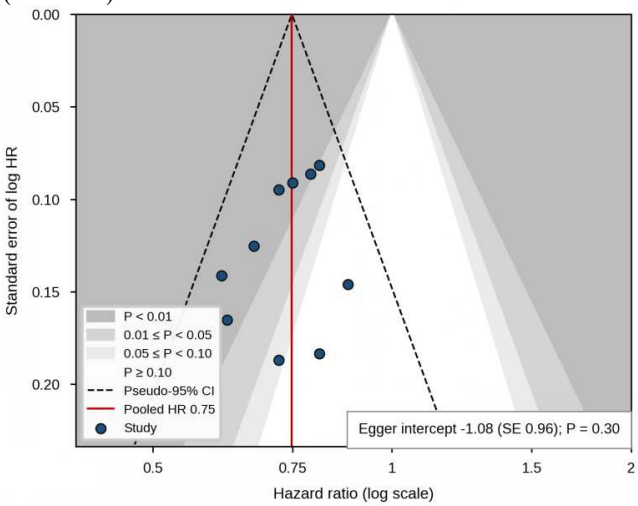


Figure 21: Contour-enhanced funnel plot of the composite outcome with Egger's regression test.

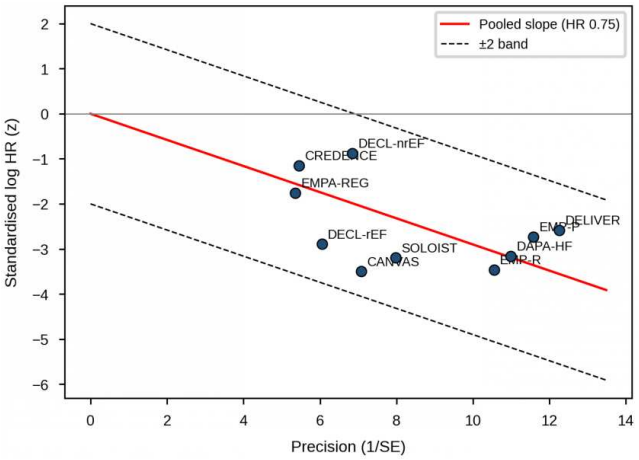


Figure 22: Galbraith (radial) plot of the composite outcome; all studies lie within the ±2 band.

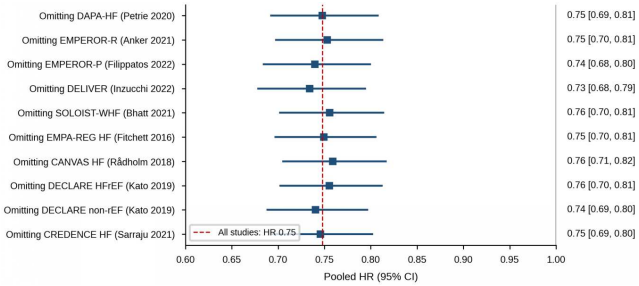


Figure 23: Leave-one-out sensitivity analysis of the composite outcome.

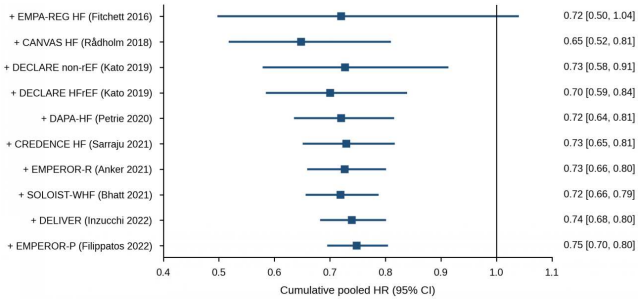


Figure 24: Cumulative random-effects meta-analysis of the composite outcome ordered by year of publication.

Table 14. Sensitivity Analyses

Analysis	k	Pooled HR (95% CI)	I^2 (%)
Primary: CV death or HHF (random effects)	10	0.75 (0.70–0.80)	0
Fixed-effect model	10	0.75 (0.70–0.80)	0
HKSJ adjustment	10	0.75 (0.70–0.80)	—
Excluding CREDENCE (secondary data)	9	0.75 (0.69–0.80)	0
Excluding SOLOIST-WHF (total events)	9	0.76 (0.70–0.81)	0
Low risk-of-bias trials only	4	0.77 (0.71–0.84)	0
Dedicated HF trials only	5	0.76 (0.70–0.82)	0
One estimate per trial	9	0.74 (0.69–0.80)	0
Leave-one-out (range)	9	0.73–0.76	0
First HHF excluding SOLOIST-WHF and CREDENCE	7	0.68 (0.61–0.76)	0
All-cause death excluding CREDENCE	6	0.80 (0.68–0.96)	54
All-cause death excluding EMPEROR-Preserved	6	0.76 (0.67–0.87)	0
Cohort all-cause death excluding Kongmalai 2024	3	0.70 (0.64–0.77)	0

HKSJ, Hartung–Knapp–Sidik–Jonkman; k, number of estimates.

M. Certainty of Evidence

Certainty of evidence was high for CV death or HHF, first HHF and serious adverse events; moderate for CV death, all-cause death, KCCQ, genital infection and volume depletion; and low for observational outcomes and for DKA (Table 15). Applying the pooled effects to median control-group risks, treatment of 1000 patients with HF and T2DM would prevent approximately 52 CV deaths or HF hospitalisations (number needed to treat ≈19), 44 first HF hospitalisations and 26 deaths over trial follow-up, at the cost of approximately 15 additional genital infections.[22,23,27,39]

Table 15. GRADE Summary of Findings: SGLT2 Inhibitors Versus Placebo or Standard Care in Adults With HF and T2DM[39]

Outcome (k; n)	Relative effect (95% CI)	Per 1000 (control → SGLT2i); absolute effect	Certainty (reason)
CV death or HHF (10; 16,111)	HR 0.75 (0.70–0.80)	228 → 176; 52 fewer (41–62 fewer)	⊕⊕⊕⊕ High
First HHF (9; 13,603)	HR 0.68 (0.62–0.75)	146 → 102; 44 fewer (34–53 fewer)	⊕⊕⊕⊕ High
CV death (7; 10,993)	HR 0.83 (0.73–0.94)	116 → 97; 19 fewer (7–30 fewer)	⊕⊕⊕◯ Moderate (imprecision)
All-cause death (7; 9,789)	HR 0.82 (0.70–0.96)	154 → 128; 26 fewer (6–44 fewer)	⊕⊕⊕◯ Moderate (inconsistency)
KCCQ score (3; 5,108)	—	MD 3.12 points higher (1.94–4.30)	⊕⊕⊕◯ Moderate (indirectness)
HHF, observational (3; 115,050)	HR 0.55 (0.44–0.67)	—	⊕⊕◯◯ Low (observational)

Outcome (k; n)	Relative effect (95% CI)	Per 1000 (control → SGLT2i); absolute effect	Certainty (reason)
Serious adverse events (3; 6,925)	RR 0.89 (0.85–0.94)	511 → 455; 56 fewer (31–77 fewer)	⊕⊕⊕⊕ High
Genital infection (2; 4,789)	RR 3.02 (1.77–5.13)	8 → 23; 15 more (6–31 more)	⊕⊕⊕◯ Moderate (imprecision)
Volume depletion (3; 6,925)	RR 1.14 (0.99–1.33)	88 → 100; 12 more (1 fewer–29 more)	⊕⊕⊕◯ Moderate (imprecision)
Diabetic ketoacidosis (2; 3,989)	Peto OR 7.33 (0.76–70.58)	0 → ≈1.5; ≈1–2 more	⊕⊕◯◯ Low (very serious imprecision)

Control risks are median event proportions in the control arms of the included diabetic subgroups over trial follow-up (median 1.5–4.2 years). GRADE: ⊕⊕⊕⊕ high; ⊕⊕⊕◯ moderate; ⊕⊕◯◯ low.

DISCUSSION

This systematic review and meta-analysis integrated 21 studies published within the last 15 years, including 18,533 randomised participants with coexisting HF and T2DM, real-world cohorts with more than 150,000 patients and a prospective case series. SGLT2 inhibitors reduced CV death or HHF by 25%, HHF by 32%, CV death by 17% and all-cause death by 18%, with high-certainty evidence for the primary outcome and a prediction interval entirely below unity. The benefit was consistent across HF phenotypes, trial settings and five different agents, observational evidence corroborated the randomised findings, and the safety profile was favourable.[13,22–24,27,47]

These findings are consistent with, and extend, previous meta-analyses (Table 2). The near-identical relative effect in this high-risk population (HR 0.75) compared with overall HF populations (HR 0.74–0.77) confirms that diabetes neither attenuates nor substantially amplifies the relative benefit of SGLT2 inhibition, while the present review adds diabetes-restricted estimates from five CVOT/renal trials, real-world cohorts and diabetes-specific safety data.[4,14,15,19,38]

Because relative effects are similar, the absolute benefit is driven by baseline risk, which is consistently higher in patients with diabetes; the median control-group risk of CV death or HHF was 22.8%, translating into a number needed to treat of approximately 19 over trial follow-up. Benefit was independent of baseline HbA1c, background glucose-lowering therapy including metformin and insulin, diabetes duration and concomitant glucagon-like peptide-1 receptor agonist therapy, and empagliflozin reduced the need for new insulin initiation. SGLT2 inhibitors should therefore be prioritised in patients with T2DM and HF regardless of glycaemic status.[22,23,27,53–57]

The magnitude of benefit was numerically larger in HFrEF (HR 0.72) than in HFmrEF/HFpEF (HR 0.80), without statistical interaction, in line with patient-level pooling of DAPA-HF and DELIVER, which showed no modification of effect by ejection fraction, and with post hoc VERTIS CV analyses suggesting greater reductions in total HHF at lower pre-trial ejection fraction. The mortality effect was weaker in HFpEF, as illustrated by the neutral EMPEROR-Preserved estimate, whereas the largest reduction was observed in DECLARE-TIMI 58 patients with HFrEF.[15,23,26,58,59]

SOLOIST-WHF, which exclusively enrolled patients with T2DM, demonstrated a 33% reduction in total CV deaths and HF events when sotagliflozin was initiated before or shortly after discharge, with early benefit within 30 and 90 days. These results are complemented by the EMPULSE and EMPA-RESPONSE-AHF trials in acute HF and by nationwide cohorts from Korea and Japan showing lower readmission and mortality when SGLT2 inhibitors were started during or after an HF hospitalisation, supporting in-hospital initiation in patients with T2DM.[13,45,46,60–62]

Mechanistic studies in diabetic HF provide biological plausibility. Empagliflozin induced reverse remodelling in HFrEF with T2DM or prediabetes, dapagliflozin reduced left ventricular mass and epicardial adipose tissue in T2DM with stage B/C HF, and empagliflozin improved diastolic and chronotropic reserves in HFpEF with T2DM, although REFORM was neutral. Comparable remodelling occurs in non-diabetic HFrEF and is confirmed by meta-analysis, together with early decongestion not explained by diuresis alone, indicating that the benefits reflect direct haemodynamic, metabolic and structural effects rather than glucose lowering.[28,29,43,50,52,63–69]

The absence of heterogeneity among dapagliflozin, empagliflozin, canagliflozin, sotagliflozin and ertugliflozin supports a class effect, reinforced by the Medicare cohort showing similar associations for all agents studied and for both HFrEF and HFpEF. Sotagliflozin additionally inhibits intestinal SGLT1, which may contribute to its effects in SCORED but at the cost of more diarrhoea and hypoglycaemia. In the absence of head-to-head trials, drug selection should be guided by licensing, kidney function, cost and availability.[30,33,47,70]

The 3.1-point improvement in KCCQ observed in diabetic patients is similar to that reported in the overall EMPEROR-Reduced, EMPULSE and CHIEF-HF populations and in DEFINE-HF. Kidney adverse events were not increased despite the expected early eGFR dip, which does not predict adverse outcomes and should not prompt discontinuation, and long-term eGFR decline was attenuated more markedly in diabetic patients — an important dual cardiorenal benefit in a population with a high prevalence of diabetic kidney disease.[71–78]

Genital mycotic infections were the principal and predictable adverse effect (≈15 additional infections per 1000 patients), usually mild and manageable with hygiene measures and topical therapy. The CANVAS amputation signal was not reproduced, and severe hypoglycaemia was not increased with

dapagliflozin or empagliflozin. Ketoacidosis was very rare but clinically important: case series in T2DM with HF, perioperative series and reports in non-diabetic patients identify reduced oral intake, acute illness, surgery and excessive insulin dose reduction as precipitants, while a recent cohort suggests that prolonged perioperative discontinuation may increase cardiac complications; patient education on sick-day rules and individualised peri-procedural management are therefore essential.[5,17,79–83]

Observational studies corroborated the direction of benefit; the most rigorous new-user, active-comparator and trial-emulation designs produced effects close to randomised estimates, whereas comparisons of users with non-users yielded implausibly large associations, highlighting residual confounding and immortal-time bias. Despite strong evidence, real-world uptake remains suboptimal, with discharge prescription rates of approximately 20–37% in contemporary registries, even though SGLT2 inhibitors are cost-effective.[44,47,49,84–88]

LIMITATIONS AND FUTURE WORK

Most randomised data derive from subgroup analyses that, although stratified in four HF trials, were not individually powered; HF diagnosis in CVOTs relied on investigator report, and ejection fraction was frequently unknown. Outcome definitions varied, the CREDENCE estimates were obtained from a secondary source, diabetes-specific safety data were available from only three trials, and estimates for rare events such as DKA were imprecise. Observational studies were heterogeneous and susceptible to residual confounding, and the search relied on an AI-assisted engine indexing major bibliographic databases, whose record counts should be reconciled with formal MEDLINE, Embase and CENTRAL searches.[21,39,41]

Future work should include head-to-head comparisons of individual agents, adequately powered mortality trials in HFpEF with T2DM, studies in advanced chronic kidney disease and dialysis, evaluation of combination therapy with glucagon-like peptide-1 receptor agonists and finerenone, and pragmatic implementation studies in low- and middle-income countries, including Indonesia.[3,16,57]

CONCLUSION AND RECOMMENDATIONS

Conclusion

In adults with coexisting heart failure and type 2 diabetes mellitus, SGLT2 inhibitors reduce the risk of cardiovascular death or hospitalisation for heart failure by approximately 25% (high-certainty evidence), reduce first heart-failure hospitalisation, cardiovascular death and all-cause mortality, and improve health status. These benefits are consistent across ejection-fraction phenotypes, trial settings and individual agents, are supported by real-world evidence, and are achieved with fewer serious adverse events and a predictable excess of genital mycotic infections.[3,15]

Recommendations

1. An SGLT2 inhibitor should be initiated in every eligible patient with heart failure and type 2 diabetes, irrespective of ejection fraction, HbA1c, background glucose-lowering therapy or care setting, including during or shortly after hospitalisation for heart failure.[3,16]
2. Initiation should be accompanied by counselling on genital hygiene, sick-day rules and peri-procedural management to minimise genital infection and ketoacidosis, without abrupt withdrawal of insulin.[17,83]
3. Health systems should implement audit- and checklist-based strategies to improve uptake of SGLT2 inhibitors at hospital discharge and in outpatient diabetes and heart-failure clinics.[86,87]
4. Further research should prioritise head-to-head trials, mortality outcomes in HFpEF with T2DM, advanced kidney disease and implementation in Indonesian and other low- and middle-income settings.[19,57]

DECLARATIONS

Ethics approval: Not applicable; this systematic review used published, de-identified aggregate data.

Author contributions: [Initials]: conceptualisation, literature search, data extraction, statistical analysis and drafting; [Initials]: supervision, clinical interpretation and critical revision; [Initials]: methodology and critical revision. All authors approved the final manuscript.

Funding: None.

Conflict of interest: None declared.

Data availability: Extracted data, analytic code and figures are available from the corresponding author on reasonable request.

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