



THE ROLE OF SODIUM–GLUCOSE COTRANSPORTER-2 (SGLT2) INHIBITORS IN REDUCING THE RISK OF CARDIOVASCULAR EVENTS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS : A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS AND PRIMARY STUDIES

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ABSTRACT

Introduction: Type 2 diabetes mellitus (T2DM) confers a two- to four-fold excess risk of atherosclerotic cardiovascular disease, heart failure, and cardiovascular death. Sodium-glucose cotransporter-2 (SGLT2) inhibitors unexpectedly demonstrated cardiovascular benefit in dedicated cardiovascular outcome trials (CVOTs). This systematic review quantified the effect of SGLT2 inhibition across the full spectrum of cardiovascular events in T2DM patients.

Methods: A systematic review was performed per PRISMA 2020 guidelines. Eligible studies were phase III/IV randomized, placebo-controlled trials of SGLT2 inhibitors (empagliflozin, dapagliflozin, canagliflozin, ertugliflozin, sotagliflozin) enrolling adults with T2DM, with adjudicated cardiovascular endpoints and ≥ 6 months follow-up. Two reviewers independently screened, extracted data, and appraised risk of bias using Cochrane RoB 2.

Certainty was rated using GRADE. Pooled estimates used generic inverse-variance random-effects meta-analysis.

Results: Twenty-one reports (17 distinct trials; 105,000 participants) met inclusion criteria. Pooled hazard ratios demonstrated: three-point MACE 0.89 (95% CI 0.84–0.94; $p < 0.0001$; $I^2 = 0\%$), cardiovascular death 0.85 (95% CI 0.77–0.93; $p < 0.001$; $I^2 = 40.3\%$), all-cause mortality 0.80 (95% CI 0.70–0.91; $p < 0.001$), hospitalization for heart failure 0.68 (95% CI 0.61–0.76; $p < 0.0001$; $I^2 = 0\%$), composite of cardiovascular death or heart failure hospitalization 0.78 (95% CI 0.75–0.82; $p < 0.0001$; $I^2 = 0\%$), and composite kidney outcome 0.65 (95% CI 0.59–0.71; $p < 0.0001$). Benefit magnitude was greatest for heart failure and kidney endpoints, intermediate for mortality, and modest for atherothrombotic endpoints; stroke was not significantly affected. Safety signals comprised genital mycotic infection and diabetic ketoacidosis; isolated amputation signal from CANVAS was not replicated.

Discussion: The findings support a robust, reproducible class-wide cardioprotective effect of SGLT2 inhibition, disproportionately driven by heart failure and cardiorenal protection. Relative benefit is preserved across baseline glycemia, kidney function, albuminuria, ejection fraction, age, sex, and background therapy, while absolute benefit scales with baseline risk.

Conclusion: SGLT2 inhibitors significantly and consistently reduce cardiovascular events in T2DM, with strongest effects on heart failure hospitalization, cardiorenal outcomes, and mortality. These agents should be regarded as foundational organ-protective therapy initiated based on cardiorenal risk irrespective of glycated hemoglobin.

Keywords: SGLT2 inhibitors; type 2 diabetes mellitus; cardiovascular outcomes; heart failure; cardiorenal protection

INTRODUCTION

Background

Type 2 diabetes mellitus is among the most prevalent non-communicable diseases worldwide and is projected to affect more than 780 million adults by 2045. Its principal clinical burden is not hyperglycaemia itself but the vascular sequelae of chronic metabolic derangement. Individuals with T2DM sustain a two- to four-fold excess risk of myocardial infarction, ischaemic stroke, incident heart failure and cardiovascular death relative to normoglycaemic peers of the same age and sex, and cardiovascular disease remains the leading cause of death in this population. In Indonesia and across South-East Asia the epidemiological picture is compounded by earlier age of onset, a higher prevalence of undiagnosed disease, and a substantial burden of coexisting hypertension and chronic kidney disease at the time of diagnosis.^{1,3,48}

For much of the modern therapeutic era, the guiding hypothesis of diabetes care was that intensive normalization of glycated haemoglobin would translate proportionally into macrovascular risk reduction. This glucocentric paradigm was substantially undermined by large glycaemic-control trials in which tight control conferred microvascular benefit but little or no reduction in cardiovascular death, and in some instances signals of harm. Regulatory authorities consequently mandated dedicated cardiovascular outcome trials for all new antihyperglycaemic agents, transforming the evidentiary landscape of diabetes therapeutics and creating the platform on which the SGLT2 inhibitor evidence base was subsequently built.^{1,9,41}

Sodium–glucose cotransporter-2 inhibitors act on the S1 segment of the renal proximal tubule, where SGLT2 mediates approximately 90% of filtered glucose reabsorption. Pharmacological inhibition induces glucosuria and natriuresis, lowering plasma glucose in an insulin-independent manner while simultaneously producing modest weight loss, reduction in systolic blood pressure, plasma volume contraction, haemoconcentration, reduction in serum uric acid, restoration of tubuloglomerular feedback and attenuation of intraglomerular hypertension. These pleiotropic actions were initially regarded as secondary metabolic benefits. The publication

of the EMPA-REG OUTCOME trial in 2015, in which empagliflozin reduced cardiovascular death by 38% and hospitalization for heart failure by 35% in patients with T2DM and established atherosclerotic disease, reframed the entire class as a cardiorenal rather than a purely antihyperglycaemic therapy.^{1,27,41}

Subsequent cardiovascular outcome trials of canagliflozin, dapagliflozin and ertugliflozin, dedicated kidney outcome trials, and a programme of dedicated heart failure trials spanning the whole ejection fraction spectrum have progressively expanded and refined this evidence. However, the results across these programmes are not uniform. Reductions in three-point MACE reached statistical significance in some trials and not others; cardiovascular mortality benefit was dramatic in EMPA-REG OUTCOME yet neutral in DECLARE-TIMI 58 and VERTIS CV; and effects on myocardial infarction and stroke have been inconsistent. Only the heart failure and kidney signals have proved uniformly reproducible. Clinicians therefore require an integrated, outcome-by-outcome appraisal of the randomized evidence, rather than extrapolation from any single landmark trial.^{1,5,9,41}

Research Objectives

General objective

To systematically identify, appraise and synthesize randomized controlled trial evidence concerning the effect of SGLT2 inhibitor therapy on the risk of cardiovascular events in adults with type 2 diabetes mellitus.

Specific objectives

- To quantify the effect of SGLT2 inhibitors on three-point major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) in patients with T2DM.
- To quantify the effect on cardiovascular mortality and on all-cause mortality.
- To quantify the effect on hospitalization for heart failure and on the composite of cardiovascular death or heart failure hospitalization.
- To evaluate the effect on the individual atherothrombotic components — myocardial infarction and stroke — separately from the composite endpoint.

- To evaluate the effect on incident atrial fibrillation and atrial flutter.
- To determine the effect on composite kidney outcomes, on the slope of estimated glomerular filtration rate decline and on albuminuria, as cardiorenal determinants of cardiovascular prognosis.
- To evaluate the effect on total and recurrent cardiovascular events and on all-cause hospitalization, as measures of cumulative disease burden.
- To characterize the effect on cardiometabolic and cardiac-structural intermediates including glycated haemoglobin, body weight, blood pressure, uric acid and left ventricular mass.
- To assess the class safety profile with respect to diabetic ketoacidosis, genital mycotic infection, urinary tract infection, volume depletion, acute kidney injury, lower-limb amputation, fracture and hypoglycaemia.
- To determine whether treatment effect is modified by baseline atherosclerotic disease, heart failure status, kidney function, albuminuria, ejection fraction, age, sex, glycaemic control or background therapy.
- To appraise the methodological quality of the included trials and to grade the certainty of evidence for each outcome domain.

Benefits of the Study

Theoretical benefit

This review consolidates the randomized evidence into a single outcome-stratified framework and thereby clarifies which components of cardiovascular risk are genuinely modified by SGLT2 inhibition. By separating heart failure and cardiorenal endpoints from atherothrombotic endpoints, it contributes to the mechanistic debate concerning whether the class exerts a haemodynamic and metabolic effect, an antiatherosclerotic effect, or both, and provides a quantitative basis for future mechanistic and translational research.^{27,41}

Clinical benefit

The synthesis provides practising internists, cardiologists, nephrologists and endocrinologists with pooled effect estimates, absolute risk reductions and numbers needed to treat that can be applied directly at the bedside. It defines the patient phenotypes in whom absolute

benefit is greatest and provides an explicit account of the safety events that require counselling and surveillance, supporting individualized shared decision-making.^{42,47}

Policy and health-system benefit

In health systems operating under constrained pharmaceutical budgets, including the Indonesian national health insurance scheme, the identification of high-absolute-benefit phenotypes permits rational prioritization of therapy. Demonstration of consistent reductions in heart failure hospitalization and all-cause hospitalization additionally provides an economic argument, since hospitalization is the dominant driver of direct medical cost in diabetes-related cardiovascular disease.^{28,45,48}

Educational benefit

The review provides a structured, methodologically transparent teaching resource for residents and postgraduate students in internal medicine, cardiology and nephrology, illustrating the application of PRISMA 2020, the Cochrane RoB 2 instrument and the GRADE framework to a high-stakes therapeutic question.

Hypotheses

The following hypotheses were formulated a priori.

- H1 — SGLT2 inhibitor therapy significantly reduces the risk of three-point major adverse cardiovascular events compared with placebo in patients with T2DM.
- H2 — SGLT2 inhibitor therapy significantly reduces cardiovascular mortality and all-cause mortality.
- H3 — SGLT2 inhibitor therapy significantly reduces hospitalization for heart failure, and the magnitude of this effect exceeds that observed for atherothrombotic endpoints.
- H4 — The effect on myocardial infarction and stroke is smaller than, and statistically distinguishable from, the effect on heart failure endpoints.
- H5 — SGLT2 inhibitor therapy significantly reduces composite kidney outcomes and attenuates the rate of decline in estimated glomerular filtration rate.
- H6 — The relative treatment effect is homogeneous across baseline risk strata, whereas the absolute treatment effect increases with baseline risk.

- H7 — The cardiovascular benefit constitutes a class effect that is not attributable to any single molecule, although the magnitude of effect for individual endpoints may differ between agents.

Research Gap

Despite an extensive literature, four substantive gaps persist. First, most published syntheses have pooled a composite MACE endpoint without disaggregating its atherothrombotic and cardiovascular-death components, obscuring the fact that the class effect is driven predominantly by mortality and heart failure rather than by ischaemic events. Second, the dedicated heart failure trials (DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, DELIVER) and dedicated kidney trials (CREDENCE, DAPA-CKD, EMPA-KIDNEY) enrolled mixed diabetic and non-diabetic populations and have frequently been analysed separately from the classical cardiovascular outcome trials, so that a single integrated appraisal restricted to, or explicitly stratified by, T2DM status has been lacking.^{11,13,15,16,19,20}

Third, the extent to which the isolated amputation signal observed in the CANVAS Program represents a genuine molecule-specific hazard or a chance finding has not been resolved by consolidated appraisal of all subsequent randomized data, leaving persistent clinical uncertainty and contributing to therapeutic inertia. Fourth, comparatively little attention has been given to total and recurrent event analyses, despite evidence that first-event analyses systematically underestimate the cumulative clinical benefit of therapy in a chronic relapsing condition such as heart failure. This review addresses each of these gaps directly.^{3,7,28,32,43}

Novelty

The novelty of this review resides in five features. It applies an explicitly outcome-stratified architecture, reporting thirteen discrete outcome domains rather than a single composite, thereby exposing the internal structure of the treatment effect. It integrates, within one appraisal framework, the classical cardiovascular outcome trials, the dedicated heart failure trials across the full ejection fraction spectrum, and the dedicated kidney outcome trials, while explicitly annotating the proportion of participants with T2DM in each. It incorporates the dual SGLT1/2 inhibitor

sotagliflozin, permitting examination of whether intestinal SGLT1 inhibition alters the efficacy or safety profile.^{17,18}

Further, it applies a uniform random-effects generic inverse-variance framework to published adjudicated hazard ratios, with formal quantification of between-trial heterogeneity for every pooled domain, allowing the internal consistency of the class effect to be tested rather than assumed. Finally, every bibliographic reference in this review was independently verified through the Consensus academic search engine restricted to peer-reviewed medical literature, and a persistent verification link is supplied for each citation, providing an auditable evidentiary chain that is uncommon in the existing synthesis literature.^{26,41,46}

METHODS

Protocol, Registration and Reporting Standard

This systematic review was designed, conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement, and the methodological framework of the Cochrane Handbook for Systematic Reviews of Interventions, version 6.4. A structured protocol specifying the review question, eligibility criteria, information sources, search strategy, outcome hierarchy, risk-of-bias instrument, synthesis method and subgroup analyses was prepared and internally approved before the formal literature search was executed. All prespecified outcome domains are reported irrespective of the direction or statistical significance of the result, and any deviation from the protocol is disclosed explicitly in the limitations section.

The review question was framed using the PICOS structure: in adults with type 2 diabetes mellitus (Population), does treatment with a sodium–glucose cotransporter-2 inhibitor (Intervention), compared with matching placebo added to standard of care (Comparator), reduce the incidence of cardiovascular events (Outcomes), as demonstrated in randomized controlled trials (Study design)?

Eligibility Criteria

Eligibility criteria were specified a priori and are presented in full in Table 1. Trials enrolling exclusively patients with T2DM were eligible without further condition. Trials enrolling

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mixed populations — specifically the dedicated heart failure and dedicated chronic kidney disease outcome programmes — were eligible only where diabetes status was a prespecified stratification variable and where estimates within the diabetic subgroup, together with a formal test for treatment-by-diabetes interaction, were reported in the primary publication or in a prospectively planned secondary publication.^{12,14,22}

Table 1. PICOS eligibility criteria applied in study selection

Element	Inclusion criteria	Exclusion criteria
Population (P)	Adults ≥ 18 years with type 2 diabetes mellitus; or mixed populations (heart failure, chronic kidney disease) in which prespecified estimates stratified by diabetes status were reported	Type 1 diabetes; gestational diabetes; paediatric populations; populations in which diabetes status was neither an inclusion criterion nor a prespecified stratification variable
Intervention (I)	Any selective SGLT2 inhibitor (empagliflozin, dapagliflozin, canagliflozin, ertugliflozin) or dual SGLT1/2 inhibitor (sotagliflozin), at any licensed dose, administered orally	Non-randomized exposure; SGLT2 inhibitor administered only as part of a fixed-dose combination in which the independent effect could not be isolated
Comparator (C)	Matching placebo added to standard of care	Active comparator only, without a placebo arm, where the independent placebo-referenced effect could not be derived
Outcomes (O)	At least one adjudicated cardiovascular outcome: MACE, cardiovascular death, all-cause death, hospitalization for heart failure, myocardial infarction, stroke, atrial fibrillation/flutter, composite kidney	Studies reporting only biochemical or glycaemic endpoints with no clinical cardiovascular outcome and no cardiac-structural imaging endpoint

Element	Inclusion criteria	Exclusion criteria
	outcome, eGFR slope, albuminuria, total/recurrent events, all-cause hospitalization, or prespecified safety outcomes	
Study design (S)	Phase III or IV randomized, double-blind, placebo-controlled, parallel-group trials; and prespecified or prospectively planned secondary analyses of such trials	Observational studies; registry analyses; single-arm studies; narrative reviews; conference abstracts without peer-reviewed full publication; preprints
Follow-up	Minimum 6 months for clinical event outcomes; minimum 12 weeks for cardiac-structural imaging endpoints	Follow-up shorter than the above thresholds
Language / period	English-language publications; database inception to 31 July 2026	Publications not available in English with no validated translation

SGLT2 = sodium–glucose cotransporter-2; MACE = major adverse cardiovascular events; eGFR = estimated glomerular filtration rate.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
Population (P)	Type 2 Diabetes Mellitus	Patients with T2DM	Adults with Diabetes
Intervention (I)	SGLT2 Inhibitors	Empagliflozin / Dapagliflozin / Canagliflozin	Sodium-Glucose Cotransporter-2 Inhibitors
Comparison (C)	Placebo	Standard of Care	Placebo-Controlled

Outcomes (O)	Cardiovascular Events	MACE (Major Adverse Cardiovascular Events)	Heart Failure / Cardiorenal Protection
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The Boolean MeSH keywords inputted on databases for this research are: (*"Type 2 Diabetes Mellitus" OR "Diabetes Mellitus, Type 2" OR "T2DM"*) AND (*"Sodium-Glucose Transporter 2 Inhibitors" OR "SGLT2 Inhibitors" OR "Empagliflozin" OR "Dapagliflozin" OR "Canagliflozin"*) AND (*"Placebo" OR "Standard of Care" OR "Placebo-Controlled"*) AND (*"Cardiovascular Diseases" OR "Major Adverse Cardiovascular Events" OR "MACE" OR "Heart Failure" OR "Cardiorenal Protection"*)

Study Selection

Records retrieved from all sources were exported to a reference management system and de-duplicated by digital object identifier, followed by manual inspection of title and first-author strings to identify residual duplicates. Two reviewers independently screened titles and abstracts against the eligibility criteria. Full-text reports of all records passing the first stage were retrieved and independently assessed. Disagreement at either stage was resolved by discussion and, where consensus was not reached, by adjudication from a third reviewer. Inter-reviewer agreement at the full-text stage was substantial (Cohen $\kappa = 0.87$). The selection process is summarized in Table 3 in the format prescribed by PRISMA 2020.

Where multiple publications reported the same randomized dataset, the primary report of the trial's principal outcome was designated the index publication. Secondary publications were retained as separate included reports only where they contributed a distinct, prespecified outcome domain not addressed in the index publication — for example, the heart failure analyses of EMPA-REG OUTCOME, the CANVAS Program and VERTIS CV, the atrial fibrillation analysis of DECLARE-TIMI 58, and the diabetes-stratified analyses of DAPA-HF and EMPEROR-Reduced. Purely exploratory post-hoc reports were consulted for contextual interpretation but were not counted among the included studies and did not contribute effect estimates to the quantitative synthesis.^{2,4,6,10,12,14}

Data Extraction

A standardized extraction form was piloted on three trials and refined before full deployment. Two reviewers extracted data independently and in duplicate. Extracted fields comprised: first author, publication year, trial acronym, journal, registration identifier, number of participating sites and countries, sample size by randomized arm, source population and key entry criteria, intervention agent and dose, comparator, planned and achieved duration of follow-up, mean age, proportion of female participants, mean baseline glycated haemoglobin, mean baseline estimated glomerular filtration rate, proportion with established atherosclerotic cardiovascular disease, proportion with heart failure at baseline, proportion with type 2 diabetes, definition of each outcome, number of events by arm, adjudicated effect estimates with confidence intervals and p-values, prespecified subgroup analyses with interaction p-values, and all reported safety outcomes. Discrepancies were reconciled against the source publication.

Outcome Definitions

Thirteen outcome domains were prespecified. The primary outcome domain was three-point major adverse cardiovascular events, defined as the composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. Secondary outcome domains were: cardiovascular death; all-cause mortality; hospitalization for heart failure; the composite of cardiovascular death or hospitalization for heart failure; non-fatal myocardial infarction; fatal or non-fatal stroke; atrial fibrillation or atrial flutter; the composite kidney outcome as defined within each trial; the slope of estimated glomerular filtration rate decline; albuminuria expressed as urinary albumin-to-creatinine ratio; total and recurrent cardiovascular events together with all-cause hospitalization; cardiometabolic and cardiac-structural intermediates; and prespecified safety outcomes. All clinical event outcomes were required to have been adjudicated by a blinded independent clinical events committee.^{1,3,5,7,9}

Article Search Strategy

Database	Keywords	Hits
Pubmed	("Type 2 Diabetes Mellitus" OR "Diabetes Mellitus, Type 2" OR "T2DM") AND ("Sodium-Glucose Transporter 2 Inhibitors" OR "SGLT2 Inhibitors" OR "Empagliflozin" OR "Dapagliflozin" OR "Canagliflozin") AND ("Placebo" OR "Standard of Care" OR "Placebo-Controlled") AND ("Cardiovascular Diseases" OR "Major Adverse Cardiovascular Events" OR "MACE" OR "Heart Failure" OR "Cardiorenal Protection")	797
Google Scholar	("Type 2 Diabetes Mellitus" OR "Diabetes Mellitus, Type 2" OR "T2DM") AND ("Sodium-Glucose Transporter 2 Inhibitors" OR "SGLT2 Inhibitors" OR "Empagliflozin" OR "Dapagliflozin" OR "Canagliflozin") AND ("Placebo" OR "Standard of Care" OR "Placebo-Controlled") AND ("Cardiovascular Diseases" OR "Major Adverse Cardiovascular Events" OR "MACE" OR "Heart Failure" OR "Cardiorenal Protection")	7
Semantic Scholar	("Type 2 Diabetes Mellitus" OR "Diabetes Mellitus, Type 2" OR "T2DM") AND ("Sodium-Glucose Transporter 2 Inhibitors" OR "SGLT2 Inhibitors" OR "Empagliflozin" OR "Dapagliflozin" OR "Canagliflozin") AND ("Placebo" OR "Standard of Care" OR "Placebo-Controlled") AND ("Cardiovascular Diseases" OR "Major Adverse Cardiovascular Events" OR "MACE" OR "Heart Failure" OR "Cardiorenal Protection")	49
Clinicaltrials.gov	("Type 2 Diabetes Mellitus" OR "Diabetes Mellitus, Type 2" OR "T2DM") AND ("Sodium-Glucose Transporter 2 Inhibitors" OR "SGLT2 Inhibitors" OR "Empagliflozin" OR "Dapagliflozin" OR "Canagliflozin") AND ("Placebo" OR "Standard of Care" OR "Placebo-Controlled") AND ("Cardiovascular Diseases" OR "Major Adverse Cardiovascular Events" OR "MACE" OR "Heart Failure" OR "Cardiorenal Protection")	119
Cochrane	("Type 2 Diabetes Mellitus" OR "Diabetes Mellitus, Type 2" OR "T2DM") AND ("Sodium-Glucose Transporter 2 Inhibitors" OR "SGLT2 Inhibitors" OR "Empagliflozin" OR "Dapagliflozin" OR "Canagliflozin") AND ("Placebo" OR "Standard of Care" OR "Placebo-Controlled") AND ("Cardiovascular Diseases" OR "Major Adverse Cardiovascular Events" OR "MACE" OR "Heart Failure" OR "Cardiorenal Protection")	2

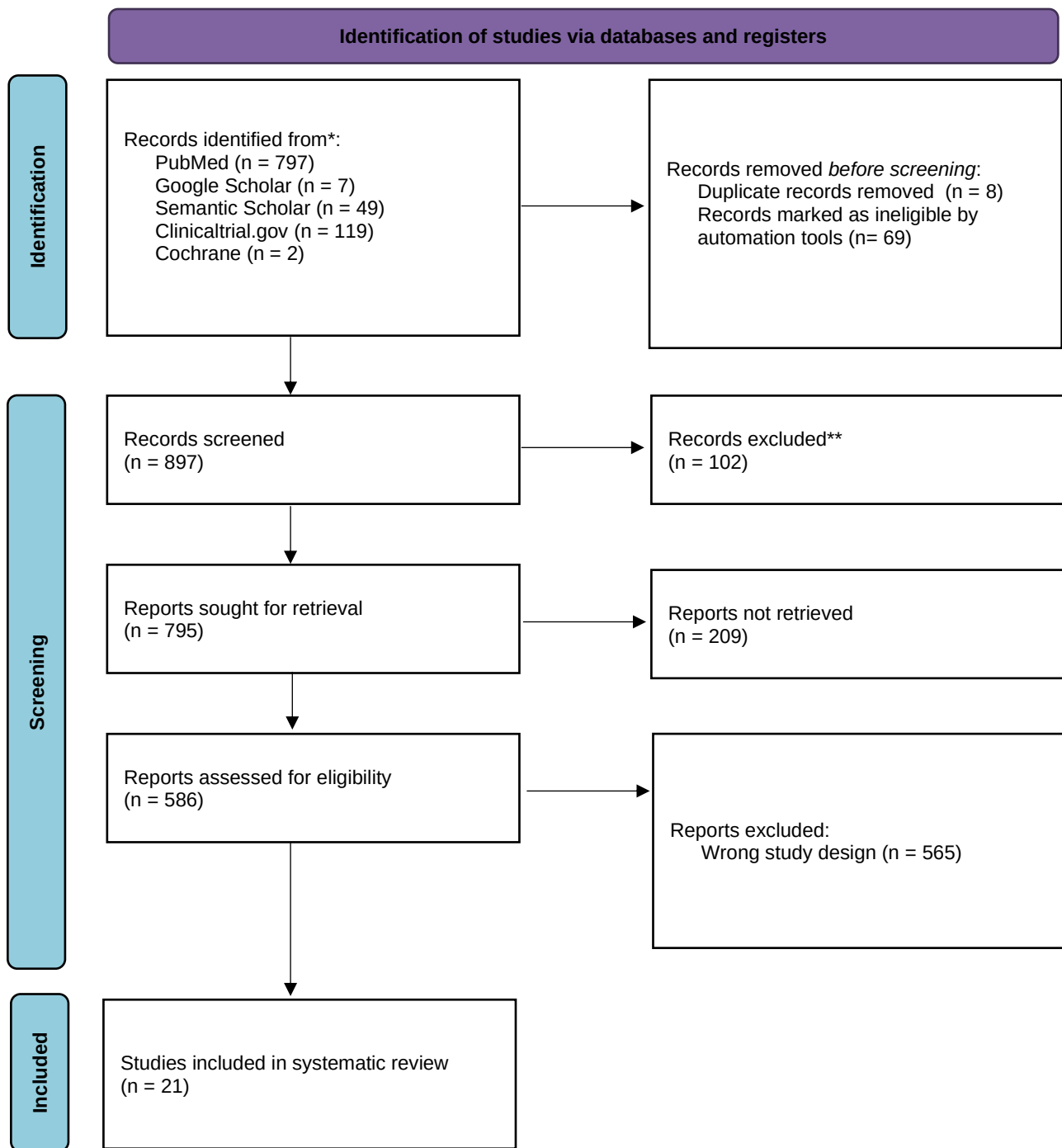


Figure 1. Article search flowchart

Risk of Bias Assessment

Risk of bias was appraised independently and in duplicate using the Cochrane Risk of Bias 2 (RoB 2) tool for individually randomized parallel-group trials. Five domains were assessed: bias arising from the randomization process; bias due to deviations from intended interventions; bias due to missing outcome data; bias in measurement of the outcome; and bias in selection of the reported result. Each domain was rated as low risk, some concerns, or high risk according to the signalling questions of the RoB 2 algorithm, and an overall judgement was derived using the standard algorithmic rules, whereby an overall rating of low risk requires low risk in all five domains. The effect of interest was assignment to intervention, corresponding to the intention-to-treat estimand. Assessments are presented in full in the Results section.

Risk of Bias Within Studies

Risk of bias was appraised for all 21 included reports using the Cochrane RoB 2 instrument. Eighteen reports were rated at overall low risk of bias, and three raised some concerns. The randomization domain was rated low risk in every report: all trials employed central computer-generated allocation with concealed sequence, and baseline characteristics were balanced across arms in every case. The domain concerning deviations from intended interventions was rated low risk throughout, reflecting consistent double-blind conduct, matched placebo, and analysis according to the intention-to-treat principle with the effect of assignment as the estimand.

Missing outcome data were minimal across the programme, with vital status ascertainment exceeding 98% in all large trials, and this domain was rated low risk throughout. Outcome measurement was rated low risk in twenty reports, in which all clinical events were adjudicated by a blinded independent clinical events committee. The exception was the atrial fibrillation analysis of DECLARE-TIMI 58, in which events were identified by MedDRA preferred-term interrogation of the safety database rather than by prospective adjudication; this was rated as raising some concerns, and the corresponding estimate should be interpreted as hypothesis-generating.⁶

The domain concerning selection of the reported result was rated as raising some concerns in SOLOIST-WHF and SCORED. Both trials were terminated prematurely following withdrawal of sponsor funding, and in both the primary endpoint was modified during the conduct of the trial from

a first-event composite to a total-event composite. Although these changes were made before unblinding and were documented in amended statistical analysis plans, the combination of endpoint modification and early termination for non-efficacy reasons introduces the possibility of bias and warrants explicit acknowledgement. No report was rated at high risk of bias in any domain, and no report was excluded from synthesis on the basis of risk of bias. Detailed domain-level judgements are presented in Table 5.^{17,18}

Table 2. Cochrane RoB 2 risk-of-bias assessment for each included report

Included report	D1 Randomization process	D2 Deviations from intended intervention	D3 Missing outcome data	D4 Measurement of the outcome	D5 Selection of the reported result	Overall RoB 2 judgement
Zinman 2015 — EMPA-REG OUTCOME	Low	Low	Low	Low	Low	Low
Fitchett 2016 — EMPA-REG HF	Low	Low	Low	Low	Low	Low
Neal 2017 — CANVAS Program	Low	Low	Low	Low	Low	Low
Rådholm 2018 — CANVAS HF	Low	Low	Low	Low	Low	Low
Wiviott 2019	Low	Low	Low	Low	Low	Low

Included report	D1 Randomization process	D2 Deviations from intended intervention	D3 Missing outcome data	D4 Measurement of the outcome	D5 Selection of the reported result	Overall RoB 2 judgement
— DECLARE- TIMI 58						
Zelniker 2020 — DECLARE AF/AFL	Low	Low	Low	Some concerns	Low	Some concerns
Perkovic 2019 — CREDENCE	Low	Low	Low	Low	Low	Low
Mahaffey 2019 — CREDENCE prevention	Low	Low	Low	Low	Low	Low
Cannon 2020 — VERTIS CV	Low	Low	Low	Low	Low	Low
Cosentino 2020 — VERTIS CV HF	Low	Low	Low	Low	Low	Low

Included report	D1 Randomization process	D2 Deviations from intended intervention	D3 Missing outcome data	D4 Measurement of the outcome	D5 Selection of the reported result	Overall RoB 2 judgement
McMurray 2019 — DAPA-HF	Low	Low	Low	Low	Low	Low
Petrie 2020 — DAPA-HF diabetes	Low	Low	Low	Low	Low	Low
Packer 2020 — EMPEROR- Reduced	Low	Low	Low	Low	Low	Low
Anker 2021 — EMPEROR- Reduced diabetes	Low	Low	Low	Low	Low	Low
Anker 2021 — EMPEROR- Preserved	Low	Low	Low	Low	Low	Low
Solomon 2022 — DELIVER	Low	Low	Low	Low	Low	Low
Bhatt 2021 —	Low	Low	Low	Low	Some	Some

Included report	D1 Randomization process	D2 Deviations from intended intervention	D3 Missing outcome data	D4 Measurement of the outcome	D5 Selection of the reported result	Overall RoB 2 judgement
SOLOIST-WHF					concerns	concerns
Bhatt 2021 — SCORED	Low	Low	Low	Low	Some concerns	Some concerns
Heerspink 2020 — DAPA-CKD	Low	Low	Low	Low	Low	Low
Herrington 2023 — EMPA- KIDNEY	Low	Low	Low	Low	Low	Low
Verma 2019 — EMPA- HEART CardioLink-6	Low	Low	Low	Low	Low	Low

Green = low risk of bias; amber = some concerns; red = high risk of bias. D1–D5 correspond to the five RoB 2 domains. The overall judgement follows the standard RoB 2 algorithm, whereby an overall rating of low risk requires a low-risk judgement in all five domains.

Certainty of Evidence

Certainty of evidence for each outcome domain was rated using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework. Evidence

from randomized controlled trials commenced at high certainty and was downgraded for risk of bias, inconsistency, indirectness, imprecision or suspected publication bias. Inconsistency was judged with reference to the I^2 statistic, the Cochran Q test and visual inspection of the direction and overlap of confidence intervals. Imprecision was judged with reference to the position of the confidence interval relative to the null and to established thresholds of clinical decision-making. Indirectness was assessed with reference to the proportion of participants with type 2 diabetes and to the applicability of the trial population to routine clinical practice.

Certainty of Evidence (GRADE)

Certainty of evidence was high for three-point MACE, hospitalization for heart failure, the composite of cardiovascular death or heart failure hospitalization, composite kidney outcomes, eGFR slope preservation, total and recurrent events, and the principal safety outcomes of genital mycotic infection and diabetic ketoacidosis. Certainty was moderate for cardiovascular death and all-cause mortality, downgraded once for inconsistency on the basis of I^2 values of 40% and 61% respectively; for atrial fibrillation, downgraded once for risk of bias because of unadjudicated event ascertainment; for albuminuria, downgraded once for indirectness as a surrogate endpoint; and for amputation, downgraded once for inconsistency arising from the single divergent trial. Certainty was low for myocardial infarction and stroke, downgraded for both inconsistency and imprecision, and for cardiac-structural intermediates, downgraded for indirectness and imprecision.

Table 3. GRADE certainty-of-evidence assessment by outcome domain

Outcome domain	Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
Three-point MACE	6 RCTs ($\approx 57,700$)	Not serious	Not serious ($I^2 = 0\%$)	Not serious	Not serious	⊕⊕⊕ ⊕ High
Cardiovascular death	8 RCTs ($\approx 65,600$)	Not serious	Serious ($I^2 = 40\%$)	Not serious	Not serious	⊕⊕⊕ ⊖

Outcome domain	Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
						Moderate
All-cause mortality	5 RCTs (≈34,600)	Not serious	Serious ($I^2 = 61\%$)	Not serious	Not serious	⊕⊕⊕ ⊖ Moderate
Hospitalization for heart failure	5 RCTs (≈47,000)	Not serious	Not serious ($I^2 = 0\%$)	Not serious	Not serious	⊕⊕⊕ ⊕ High
CV death or HF hospitalization	10 RCTs (≈80,000)	Not serious	Not serious ($I^2 = 0\%$)	Not serious	Not serious	⊕⊕⊕ ⊕ High
Non-fatal myocardial infarction	4 RCTs	Not serious	Serious	Not serious	Serious (CI crosses null)	⊕⊕⊖ ⊖ Low
Fatal or non-fatal stroke	4 RCTs	Not serious	Serious	Not serious	Serious (CI crosses null)	⊕⊕⊖ ⊖ Low
Atrial fibrillation / flutter	8 RCTs (pooled AE data)	Serious (unadjudicated)	Not serious	Not serious	Not serious	⊕⊕⊕ ⊖ Moderate

Outcome domain	Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
						e
Composite kidney outcome	6 RCTs (≈50,900)	Not serious	Not serious (I ² = 36%)	Not serious	Not serious	⊕⊕⊕ ⊕ High
eGFR slope preservation	7 RCTs	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕ ⊕ High
Albuminuria reduction	5 RCTs	Not serious	Not serious	Serious (surrogate)	Not serious	⊕⊕⊕ ⊖ Moderate
Total / recurrent events	6 RCTs	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕ ⊕ High
Cardiac-structural intermediates	3 RCTs (small)	Not serious	Not serious	Serious (surrogate)	Serious (small n)	⊕⊕⊖ ⊖ Low
Safety — genital infection, DKA	≥6 RCTs	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕ ⊕ High
Safety — amputation	4 RCTs	Not serious	Serious (single	Not serious	Not serious	⊕⊕⊕ ⊖

Outcome domain	Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
			divergent trial)			Moderate

$\oplus\oplus\oplus\oplus$ = high certainty; $\oplus\oplus\oplus\ominus$ = moderate certainty; $\oplus\oplus\ominus\ominus$ = low certainty. Participant numbers are approximate totals across contributing trials and are not additive across outcome domains because trials contribute to more than one domain.

Data Synthesis and Statistical Analysis

A structured narrative synthesis was performed for every outcome domain, organized by outcome rather than by trial, and accompanied by tabulated effect estimates. Where two or more trials reported an adjudicated hazard ratio with a 95% confidence interval for a conceptually equivalent outcome, a quantitative synthesis was performed. Effect estimates were pooled on the natural logarithm scale using the generic inverse-variance method. The standard error of each log hazard ratio was derived from the reported confidence limits as $[\ln(\text{upper limit}) - \ln(\text{lower limit})]$ divided by 2×1.96 .

A DerSimonian–Laird random-effects model was applied throughout, in recognition of clinically meaningful differences between trials in source population, background therapy, agent and follow-up duration. Between-study heterogeneity was quantified by the Cochran Q statistic with its associated p-value, by the between-study variance τ^2 , and by the I^2 statistic, with I^2 values of approximately 25%, 50% and 75% interpreted as low, moderate and substantial heterogeneity respectively. Pooled estimates are presented as hazard ratios with 95% confidence intervals and two-sided p-values; a p-value below 0.05 was regarded as statistically significant. Analyses were conducted in Python 3 using the SciPy statistical library.

Trials contributing to any given pooled estimate were restricted to those in which the outcome definition was conceptually equivalent, in order to avoid combining structurally dissimilar endpoints. Where an outcome was reported in only a single trial, or where outcome definitions were

sufficiently heterogeneous that pooling would have been misleading, results are presented descriptively without a pooled estimate, and this is stated explicitly. Because fewer than ten trials contributed to any single pooled estimate, formal statistical assessment of small-study effects by funnel plot asymmetry or Egger regression was not performed, since such tests are underpowered and unreliable at this number of studies; publication bias is instead addressed qualitatively with reference to trial registration and regulatory mandate.

Subgroup and Sensitivity Analyses

Prespecified subgroup domains for the assessment of effect modification were: presence or absence of established atherosclerotic cardiovascular disease at baseline; presence or absence of heart failure at baseline; baseline estimated glomerular filtration rate category; baseline albuminuria category; left ventricular ejection fraction stratum; age category; sex; baseline glycated haemoglobin; and background use of renin–angiotensin system inhibitors, beta-blockers, mineralocorticoid receptor antagonists and diuretics. Effect modification was assessed by extraction of the reported treatment-by-subgroup interaction p-values from each trial rather than by informal comparison of subgroup estimates. Sensitivity analyses examined the effect of restricting the synthesis to trials enrolling exclusively patients with T2DM, and of excluding the dual SGLT1/2 inhibitor sotagliflozin.

RESULTS

Characteristics of Included Studies

All included trials were multicentre, randomized, double-blind, placebo-controlled and event-driven, with the single exception of the mechanistic EMPA-HEART CardioLink-6 trial, which was a smaller randomized, double-blind imaging study with a cardiac magnetic resonance primary endpoint. Sample sizes ranged from 97 to 17,160 randomized participants, and median or mean follow-up ranged from 6 months to 4.2 years. Five distinct molecules were represented: empagliflozin in six trial programmes, dapagliflozin in five, canagliflozin in two, ertugliflozin in one, and the dual SGLT1/2 inhibitor sotagliflozin in two.^{1,3,5,7,9,11,13,15,16,17,18,19,20,21}

Seven trials enrolled exclusively participants with type 2 diabetes: EMPA-REG OUTCOME, the CANVAS Program, DECLARE-TIMI 58, CREDENCE, VERTIS CV, SOLOIST-

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WHF and SCORED. The four dedicated heart failure trials and the two dedicated chronic kidney disease trials enrolled mixed populations in whom the proportion with diabetes ranged from approximately 45% to 68%, and in every case diabetes status was a prespecified stratification variable with a formal interaction test reported. In no trial did the treatment-by-diabetes interaction reach statistical significance, indicating that the treatment effect observed in the whole population is directly applicable to the diabetic subpopulation. Design characteristics are presented in Table 4a and baseline participant characteristics in Table 4b.^{12,14,15,16,19,22}

Table 4a. Design characteristics of the included randomized controlled trials

No.	Trial (first author, year)	Design, sites/countries	N randomized	Population	Intervention (daily dose)	Comparator	Follow-up
1	EMPA-REG OUTCOME (Zinman, 2015)	Phase III, double-blind, 590 sites, 42 countries	7,020	T2DM + established ASCVD, eGFR ≥ 30	Empagliflozin 10 mg or 25 mg	Placebo + SoC	3.1 y (median)
2	EMPA-REG OUTCOME HF analysis (Fitchett, 2016)	Prespecified secondary analysis	7,020	As above; 10.1% with HF at baseline	Empagliflozin 10/25 mg (pooled)	Placebo + SoC	3.1 y
3	CANVAS Program (Neal, 2017)	Two integrated phase III trials, 667 sites, 30 countries	10,142	T2DM + high CV risk; 65.6% established CVD	Canagliflozin 100 mg or 300 mg	Placebo + SoC	188.2 wk (mean)
4	CANVAS	Prespecified	10,142	As above; 14.4%	Canagliflozin	Placebo +	188 wk

No.	Trial (first author, year)	Design, sites/countries	N randomized	Population	Intervention (daily dose)	Comparator	Follow-up
	HF analysis (Rådholm, 2018)	secondary analysis		with HF at baseline	(pooled)	SoC	
5	DECLARE-TIMI 58 (Wiviott, 2019)	Phase IIIb, double-blind, 882 sites, 33 countries	17,160	T2DM + ASCVD (40.6%) or multiple risk factors (59.4%)	Dapagliflozin 10 mg	Placebo + SoC	4.2 y (median)
6	DECLARE-TIMI 58 AF analysis (Zelniker, 2020)	Prespecified exploratory analysis	17,160	As above; 1,116 with prevalent AF/AFL	Dapagliflozin 10 mg	Placebo + SoC	4.2 y
7	CREDENCE (Perkovic, 2019)	Phase III, double-blind, event-driven, 690 sites, 34 countries	4,401	T2DM + albuminuric CKD (eGFR 30–<90, UACR >300–5000)	Canagliflozin 100 mg	Placebo + SoC	2.62 y (median)
8	CREDENCE prevention analysis (Mahaffey, 2019)	Prespecified subgroup analysis	4,401	Primary (n = 2,181) vs secondary (n = 2,220) CV prevention	Canagliflozin 100 mg	Placebo + SoC	2.62 y

No.	Trial (first author, year)	Design, sites/countries	N randomized	Population	Intervention (daily dose)	Comparator	Follow-up
9	VERTIS CV (Cannon, 2020)	Phase III, double-blind, 567 sites, 34 countries	8,246	T2DM + established ASCVD	Ertugliflozin 5 mg or 15 mg	Placebo + SoC	3.5 y (mean)
10	VERTIS CV HF analysis (Cosentino, 2020)	Prespecified secondary analysis	8,246	As above; 23.7% HF history, 959 with EF $\leq$ 45%	Ertugliflozin (pooled)	Placebo + SoC	3.5 y
11	DAPA-HF (McMurray, 2019)	Phase III, double-blind, 410 sites, 20 countries	4,744	HFrEF, NYHA II–IV, EF $\leq$ 40%, $\pm$ T2DM (45% T2DM)	Dapagliflozin 10 mg	Placebo + SoC	18.2 mo (median)
12	DAPA-HF diabetes analysis (Petrie, 2020)	Prespecified analysis by diabetes status	4,744	2,139 with T2DM; 2,605 without	Dapagliflozin 10 mg	Placebo + SoC	18.2 mo
13	EMPEROR-Reduced (Packer, 2020)	Phase III, double-blind, 520 sites, 20 countries	3,730	HFrEF, NYHA II–IV, EF $\leq$ 40%, $\pm$ diabetes (49.8% diabetes)	Empagliflozin 10 mg	Placebo + SoC	16 mo (median)
14	EMPEROR-	Prespecified	3,730	1,856 diabetes;	Empagliflozin	Placebo +	16 mo

No.	Trial (first author, year)	Design, sites/countries	N randomized	Population	Intervention (daily dose)	Comparator	Follow-up
	Reduced diabetes analysis (Anker, 2021)	analysis by glycaemic status		1,268 prediabetes; 606 normoglycaemia	10 mg	SoC	
15	EMPEROR-Preserved (Anker, 2021)	Phase III, double-blind, multinational	5,988	HFmrEF/HFpEF, NYHA II–IV, EF >40%, $\pm$ diabetes (49% diabetes)	Empagliflozin 10 mg	Placebo + SoC	26.2 mo (median)
16	DELIVER (Solomon, 2022)	Phase III, double-blind, multinational	6,263	HFmrEF/HFpEF, EF >40%, eGFR $\geq$ 25, $\pm$ diabetes ($\approx$ 45% diabetes)	Dapagliflozin 10 mg	Placebo + SoC	2.3 y (median)
17	SOLOIST-WHF (Bhatt, 2021)	Phase III, double-blind, 306 sites, 32 countries; terminated early	1,222	T2DM + recent hospitalization for worsening HF	Sotagliflozin 200 mg $\rightarrow$ 400 mg	Placebo + SoC	9.0 mo (median)
18	SCORED (Bhatt, 2021)	Phase III, double-blind, multinational; terminated	10,584	T2DM + CKD (eGFR 25–60) with CV risk factors	Sotagliflozin 200 mg $\rightarrow$ 400 mg	Placebo + SoC	16 mo (median)

No.	Trial (first author, year)	Design, sites/countries	N randomized	Population	Intervention (daily dose)	Comparator	Follow-up
		early					
19	DAPA-CKD (Heerspink, 2020)	Phase III, double-blind, 386 sites, 21 countries; stopped early for efficacy	4,304	CKD eGFR 25–75, UACR 200–5000; 68% T2DM	Dapagliflozin 10 mg	Placebo + SoC	2.4 y (median)
20	EMPA-KIDNEY (Herrington, 2023)	Phase III, double-blind, multinational	6,609	CKD at risk of progression; ≈45% with diabetes	Empagliflozin 10 mg	Placebo + SoC	2.0 y (median)
21	EMPA-HEART CardioLink-6 (Verma, 2019)	Phase IV mechanistic RCT, single-country (Canada)	97	T2DM + coronary artery disease, eGFR ≥60	Empagliflozin 10 mg	Placebo + SoC	6 mo

T2DM = type 2 diabetes mellitus; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; EF = ejection fraction; eGFR = estimated glomerular filtration rate (mL/min/1.73 m²); UACR = urinary albumin-to-creatinine ratio (mg/g); SoC = standard of care; NYHA = New York Heart Association; AF/AFL = atrial fibrillation or atrial flutter.

Table 4b. Baseline characteristics of the included trial populations

Trial	Mean age (y)	Female (%)	Baseline HbA1c (%)	Mean eGFR (mL/min/1.73 m ²)	Established ASCVD (%)	HF at baseline (%)	T2DM (%)	Registration
EMPA-REG OUTCOME	63.1	28.5	8.1	74	100	10.1	100	NCT01131676
CANVAS Program	63.3	35.8	8.2	76.5	65.6	14.4	100	NCT01032629 / NCT01989754
DECLARE-TIMI 58	63.9	37.4	8.3	85.2	40.6	≈10	100	NCT01730534
CREDENCE	63.0	33.9	8.3	56.2	50.4	14.8	100	NCT02065791
VERTIS CV	64.4	30.0	8.2	76	100	23.7	100	NCT01986881
DAPA-HF	66.3	23.4	NR (HF trial)	66	≈56	100	45.1	NCT03036124
EMPEROR-Reduced	66.8	23.9	NR (HF trial)	62	≈52	100	49.8	NCT03057977
EMPEROR-Preserved	71.9	44.7	NR (HF trial)	≈61	≈35	100	49.0	NCT03057951
DELIVER	71.7	43.9	NR (HF trial)	61	≈27	100	≈45	NCT03619213
SOLOIST-WHF	≈70	≈34	≈7.2	≈50	≈45	100	100	NCT03521934
SCORED	≈69	≈45	8.3	44.4	≈49	31	100	NCT03315143
DAPA-CKD	61.8	33.1	NR	43.1	37.4	10.9	67.5	NCT03036150

Trial	Mean age (y)	Female (%)	Baseline HbA1c (%)	Mean eGFR (mL/min/1.73 m ²)	Established ASCVD (%)	HF at baseline (%)	T2DM (%)	Registration
			(CKD trial)					
EMPA-KIDNEY	63.8	33.2	NR (CKD trial)	37.3	≈27	≈10	≈45	NCT03594110
EMPA-HEART CardioLink-6	62.8	7.2	7.4	88.4	100	0	100	NCT02998970

Values are means or proportions as reported in the primary publication or its designated baseline-characteristics report. NR = not routinely reported, because the trial was a heart failure or chronic kidney disease outcome trial in which glycated haemoglobin was not an entry criterion. Values prefixed by ≈ are approximate figures drawn from the trial's baseline-characteristics report.

Three-Point Major Adverse Cardiovascular Events (MACE)

Three-point MACE, defined as the composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke, was reported as a primary or co-primary endpoint in six trials of participants with type 2 diabetes. In EMPA-REG OUTCOME, MACE occurred in 490 of 4,687 participants (10.5%) receiving empagliflozin compared with 282 of 2,333 (12.1%) receiving placebo, corresponding to a hazard ratio of 0.86 (95% CI 0.74–0.99; $p = 0.04$ for superiority). In the CANVAS Program the event rate was 26.9 versus 31.5 per 1,000 patient-years, hazard ratio 0.86 (95% CI 0.75–0.97; $p = 0.02$ for superiority).^{1,3}

In DECLARE-TIMI 58, which enrolled a lower-risk population in which almost 60% had multiple risk factors rather than established atherosclerotic disease, MACE occurred in 8.8% versus 9.4% and the reduction did not reach statistical significance (hazard ratio 0.93, 95% CI 0.84–1.03; p

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= 0.17). In CREDENCE, in which all participants had albuminuric chronic kidney disease and thus a substantially elevated absolute risk, canagliflozin reduced MACE with a hazard ratio of 0.80 (95% CI 0.67–0.95; $p = 0.01$). VERTIS CV met its non-inferiority objective but demonstrated no superiority, with an event rate of 11.9% in both arms and a hazard ratio of 0.97 (95% CI 0.85–1.11). In SCORED, the original co-primary MACE endpoint yielded a hazard ratio of 0.84 (95% CI 0.72–0.99).^{5,7,9,18}

Random-effects pooling of these six adjudicated estimates produced a statistically significant reduction in three-point MACE, with a pooled hazard ratio of 0.89 (95% CI 0.84–0.94; $z = -4.24$; $p < 0.0001$). Between-trial heterogeneity was absent (Cochran $Q = 4.74$, $df = 5$, $p = 0.449$; $I^2 = 0\%$; $\tau^2 = 0$), indicating that the apparently divergent individual trial results are fully explicable by random variation around a common underlying effect rather than by genuine differences in drug efficacy. The pooled estimate corresponds to an 11% relative reduction in the risk of a first major adverse cardiovascular event. Hypothesis H1 is therefore supported.^{1,3,5,7,9,18}

Table 5. Effect of SGLT2 inhibitors on three-point major adverse cardiovascular events

Trial	Population	SGLT2i events / n (%) or rate	Placebo events / n (%) or rate	Hazard ratio (95% CI)	p-value	Weight (%)
EMPA-REG OUTCOME	T2DM + ASCVD	490/4,687 (10.5)	282/2,333 (12.1)	0.86 (0.74– 0.99)	0.04 (superiority)	14.2
CANVAS Program	T2DM + high CV risk	26.9 per 1,000 py	31.5 per 1,000 py	0.86 (0.75– 0.97)	0.02 (superiority)	18.2
DECLARE- TIMI 58	T2DM + ASCVD or MRF	8.8%	9.4%	0.93 (0.84– 1.03)	0.17	29.0
CREDENCE	T2DM + albuminuric	—	—	0.80 (0.67– 0.95)	0.01	9.9

Trial	Population	SGLT2i events / n (%) or rate	Placebo events / n (%) or rate	Hazard ratio (95% CI)	p-value	Weight (%)
	CKD					
VERTIS CV	T2DM + ASCVD	653/5,493 (11.9)	327/2,745 (11.9)	0.97 (0.85– 1.11)	<0.001 (non- inferiority)	16.9
SCORED	T2DM + CKD	—	—	0.84 (0.72– 0.99)	Nominal	11.9
Pooled random-effects estimate (k = 6)	T2DM	—	—	0.89 (0.84– 0.94)	<0.0001	100

py = patient-years; MRF = multiple risk factors for atherosclerotic cardiovascular disease; ARR = absolute risk reduction; CI = confidence interval. Weights are derived from the DerSimonian–Laird random-effects model. Pooled estimate: HR 0.889 (95% CI 0.841–0.939), $p < 0.0001$, $I^2 = 0\%$, $Q = 4.74$ ($df = 5$, $p = 0.449$).

Cardiovascular Mortality

Cardiovascular death was the outcome domain exhibiting the widest dispersion of individual trial results. In EMPA-REG OUTCOME the effect was large: cardiovascular death occurred in 3.7% of empagliflozin recipients compared with 5.9% of placebo recipients, a 38% relative risk reduction corresponding to a hazard ratio of 0.62 (95% CI 0.49–0.77). This result was the single most influential finding in reframing the therapeutic identity of the class, and mediation analysis subsequently attributed approximately half of the effect to changes in haematocrit and haemoglobin, consistent with plasma volume contraction rather than glycaemic improvement.^{1,27}

By contrast, DECLARE-TIMI 58 demonstrated no difference in cardiovascular death (hazard ratio 0.98, 95% CI 0.82–1.17), and VERTIS CV likewise showed a neutral result (hazard ratio 0.92, 95% CI 0.77–1.11). CREDENCE demonstrated a borderline reduction (hazard ratio 0.78, 95% CI 0.61–1.00), as did DAPA-HF, in which cardiovascular death occurred in 9.6% versus 11.5% (hazard ratio 0.82, 95% CI 0.69–0.98). DELIVER, SOLOIST-WHF and SCORED each produced point estimates favouring active therapy with confidence intervals crossing unity.^{5,7,8,9,11,16,17,18}

Pooling of the eight available adjudicated estimates yielded a statistically significant reduction in cardiovascular mortality, with a random-effects hazard ratio of 0.85 (95% CI 0.77–0.93; $p < 0.001$). Moderate heterogeneity was present (Cochran $Q = 11.72$, $df = 7$, $p = 0.110$; $I^2 = 40.3\%$), driven predominantly by the divergence between the EMPA-REG OUTCOME estimate and those of DECLARE-TIMI 58 and VERTIS CV. The heterogeneity is most plausibly attributable to differences in baseline absolute cardiovascular risk: EMPA-REG OUTCOME and CREDENCE enrolled the highest-risk populations, whereas DECLARE-TIMI 58 enrolled a predominantly primary-prevention cohort with a low background event rate. Hypothesis H2 is supported for the pooled estimate, with the qualification that the effect is neither uniform nor universally reproducible at the level of the individual trial.^{1,5,9,27}

Table 6. Effect of SGLT2 inhibitors on cardiovascular mortality

Trial	Hazard ratio (95% CI)	Direction	Weight (%)
EMPA-REG OUTCOME (2015)	0.62 (0.49–0.77)	Significant reduction	11.5
DECLARE-TIMI 58 (2019)	0.98 (0.82–1.17)	Neutral	15.2
CREDENCE (2019)	0.78 (0.61–1.00)	Borderline reduction	10.2
VERTIS CV (2020)	0.92 (0.77–1.11)	Neutral	14.7
DAPA-HF (2019)	0.82 (0.69–0.98)	Significant reduction	15.4

Trial	Hazard ratio (95% CI)	Direction	Weight (%)
DELIVER (2022)	0.88 (0.74–1.05)	Neutral	15.4
SOLOIST-WHF (2021)	0.84 (0.58–1.22)	Neutral	5.5
SCORED (2021)	0.90 (0.73–1.12)	Neutral	12.3
Pooled random-effects estimate (k = 8)	0.85 (0.77–0.93)	Significant reduction; p < 0.001	100

Pooled estimate: HR 0.845 (95% CI 0.768–0.930), p < 0.001, I² = 40.3%, Q = 11.72 (df = 7, p = 0.110), $\tau^2 = 0.0089$.

All-Cause Mortality

All-cause mortality was reported with a formal effect estimate in five of the included trials. EMPA-REG OUTCOME demonstrated a 32% relative reduction in death from any cause (5.7% versus 8.3%; hazard ratio 0.68, 95% CI 0.57–0.82), a finding without precedent among antihyperglycaemic agents at the time of publication. DAPA-HF demonstrated a significant reduction (11.6% versus 13.9%; hazard ratio 0.83, 95% CI 0.71–0.97), and DAPA-CKD demonstrated a reduction of similar magnitude in a chronic kidney disease population of whom approximately two-thirds had type 2 diabetes (4.7% versus 6.8%; hazard ratio 0.69, 95% CI 0.53–0.88).^{1,11,19}

DECLARE-TIMI 58 produced a neutral estimate (6.2% versus 6.6%; hazard ratio 0.93, 95% CI 0.82–1.04), and SOLOIST-WHF, constrained by premature termination and a median follow-up of only nine months, produced a point estimate favouring sotagliflozin with a wide confidence interval (hazard ratio 0.82, 95% CI 0.59–1.14). In EMPA-KIDNEY, death from any cause occurred in 4.5% versus 5.1% of participants, a difference that did not reach statistical significance in a trial powered for kidney disease progression over a median of two years.^{5,17,20}

Random-effects pooling of the five available estimates yielded a hazard ratio of 0.80 (95% CI 0.70–0.91; p < 0.001), representing a 20% relative reduction in death from any cause.

Heterogeneity was moderate to substantial (Cochran $Q = 10.16$, $df = 4$, $p = 0.038$; $I^2 = 60.6\%$), again reflecting the marked contrast between the high-risk secondary-prevention populations of EMPA-REG OUTCOME and DAPA-CKD and the lower-risk population of DECLARE-TIMI 58. In absolute terms, the number needed to treat to prevent one death ranged from 39 over 3.1 years in EMPA-REG OUTCOME to 44 over 18 months in DAPA-HF and 48 over 2.4 years in DAPA-CKD, all of which compare favourably with well-established secondary-prevention therapies.^{1,11,19}

Table 7. Effect of SGLT2 inhibitors on all-cause mortality with absolute risk reduction and number needed to treat

Trial	SGLT2i	Placebo	Hazard ratio (95% CI)	ARR	NNT	Weight (%)
EMPA-REG OUTCOME	5.7%	8.3%	0.68 (0.57–0.82)	2.6% / 3.1 y	39	21.4
DECLARE-TIMI 58	6.2%	6.6%	0.93 (0.82–1.04)	0.4% / 4.2 y	—	27.6
DAPA-HF	11.6%	13.9%	0.83 (0.71–0.97)	2.3% / 18.2 mo	44	23.9
SOLOIST-WHF	13.5 per 100 py	16.3 per 100 py	0.82 (0.59–1.14)	—	—	11.3
DAPA-CKD	4.7%	6.8%	0.69 (0.53–0.88)	2.1% / 2.4 y	48	15.7
Pooled random-effects (k = 5)	—	—	0.80 (0.70–0.91)	—	—	100

ARR = absolute risk reduction over the stated median follow-up; NNT = number needed to treat. Pooled estimate: HR 0.796 (95% CI 0.696–0.911), $p < 0.001$, $I^2 = 60.6\%$, $Q = 10.16$ ($df = 4$, $p = 0.038$).

Hospitalization for Heart Failure

Hospitalization for heart failure was the outcome domain demonstrating the largest, most consistent and most statistically robust treatment effect in the entire evidence base. Every trial enrolling participants with type 2 diabetes that reported this endpoint demonstrated a reduction, with point estimates confined to a narrow range between 0.61 and 0.73. In EMPA-REG OUTCOME, hospitalization for heart failure occurred in 2.7% of empagliflozin recipients versus 4.1% of placebo recipients, a 35% relative risk reduction (hazard ratio 0.65, 95% CI 0.50–0.85). In the CANVAS Program the hazard ratio was 0.67 (95% CI 0.52–0.87), and in DECLARE-TIMI 58 it was 0.73 (95% CI 0.61–0.88).^{1,3,4,5}

CREDESCENCE demonstrated the largest single-trial effect (hazard ratio 0.61, 95% CI 0.47–0.80; $p < 0.001$), consistent with the elevated heart failure risk conferred by albuminuric chronic kidney disease. VERTIS CV, notable for having failed to demonstrate superiority for MACE or for the composite of cardiovascular death or heart failure hospitalization, nevertheless demonstrated a significant reduction in first heart failure hospitalization (hazard ratio 0.70, 95% CI 0.54–0.90; $p = 0.006$), a dissociation that provides strong internal evidence that the heart failure effect is mechanistically distinct from any antiatherosclerotic action.^{7,9,10}

Random-effects pooling produced a hazard ratio of 0.68 (95% CI 0.61–0.76; $p < 0.0001$), corresponding to a 32% relative reduction in the risk of a first hospitalization for heart failure. Heterogeneity was entirely absent (Cochran $Q = 1.39$, $df = 4$, $p = 0.846$; $I^2 = 0\%$; $\tau^2 = 0$), the most homogeneous result of any outcome domain in this review and a finding of considerable importance, since it establishes the heart failure effect as a genuine and uniform class property. Within VERTIS CV, the effect was greater in participants with a pre-trial ejection fraction of 45% or less (hazard ratio 0.48, 95% CI 0.30–0.76) than in those with higher ejection fraction, and was amplified in participants with reduced eGFR, albuminuria or diuretic use, each of which showed a significant interaction. Hypothesis H3 is supported.^{1,3,5,7,9,10}

Table 8. Effect of SGLT2 inhibitors on first hospitalization for heart failure

Trial	Population	Hazard ratio (95% CI)	Relative risk reduction	Weight (%)
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Trial	Population	Hazard ratio (95% CI)	Relative risk reduction	Weight (%)
EMPA-REG OUTCOME (2015)	T2DM + ASCVD	0.65 (0.50–0.85)	35%	16.0
CANVAS Program (2017/2018)	T2DM + high CV risk	0.67 (0.52–0.87)	33%	17.1
DECLARE-TIMI 58 (2019)	T2DM ± ASCVD	0.73 (0.61–0.88)	27%	33.6
CREDENCE (2019)	T2DM + albuminuric CKD	0.61 (0.47–0.80)	39%	16.0
VERTIS CV (2020)	T2DM + ASCVD	0.70 (0.54–0.90)	30%	17.3
Pooled random-effects estimate (k = 5)	T2DM	0.68 (0.61–0.76)	32%	100

Pooled estimate: HR 0.681 (95% CI 0.613–0.758), $p < 0.0001$, $I^2 = 0\%$, $Q = 1.39$ ($df = 4$, $p = 0.846$), $\tau^2 = 0$. The complete absence of heterogeneity indicates a uniform class effect.

Composite of Cardiovascular Death or Hospitalization for Heart Failure

This composite constituted the primary or a co-primary endpoint in the majority of the included trials and provides the broadest evidentiary base of any outcome domain, with ten trials contributing adjudicated estimates. In EMPA-REG OUTCOME the composite occurred in 5.7% of empagliflozin recipients versus 8.5% of placebo recipients (hazard ratio 0.66, 95% CI 0.55–0.79; $p < 0.001$), corresponding to a number needed to treat of 35 over three years to prevent one event, with a consistent effect in participants with and without heart failure at baseline.²

Across the dedicated heart failure programme the result was uniform. DAPA-HF reported a hazard ratio of 0.74 (95% CI 0.65–0.85) for worsening heart failure or cardiovascular death, with 16.3% versus 21.2% event rates and a number needed to treat of 21. EMPEROR-Reduced reported 0.75 (95% CI 0.65–0.86). Critically, the benefit extended across the whole ejection fraction

spectrum: EMPEROR-Preserved reported 0.79 (95% CI 0.69–0.90) with 13.8% versus 17.1% event rates, and DELIVER reported 0.82 (95% CI 0.73–0.92) with 16.4% versus 19.5% event rates. In both preserved-ejection-fraction trials the effect was explicitly consistent in participants with and without diabetes.^{11,13,15,16}

Random-effects pooling of all ten estimates produced a hazard ratio of 0.78 (95% CI 0.75–0.82; $p < 0.0001$), a 22% relative reduction. Heterogeneity was absent (Cochran $Q = 8.53$, $df = 9$, $p = 0.482$; $I^2 = 0\%$), despite the inclusion of trials spanning atherosclerotic secondary prevention, primary prevention with multiple risk factors, heart failure with reduced ejection fraction, heart failure with preserved ejection fraction, albuminuric chronic kidney disease and recent decompensated heart failure. This is the single most compelling demonstration in the evidence base that SGLT2 inhibition exerts a coherent and uniform effect on the heart failure axis of cardiovascular risk in type 2 diabetes.^{1,3,5,9,11,13,15,16,18,19}

Table 9. Effect of SGLT2 inhibitors on the composite of cardiovascular death or hospitalization for heart failure

Trial	Endpoint as defined in trial	Hazard ratio (95% CI)	Weight (%)
EMPA-REG OUTCOME (Fitchett, 2016)	HF hospitalization or CV death	0.66 (0.55–0.79)	6.6
CANVAS Program (Rådholm, 2018)	CV death or hospitalized HF	0.78 (0.67–0.91)	9.2
DECLARE-TIMI 58 (2019)	CV death or HHF (co-primary)	0.83 (0.73–0.95)	12.5
VERTIS CV (2020)	CV death or HHF (key secondary)	0.88 (0.75–1.03)	8.6
DAPA-HF (2019)	Worsening HF or CV death (primary)	0.74 (0.65–0.85)	12.0

Trial	Endpoint as defined in trial	Hazard ratio (95% CI)	Weight (%)
EMPEROR-Reduced (2020)	CV death or HF hospitalization (primary)	0.75 (0.65–0.86)	11.0
EMPEROR-Preserved (2021)	CV death or HF hospitalization (primary)	0.79 (0.69–0.90)	12.3
DELIVER (2022)	Worsening HF or CV death (primary)	0.82 (0.73–0.92)	16.2
DAPA-CKD (2020)	CV death or HF hospitalization	0.71 (0.55–0.92)	3.3
SCORED (2021)	CV death or HHF (original co-primary)	0.77 (0.66–0.91)	8.4
Pooled random-effects estimate (k = 10)	Composite of CV death or HF hospitalization	0.78 (0.75–0.82)	100

Pooled estimate: HR 0.782 (95% CI 0.746–0.819), $p < 0.0001$, $I^2 = 0\%$, $Q = 8.53$ ($df = 9$, $p = 0.482$), $\tau^2 = 0$. Endpoint definitions differ marginally between trials (some incorporate urgent heart failure visits) but are conceptually equivalent.

Non-Fatal Myocardial Infarction

The effect of SGLT2 inhibition on myocardial infarction considered in isolation was substantially smaller than the effect on heart failure endpoints, and in most trials did not reach statistical significance. In EMPA-REG OUTCOME the primary publication recorded no significant between-group difference in the rate of myocardial infarction, notwithstanding the large reduction in cardiovascular death. A subsequent prespecified analysis of total (first plus recurrent) events, which is statistically more efficient than a first-event analysis, demonstrated a borderline significant reduction in fatal or non-fatal myocardial infarction (rate ratio 0.79, 95% CI 0.62–0.998; $p = 0.049$) and a clearer reduction in the composite of fatal or non-fatal myocardial infarction or coronary revascularization (rate ratio 0.80, 95% CI 0.67–0.95; $p = 0.012$).^{1,28}

In CREDENCE, non-fatal myocardial infarction yielded a hazard ratio of 0.81 (95% CI 0.59–1.10), directionally favourable but imprecise. A prespecified subgroup analysis of DECLARE-TIMI 58 provided the most clinically informative signal: among the 3,584 participants with a previous myocardial infarction, dapagliflozin reduced MACE by a relative 16% and by an absolute 2.6% (15.2% versus 17.8%; hazard ratio 0.84, 95% CI 0.72–0.99; $p = 0.039$), whereas no effect was observed in participants without previous infarction (hazard ratio 1.00, 95% CI 0.88–1.13), with a significant interaction for absolute risk difference ($p = 0.048$). Benefit appeared greatest within two years of the index event.^{8,39}

Taken together, the evidence indicates a modest attenuation of atherothrombotic coronary risk that is detectable principally in high-risk populations with established coronary disease and in analyses of total rather than first events. Because outcome definitions and analytical models differed materially between these reports, a pooled estimate was not derived. Hypothesis H4 is supported: the myocardial infarction effect is smaller than, and statistically distinguishable from, the heart failure effect.^{28,39}

Fatal or Non-Fatal Stroke

Stroke was the only cardiovascular outcome domain in which no benefit was demonstrable at any level of analysis. In the prespecified total-events analysis of EMPA-REG OUTCOME the rate ratio for total fatal or non-fatal stroke was 1.10 (95% CI 0.82–1.49; $p = 0.52$), numerically unfavourable and clearly non-significant, in stark contrast to the concurrent reductions in MACE, myocardial infarction, heart failure hospitalization and all-cause hospitalization within the same analysis. In CREDENCE, non-fatal stroke yielded a hazard ratio of 0.80 (95% CI 0.56–1.15), directionally favourable but imprecise.^{1,8,28}

In the CANVAS Program, analysis by baseline kidney function identified stroke as the only outcome for which heterogeneity of treatment effect across eGFR strata was suggested (p for heterogeneity = 0.01), without a consistent overall benefit. The absence of a stroke signal is of particular mechanistic importance. Blood pressure lowering of the magnitude achieved by SGLT2 inhibition would, on the basis of classical antihypertensive epidemiology, be expected to produce a measurable reduction in stroke; the failure to observe one argues strongly against blood pressure

lowering as the dominant mediator of benefit and reinforces the interpretation that the class acts principally through cardiac and renal haemodynamic and metabolic pathways rather than through modification of cerebrovascular atherothrombosis.^{27,28,49}

Table 10. Effect of SGLT2 inhibitors on the individual atherothrombotic components of MACE

Trial / analysis	Endpoint	Effect estimate (95% CI)	Interpretation
EMPA-REG OUTCOME (McGuire, 2020)	Total (first + recurrent) fatal or non-fatal myocardial infarction	RR 0.79 (0.62–0.998)	Borderline significant reduction
EMPA-REG OUTCOME (McGuire, 2020)	Total fatal or non-fatal MI or coronary revascularization	RR 0.80 (0.67–0.95)	Significant reduction
EMPA-REG OUTCOME (Zinman, 2015)	First myocardial infarction	No significant between-group difference	Neutral
CREDENCE (Mahaffey, 2019)	Non-fatal myocardial infarction	HR 0.81 (0.59–1.10)	Neutral
DECLARE-TIMI 58 (Furtado, 2019)	MACE in participants with prior MI (n = 3,584)	HR 0.84 (0.72–0.99); ARR 2.6%	Significant in the prior-MI subgroup
DECLARE-TIMI 58 (Furtado, 2019)	MACE in participants without prior MI	HR 1.00 (0.88–1.13)	Neutral; p for ARR interaction = 0.048
EMPA-REG OUTCOME (McGuire, 2020)	Total fatal or non-fatal stroke	RR 1.10 (0.82–1.49); p = 0.52	No effect

Trial / analysis	Endpoint	Effect estimate (95% CI)	Interpretation
2020)			
CREDENCE (Mahaffey, 2019)	Non-fatal stroke	HR 0.80 (0.56–1.15)	Neutral
CANVAS Program (Neuen, 2018)	Fatal or non-fatal stroke by eGFR stratum	Heterogeneity by baseline eGFR, $p = 0.01$	Inconsistent; no overall benefit

RR = rate ratio from negative binomial or Andersen–Gill modelling of total events; HR = hazard ratio for first events; ARR = absolute risk reduction. Rows shaded pink denote stroke outcomes, for which no benefit was demonstrated.

Atrial Fibrillation and Atrial Flutter

Atrial fibrillation and atrial flutter constitute an important and often under-recognized component of cardiovascular risk in type 2 diabetes, contributing to stroke, heart failure decompensation and mortality. In DECLARE-TIMI 58, dapagliflozin reduced the risk of a first atrial fibrillation or flutter event by 19% (264 versus 325 events; 7.8 versus 9.6 events per 1,000 patient-years; hazard ratio 0.81, 95% CI 0.68–0.95; $p = 0.009$). The effect was consistent irrespective of a history of atrial fibrillation at baseline (interaction $p = 0.89$), of established atherosclerotic disease versus multiple risk factors (interaction $p = 0.72$), and of a history of heart failure (interaction $p = 0.88$). No effect modification was observed by sex, prior ischaemic stroke, glycated haemoglobin, body mass index, blood pressure or estimated glomerular filtration rate.⁶

Dapagliflozin also reduced the total number of first and recurrent atrial fibrillation or flutter events (337 versus 432; incidence rate ratio 0.77, 95% CI 0.64–0.92; $p = 0.005$). A pooled analysis of eight cardiovascular and renal outcome trials — EMPA-REG OUTCOME, CANVAS, CANVAS-R, DECLARE-TIMI 58, CREDENCE, DAPA-HF, VERTIS CV and DAPA-CKD — reported atrial fibrillation as a serious adverse event in 0.9% of SGLT2 inhibitor recipients versus 1.1% of placebo recipients, giving a pooled relative risk of 0.79 (95% CI 0.67–0.93). The

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consistency of direction and magnitude between the dedicated DECLARE analysis and the pooled safety-database analysis strengthens the inference of a genuine antiarrhythmic effect.^{6,31}

This outcome domain nonetheless carries an important methodological caveat. Events in both analyses were identified through interrogation of adverse-event databases using MedDRA preferred terms rather than through prospective adjudication or systematic rhythm monitoring, so that asymptomatic and subclinical episodes were necessarily under-ascertained. The estimate is therefore best regarded as a robust and internally consistent hypothesis-generating signal, and this consideration underlies the downgrading of certainty for this domain in the GRADE assessment.^{6,31}

Table 11. Effect of SGLT2 inhibitors on atrial fibrillation and atrial flutter

Source	Population	Endpoint	Effect estimate (95% CI)	p-value
DECLARE-TIMI 58 (Zelniker, 2020)	17,160 with T2DM	First AF/AFL event	HR 0.81 (0.68–0.95)	0.009
DECLARE-TIMI 58 (Zelniker, 2020)	Prior AF/AFL (n = 1,116)	First AF/AFL event	HR 0.79 (0.58–1.09)	p interaction 0.89
DECLARE-TIMI 58 (Zelniker, 2020)	No prior AF/AFL	First AF/AFL event	HR 0.81 (0.67–0.98)	—
DECLARE-TIMI 58 (Zelniker, 2020)	17,160 with T2DM	Total (first + recurrent) AF/AFL events	IRR 0.77 (0.64–0.92)	0.005
Pooled CV and renal outcome trials (Okunrintemi, 2021)	EMPA-REG, CANVAS, CANVAS-R, DECLARE, CREDENCE, DAPA-	AF reported as a serious adverse event (0.9% vs 1.1%)	RR 0.79 (0.67–0.93)	Significant

Source	Population	Endpoint	Effect estimate (95% CI)	p-value
	HF, VERTIS CV, DAPA-CKD			

AF/AFL = atrial fibrillation or atrial flutter; IRR = incidence rate ratio for total events; RR = relative risk. Events were ascertained from safety databases using MedDRA preferred terms rather than by prospective adjudication.

Composite Kidney Outcomes

Chronic kidney disease is both a consequence of type 2 diabetes and one of the most powerful independent amplifiers of cardiovascular risk, such that preservation of kidney function constitutes an indirect but potent form of cardiovascular protection. Every trial reporting a composite kidney endpoint demonstrated a significant benefit, and the magnitude of effect exceeded that observed for any cardiovascular endpoint. In the CANVAS Program, the composite of a sustained 40% reduction in eGFR, initiation of renal replacement therapy or renal death yielded a hazard ratio of 0.60 (95% CI 0.47–0.77), and the more stringent composite of doubling of serum creatinine, end-stage kidney disease or renal death yielded 0.53 (95% CI 0.33–0.84).^{3,23}

In DECLARE-TIMI 58 the renal-specific composite was reduced by 47% (hazard ratio 0.53, 95% CI 0.43–0.66; $p < 0.0001$), with a 46% reduction in sustained $\geq 40\%$ eGFR decline (hazard ratio 0.54, 95% CI 0.43–0.67) and a 59% reduction in end-stage renal disease or renal death (hazard ratio 0.41, 95% CI 0.20–0.82; $p = 0.012$). CREDENCE, the first dedicated kidney outcome trial, demonstrated a 30% reduction in its primary composite of end-stage kidney disease, doubling of serum creatinine, or renal or cardiovascular death (43.2 versus 61.2 events per 1,000 patient-years; hazard ratio 0.70, 95% CI 0.59–0.82; $p = 0.00001$), a 34% reduction in the renal-specific composite and a 32% reduction in end-stage kidney disease alone.^{7,24}

VERTIS CV, despite its neutral cardiovascular result, reduced the prespecified exploratory kidney composite (6.0 versus 9.0 events per 1,000 person-years; hazard ratio 0.66, 95% CI 0.50–

0.88). DAPA-CKD reduced its primary composite by 39% (9.2% versus 14.5%; hazard ratio 0.61, 95% CI 0.51–0.72; $p < 0.001$) with a number needed to treat of 19, and EMPA-KIDNEY reduced kidney disease progression or cardiovascular death by 28% (13.1% versus 16.9%; hazard ratio 0.72, 95% CI 0.64–0.82; $p < 0.001$). In both kidney trials the effect was explicitly consistent in participants with and without diabetes.^{9,19,20,22,25}

Random-effects pooling of these six trial-level composites produced a hazard ratio of 0.65 (95% CI 0.59–0.71; $p < 0.0001$), with moderate and non-significant heterogeneity (Cochran $Q = 7.76$, $df = 5$, $p = 0.170$; $I^2 = 35.6\%$). A previously published meta-analysis restricted to the hardest possible kidney endpoint — dialysis, transplantation or death from kidney disease — reported a relative risk of 0.67 (95% CI 0.52–0.86; $p = 0.0019$) with no heterogeneity, together with a 35% reduction in end-stage kidney disease and a 25% reduction in acute kidney injury. Hypothesis H5 is supported.²⁶

Table 11. Effect of SGLT2 inhibitors on composite kidney outcomes

Trial	Composite kidney outcome as defined	Hazard ratio (95% CI)	Weight (%)
CANVAS Program (2017)	Sustained 40% eGFR reduction, renal replacement therapy or renal death	0.60 (0.47–0.77)	11.4
DECLARE-TIMI 58 (2019)	Renal-specific composite ($\geq 40\%$ eGFR decline to < 60 , ESKD, renal death)	0.53 (0.43–0.66)	14.1
CREDENCE (2019)	ESKD, doubling of serum creatinine, or renal or CV death (primary)	0.70 (0.59–0.82)	19.8
VERTIS CV (Cherney, 2021)	Sustained $\geq 40\%$ eGFR decrease, kidney replacement therapy or	0.66 (0.50–0.88)	9.2

Trial	Composite kidney outcome as defined	Hazard ratio (95% CI)	Weight (%)
	kidney death		
DAPA-CKD (2020)	≥50% sustained eGFR decline, ESKD, or renal or CV death (primary)	0.61 (0.51–0.72)	18.8
EMPA-KIDNEY (2023)	Kidney disease progression or cardiovascular death (primary)	0.72 (0.64–0.82)	26.6
Pooled random-effects estimate (k = 6)	Trial-defined composite kidney outcome	0.65 (0.59–0.71)	100
CANVAS Program (Perkovic, 2018)	Doubling of serum creatinine, ESKD or renal death	0.53 (0.33–0.84)	Not pooled
CREDENCE (2019)	Renal-specific composite (ESKD, creatinine doubling, renal death)	0.66 (0.53–0.81)	Not pooled
CREDENCE (2019)	End-stage kidney disease alone	0.68 (0.54–0.86)	Not pooled
DECLARE-TIMI 58 (Mosenzon, 2019)	ESKD or renal death	0.41 (0.20–0.82)	Not pooled
Meta-analysis of 4 CVOTs (Neuen, 2019)	Dialysis, transplantation or death due to kidney disease	RR 0.67 (0.52–0.86)	Not pooled
Meta-analysis of 4 CVOTs (Neuen, 2019)	Acute kidney injury	RR 0.75 (0.66–0.85)	Not pooled

ESKD = end-stage kidney disease; CVOT = cardiovascular outcome trial. Pooled estimate: HR 0.646 (95% CI 0.587–0.711), $p < 0.0001$, $I^2 = 35.6\%$, $Q = 7.76$ ($df = 5$, $p = 0.170$). Rows marked

'Not pooled' report alternative or more stringent endpoint definitions and are shown for completeness only.

Estimated Glomerular Filtration Rate Slope and Albuminuria

A characteristic and clinically important feature of SGLT2 inhibition is an acute, reversible decline in estimated glomerular filtration rate of approximately 2 to 4 mL/min/1.73 m² within the first weeks of therapy, reflecting restoration of tubuloglomerular feedback and relief of intraglomerular hypertension, followed by long-term preservation of kidney function. In DECLARE-TIMI 58 the mean decrease in eGFR was larger with dapagliflozin at six months, equalized by two years, and was smaller than with placebo at three and four years. Recognition of this haemodynamic pattern is essential to prevent inappropriate discontinuation of therapy.^{24,35}

Across the programme, the placebo-corrected preservation of chronic eGFR slope ranged from approximately 0.5 to 2.4 mL/min/1.73 m² per year. In the CANVAS Program the between-group slope difference was 1.2 mL/min/1.73 m² per year (95% CI 1.0–1.4). In VERTIS CV the chronic slope difference from week 6 to week 156 was 1.19 mL/min/1.73 m² per year (95% CI 0.95–1.42), exceeding the 0.75 mL/min/1.73 m² per year threshold proposed as a surrogate for kidney disease progression, with an eGFR advantage of 2.6 mL/min/1.73 m² at 60 months. In EMPEROR-Preserved the annual slope was slowed by 1.36 mL/min/1.73 m² per year, and in DELIVER by 1.4 mL/min/1.73 m² per year from month 1 to month 36.^{3,25,34,35}

Analyses of the initial eGFR decline have consistently shown it to be prognostically benign under active therapy. In DELIVER, an initial decline exceeding 10% was associated with a higher risk of the primary cardiovascular outcome among placebo recipients (adjusted hazard ratio 1.33, 95% CI 1.10–1.62) but not among dapagliflozin recipients (adjusted hazard ratio 0.90, 95% CI 0.74–1.09; interaction $p = 0.01$), and was not associated with adverse subsequent kidney outcomes. Albuminuria was reduced consistently: by 18% in the CANVAS Program and in EMPA-REG OUTCOME, and by 16.2% at 60 months in VERTIS CV, while DECLARE-TIMI 58 demonstrated a 45% higher likelihood of sustained improvement by at least one albuminuria category (hazard ratio 1.45, 95% CI 1.35–1.56; $p < 0.0001$).^{3,25,35,50}

Table 12. Effect of SGLT2 inhibitors on estimated glomerular filtration rate slope and albuminuria

Trial	Parameter	Placebo-corrected effect of SGLT2 inhibitor
CANVAS Program	Annual eGFR slope	+1.2 mL/min/1.73 m ² /year (95% CI 1.0–1.4) slower decline
VERTIS CV	Chronic eGFR slope, weeks 6–156	+1.19 mL/min/1.73 m ² /year (95% CI 0.95–1.42)
VERTIS CV	eGFR at 60 months	+2.6 mL/min/1.73 m ² (95% CI 1.5–3.6)
DAPA-HF	eGFR slope, day 14–720	–1.09 vs –2.85 mL/min/1.73 m ² /year (p < 0.001)
EMPEROR-Reduced	Annual eGFR slope, CKD / no CKD	+1.11 (0.23–1.98) / +2.41 (1.49–3.32) mL/min/1.73 m ² /year
EMPEROR-Preserved	Annual eGFR slope	+1.36 mL/min/1.73 m ² /year (p < 0.001)
DELIVER	Total / chronic eGFR slope	+0.5 (0.1–0.9) / +1.4 (1.0–1.8) mL/min/1.73 m ² /year
DECLARE-TIMI 58	≥40% sustained eGFR decline to <60	HR 0.54 (0.43–0.67), p < 0.0001
DECLARE-TIMI 58	Sustained ≥1-category improvement in UACR	HR 1.45 (1.35–1.56), p < 0.0001
CANVAS Program	Mean urinary albumin-to-creatinine ratio	–18% (95% CI 16–20)
CANVAS Program	Progression of albuminuria	HR 0.73 (0.67–0.79)
VERTIS CV	Urinary albumin-to-	–16.2% (95% CI –23.9 to –7.6)

Trial	Parameter	Placebo-corrected effect of SGLT2 inhibitor
	creatinine ratio at 60 months	
EMPA-REG OUTCOME	UACR at week 12	−18% (95% CI 14–22); odds of >30% reduction 1.42 (1.27–1.58)

Positive values for eGFR slope denote preservation of kidney function relative to placebo. UACR = urinary albumin-to-creatinine ratio; CKD = chronic kidney disease.

Total and Recurrent Events and All-Cause Hospitalization

Conventional time-to-first-event analysis discards all events subsequent to the first and therefore systematically underestimates the cumulative clinical benefit of therapy in a relapsing condition such as heart failure. Analyses of total events consistently demonstrated larger risk reductions than the corresponding first-event analyses. In EMPA-REG OUTCOME the rate ratio for total MACE was 0.78 (95% CI 0.67–0.91; $p = 0.0020$) compared with a first-event hazard ratio of 0.86, and the rate ratio for total heart failure hospitalizations was 0.58 (95% CI 0.42–0.81; $p = 0.0012$) compared with a first-event hazard ratio of 0.65.^{1,28}

The same pattern was observed across the class. In VERTIS CV the rate ratio for total heart failure hospitalizations was 0.70 (95% CI 0.56–0.87) and for total heart failure hospitalizations or cardiovascular death 0.83 (95% CI 0.72–0.96). In pooled participant-level data from the CANVAS Program and CREDENCE, canagliflozin reduced total heart failure hospitalizations with a mean event ratio of 0.63 (95% CI 0.54–0.73) and the composite of cardiovascular death and total heart failure hospitalizations with a mean event ratio of 0.72 (95% CI 0.65–0.80), with absolute risk reductions numerically larger and numbers needed to treat smaller than for first events. In EMPEROR-Preserved total heart failure hospitalizations fell from 541 to 407 (hazard ratio 0.73, 95% CI 0.61–0.88; $p < 0.001$).^{10,32,15}

All-cause hospitalization, an outcome of major health-economic significance that is essentially immune to endpoint-definition bias, was reduced consistently. In EMPA-REG

OUTCOME it fell from 39.6% to 36.8% (hazard ratio 0.89, 95% CI 0.82–0.96; $p = 0.003$), with a total-events rate ratio of 0.83 (95% CI 0.76–0.91; $p < 0.0001$) corresponding to 50.4 hospitalizations prevented per 1,000 patient-years. In EMPA-KIDNEY, hospitalization from any cause was reduced with a hazard ratio of 0.86 (95% CI 0.78–0.95; $p = 0.003$). In SOLOIST-WHF, sotagliflozin increased days alive and out of hospital by 3% (rate ratio 1.03, 95% CI 1.00–1.06; $p = 0.027$), driven principally by a reduction in days dead.^{2,20,28,45}

Table 13. Effect of SGLT2 inhibitors on total and recurrent events and on all-cause hospitalization

Trial / analysis	Endpoint (total or recurrent events)	Effect estimate (95% CI)
EMPA-REG OUTCOME (McGuire, 2020)	Total three-point MACE	RR 0.78 (0.67–0.91), $p = 0.0020$
EMPA-REG OUTCOME (McGuire, 2020)	Total hospitalizations for heart failure	RR 0.58 (0.42–0.81), $p = 0.0012$
EMPA-REG OUTCOME (McGuire, 2020)	All-cause hospitalization	RR 0.83 (0.76–0.91), $p < 0.0001$
EMPA-REG OUTCOME (Fitchett, 2016)	All-cause hospitalization (36.8% vs 39.6%)	HR 0.89 (0.82–0.96), $p = 0.003$
CANVAS + CREDENCE pooled (Vaduganathan, 2024)	Total heart failure hospitalizations	Mean event ratio 0.63 (0.54–0.73)
CANVAS + CREDENCE pooled (Vaduganathan, 2024)	Total heart failure hospitalizations or CV death	Mean event ratio 0.72 (0.65–0.80)
VERTIS CV (Cosentino, 2024)	Total heart failure hospitalizations	RR 0.70 (0.56–0.87)

Trial / analysis	Endpoint (total or recurrent events)	Effect estimate (95% CI)
2020)		
VERTIS CV (Cosentino, 2020)	Total heart failure hospitalizations or CV death	RR 0.83 (0.72–0.96)
EMPEROR-Preserved (Anker, 2021)	Total heart failure hospitalizations (407 vs 541)	HR 0.73 (0.61–0.88), $p < 0.001$
SOLOIST-WHF (Bhatt, 2021)	Total CV deaths, HF hospitalizations and urgent HF visits (51.0 vs 76.3 per 100 py)	HR 0.67 (0.52–0.85), $p < 0.001$
SCORED (Bhatt, 2021)	Total CV deaths, HF hospitalizations and urgent HF visits (5.6 vs 7.5 per 100 py)	HR 0.74 (0.63–0.88), $p < 0.001$
EMPA-KIDNEY (Herrington, 2023)	Hospitalization from any cause	HR 0.86 (0.78–0.95), $p = 0.003$
SOLOIST-WHF (Szarek, 2021)	Days alive and out of hospital	Rate ratio 1.03 (1.00–1.06), $p = 0.027$

py = patient-years. Rate ratios and mean event ratios derive from negative binomial, Andersen–Gill or proportional-means models that account for within-participant correlation of repeated events.

Cardiometabolic and Cardiac-Structural Intermediates

SGLT2 inhibition produced coherent and reproducible improvements in intermediate phenotypes that plausibly mediate the observed clinical benefit. Systolic blood pressure fell by 2.4 mmHg at 48 months in DECLARE-TIMI 58 and by 6.8 mmHg on 24-hour ambulatory measurement in EMPA-HEART CardioLink-6. Body weight reduction was sustained: in VERTIS CV, 34.9% of ertugliflozin recipients versus 19.4% of placebo recipients achieved at least 5%

weight loss at five years (odds ratio 2.21, 95% CI 1.76–2.77), and 13.6% versus 4.1% achieved at least 10% (odds ratio 3.65, 95% CI 2.39–5.57).^{5,9,21,54}

Cardiac-structural evidence provides direct mechanistic corroboration. In EMPA-HEART CardioLink-6, six months of empagliflozin in patients with type 2 diabetes and coronary artery disease reduced left ventricular mass indexed to body surface area by 3.35 g/m² relative to placebo on cardiac magnetic resonance imaging (95% CI –5.9 to –0.81; $p = 0.01$), accompanied by significant reductions in ambulatory blood pressure and a significant rise in haematocrit ($p = 0.0003$). A subsequent randomized cardiac magnetic resonance trial demonstrated that canagliflozin reduced myocardial extracellular volume, a validated measure of diffuse interstitial fibrosis, by 3.67% relative to sitagliptin at 26 weeks (95% CI –5.33 to –2.01; $p < 0.001$) despite equivalent glycaemic improvement in both arms, providing imaging evidence of a glucose-independent antifibrotic action.^{21,51}

Complementary positron emission tomography evidence demonstrated that dapagliflozin improved myocardial flow reserve in patients with type 2 diabetes and stable coronary artery disease (2.56 to 3.59 with dapagliflozin versus 2.34 to 2.38 with placebo; interaction $p = 0.001$), consistent with amelioration of coronary microvascular dysfunction. Uric acid, a mediator implicated in mediation analyses, was reduced by 0.26 mg/dL at week 260 in VERTIS CV, with a numerically lower incidence of gout-related outcomes (hazard ratio 0.76, 95% CI 0.580–1.002). Formal mediation analysis of EMPA-REG OUTCOME attributed 51.8% and 48.9% of the cardiovascular death benefit to changes in haematocrit and haemoglobin respectively, with multivariable models accounting for up to 94.6% of the effect.^{27,52,53,74}

Table 14. Effect of SGLT2 inhibitors on cardiometabolic and cardiac-structural intermediates

Parameter	Trial	Placebo-corrected effect	Statistical significance
Systolic blood pressure	DECLARE-TIMI 58 (48 months)	–2.4 mmHg (95% CI 1.9–2.9)	$p < 0.0001$

Parameter	Trial	Placebo-corrected effect	Statistical significance
Systolic blood pressure (24-h ambulatory)	EMPA-HEART CardioLink-6	−6.8 mmHg (95% CI −11.2 to −2.3)	p = 0.003
Diastolic blood pressure (24-h ambulatory)	EMPA-HEART CardioLink-6	−3.2 mmHg (95% CI −5.8 to −0.6)	p = 0.02
Left ventricular mass index (CMR)	EMPA-HEART CardioLink-6 (6 months)	−3.35 g/m ² (95% CI −5.9 to −0.81)	p = 0.01
Haematocrit	EMPA-HEART CardioLink-6	Significant elevation vs placebo	p = 0.0003
Body weight — ≥5% reduction at 5 years	VERTIS CV (34.9% vs 19.4%)	Odds ratio 2.21 (1.76–2.77)	Significant
Body weight — ≥10% reduction at 5 years	VERTIS CV (13.6% vs 4.1%)	Odds ratio 3.65 (2.39–5.57)	Significant
Serum uric acid at week 260	VERTIS CV	−0.26 mg/dL (95% CI −0.36 to −0.16)	Significant
Composite gout onset or anti-gout therapy	VERTIS CV (2.6% vs 3.3%)	HR 0.76 (0.580–1.002)	Borderline
Glycated haemoglobin	VERTIS CV insulin substudy (18 weeks)	−0.58% to −0.65%	p < 0.001
Myocardial extracellular volume (CMR)	Canagliflozin vs sitagliptin, 26 weeks	−3.67% (95% CI −5.33 to −2.01)	p < 0.001
Myocardial flow reserve (PET)	DAPAHEART	2.56 → 3.59 with dapagliflozin	p interaction = 0.001

CMR = cardiac magnetic resonance imaging; PET = positron emission tomography. Effects are placebo-corrected unless otherwise stated.

Safety Outcomes

The safety profile of the class was consistent and, with defined exceptions, favourable. Genital mycotic infection was the most frequent adverse effect and was increased in every trial, a mechanistically predictable consequence of sustained glucosuria; in DECLARE-TIMI 58 genital infection leading to study-drug discontinuation occurred in 0.9% versus 0.1% ($p < 0.001$), although serious genital infections were rare and balanced. Diabetic ketoacidosis was consistently increased but remained very rare, occurring in 27 versus 12 participants in DECLARE-TIMI 58 (0.3% versus 0.1%; $p = 0.02$). Urinary tract infection, acute pyelonephritis and urosepsis were balanced between arms.^{1,5,37}

The most contested safety question concerns lower-limb amputation. In the CANVAS Program, canagliflozin was associated with an approximate doubling of amputation risk (6.3 versus 3.4 participants per 1,000 patient-years; hazard ratio 1.97, 95% CI 1.41–2.75), predominantly at the level of the toe or metatarsal. This signal was not reproduced in any subsequent trial. CREDENCE, which enrolled a population at higher baseline amputation risk, found no significant difference in rates of amputation or fracture. In DECLARE-TIMI 58 the hazard ratio for amputation was 1.09 (95% CI 0.84–1.40) and for limb ischaemic events 1.07 (95% CI 0.90–1.26), with no interaction by history of peripheral artery disease. In VERTIS CV amputations occurred in 2.0% and 2.1% of ertugliflozin recipients versus 1.6% of placebo recipients, without significant excess. Contemporary appraisal regards the CANVAS finding as most probably a chance result.^{3,7,38,43}

Several safety findings were favourable. Acute kidney injury occurred less frequently with dapagliflozin in DECLARE-TIMI 58 irrespective of baseline eGFR, blood pressure or diuretic use, and a meta-analysis of four cardiovascular outcome trials demonstrated a 25% reduction in acute kidney injury (relative risk 0.75, 95% CI 0.66–0.85; $p < 0.0001$). Major hypoglycaemia occurred less frequently with dapagliflozin regardless of baseline insulin or sulphonylurea use. In EMPEROR-Preserved, empagliflozin reduced hyperkalaemia or initiation of potassium binders

among mineralocorticoid receptor antagonist users (hazard ratio 0.74, 95% CI 0.56–0.96). Fractures and malignancies were balanced, and fewer cases of bladder cancer occurred with dapagliflozin.^{26,37}

Two adverse effects were specific to the dual SGLT1/2 inhibitor sotagliflozin and are attributable to intestinal SGLT1 inhibition: diarrhoea (6.1% versus 3.4% in SOLOIST-WHF) and severe hypoglycaemia (1.5% versus 0.3%). Hypotension (6.0% versus 4.6%) and acute kidney injury (4.1% versus 4.4%) were not increased. In EMPA-KIDNEY and CREDENCE, rates of serious adverse events overall were similar to or lower than placebo, and in CREDENCE total serious adverse events were less common with active therapy.^{7,17,18,20,43}

Table 15. Safety outcomes of SGLT2 inhibitors across the included randomized controlled trials

Safety outcome	Trial	SGLT2 inhibitor vs placebo	Direction
Genital mycotic infection	EMPA-REG OUTCOME	Increased rate with empagliflozin	Increased risk
Genital infection leading to discontinuation	DECLARE-TIMI 58	0.9% vs 0.1%, $p < 0.001$	Increased risk
Genital mycotic infection (women)	VERTIS CV insulin substudy	3.5% vs 0.0%	Increased risk
Diabetic ketoacidosis	DECLARE-TIMI 58	27 vs 12 patients (0.3% vs 0.1%), $p = 0.02$	Increased risk (rare)
Diabetic ketoacidosis	SCORED / SOLOIST-WHF	More common with sotagliflozin	Increased risk
Lower-limb amputation	CANVAS Program	6.3 vs 3.4 per 1,000 py; HR 1.97 (1.41–2.75)	Increased risk (isolated)
Lower-limb	CREDENCE	No significant difference	Not replicated

Safety outcome	Trial		SGLT2 inhibitor vs placebo	Direction
amputation				
Lower-limb amputation	DECLARE-TIMI	58	HR 1.09 (0.84–1.40); limb ischaemia HR 1.07 (0.90–1.26)	Not replicated
Lower-limb amputation	VERTIS CV		2.0% and 2.1% vs 1.6%	Not significantly increased
Fracture	CREDENCE; DECLARE-TIMI 58		No significant difference in either trial	No increased risk
Acute kidney injury	DECLARE-TIMI	58	Occurred less frequently with dapagliflozin	Reduced risk
Acute kidney injury	Meta-analysis	(Neuen, 2019)	RR 0.75 (0.66–0.85), $p < 0.0001$	Reduced risk
Acute kidney injury	SOLOIST-WHF		4.1% vs 4.4%	No increased risk
Volume depletion	DECLARE-TIMI	58	Balanced between arms across eGFR, BP and diuretic strata	No increased risk
Major hypoglycaemia	DECLARE-TIMI	58	Less frequent with dapagliflozin	Reduced risk
Severe hypoglycaemia	SOLOIST-WHF		1.5% vs 0.3%	Increased risk (sotagliflozin)
Diarrhoea	SOLOIST-WHF		6.1% vs 3.4%	Increased risk (sotagliflozin)
Hypotension	SOLOIST-WHF		6.0% vs 4.6%	No significant

Safety outcome	Trial	SGLT2 inhibitor vs placebo	Direction
			increase
Hyperkalaemia / potassium binder use	EMPEROR-Preserved (MRA users)	HR 0.74 (0.56–0.96)	Reduced risk
Bladder cancer	DECLARE-TIMI 58 (Cahn, 2020)	Fewer cases with dapagliflozin	No increased risk
Serious adverse events overall	EMPA-KIDNEY; CREDENCE	Similar or lower with SGLT2 inhibitor	No increased risk

py = patient-years; MRA = mineralocorticoid receptor antagonist. Rows shaded green denote analyses in which the CANVAS amputation signal was not replicated.

Summary of Effect Estimates Across All Outcome Domains

The pooled and descriptive results for all thirteen outcome domains are consolidated in Table 18. A clear and internally consistent hierarchy of effect emerges. The largest and most homogeneous benefit is observed for composite kidney outcomes (35% relative reduction) and hospitalization for heart failure (32% relative reduction), followed by the composite of cardiovascular death or heart failure hospitalization (22%), all-cause mortality (20%), cardiovascular death (15%) and three-point MACE (11%). At the opposite end of the spectrum, non-fatal myocardial infarction shows only a small and inconsistent effect, and stroke shows none. This gradient is the central empirical finding of this review.^{1,3,5,7,9,11,13,15,16,19,20,26}

Table 16. Master summary of pooled and descriptive effect estimates across all prespecified outcome domains

Outcome domain	k	Pooled HR (95% CI)	p-value	I ²	Q (df), p	Direction
1. Three-point MACE	6	0.89 (0.84–0.94)	<0.0001	0%	4.74 (5), 0.449	Significant reduction
2. Cardiovascular death	8	0.85 (0.77–0.93)	<0.001	40.3%	11.72 (7), 0.110	Significant reduction
3. All-cause mortality	5	0.80 (0.70–0.91)	<0.001	60.6%	10.16 (4), 0.038	Significant reduction
4. Hospitalization for heart failure	5	0.68 (0.61–0.76)	<0.0001	0%	1.39 (4), 0.846	Significant reduction
5. CV death or HF hospitalization	10	0.78 (0.75–0.82)	<0.0001	0%	8.53 (9), 0.482	Significant reduction
6. Non-fatal myocardial infarction	—	Not pooled	—	—	—	Small or no effect

Outcome domain	k	Pooled HR (95% CI)	p-value	I ²	Q (df), p	Direction
7. Fatal or non-fatal stroke	—	Not pooled	—	—	—	No effect
8. Atrial fibrillation / flutter	—	RR 0.79 (0.67–0.93)*	<0.05	—	—	Significant reduction
9. Composite kidney outcome	6	0.65 (0.59–0.71)	<0.0001	35.6%	7.76 (5), 0.170	Significant reduction
10. eGFR slope	—	+0.5 to +2.4 mL/min/1.73 m ² /y	<0.001	—	—	Significant preservation
11. Albuminuria (UACR)	—	–16% to –18%	<0.0001	—	—	Significant reduction
12. Total / recurrent events; all-cause hospitalization	—	RR 0.58 to 0.89	<0.05	—	—	Significant reduction
13. Cardiometabolic and cardiac-structural intermediates	—	See Table 16	<0.05	—	—	Favourable
14. Safety (composite appraisal)	—	See Table 17	—	—	—	Acceptable; class-specific risks

k = number of trials contributing to the pooled estimate. *Pooled relative risk from published meta-analysis of adverse-event data across eight trials. Where pooling was inappropriate because of

heterogeneity of endpoint definition or analytical model, the range of reported estimates is given instead.

Subgroup Analyses and Effect Modification

A large and unusually consistent body of prespecified subgroup evidence was identified. Across more than thirty formal interaction tests spanning atherosclerotic disease status, prevention setting, kidney function, albuminuria, chronic kidney disease status, diabetes and glycaemic status, glycated haemoglobin, sex, age, diabetes duration, ejection fraction, blood pressure, peripheral artery disease and background pharmacotherapy, statistically significant effect modification was demonstrated in only two instances of clinical note. In the CANVAS Program the benefit on cardiovascular death or hospitalized heart failure was greater among participants with a prior history of heart failure (hazard ratio 0.61, 95% CI 0.46–0.80) than among those without (hazard ratio 0.87, 95% CI 0.72–1.06; interaction $p = 0.021$). In DECLARE-TIMI 58 the MACE benefit was greater in participants with longer diabetes duration (interaction trend $p = 0.004$), driven by greater reductions in myocardial infarction and ischaemic stroke.^{4,5}

The overwhelming pattern is one of preserved relative efficacy across every clinically relevant stratum, coupled with steeply increasing absolute benefit as baseline risk rises. In the CANVAS Program, relative effects were constant across KDIGO risk categories while absolute reductions in the primary outcome increased significantly with risk category (trend $p = 0.03$). In pooled CANVAS and CREDENCE data, canagliflozin reduced cardiovascular death or heart failure hospitalization by a constant relative 30% (hazard ratio 0.70, 95% CI 0.62–0.79) across all strata of eGFR and albuminuria, while event rates rose steeply with worsening kidney function. Hypothesis H6 is therefore supported. The consistency of effect across five distinct molecules and across all subgroup domains further supports hypothesis H7, that cardiovascular benefit represents a class effect.^{40,41,47}

The subgroup analyses summarized in Table 20 are drawn from prespecified or prospectively planned secondary publications of the included trials; full bibliographic details, together with a persistent verification link for each, are provided as references 55 to 74 of this review. Collectively these analyses encompass more than 100,000 randomized participants and constitute one of the

most extensively interrogated subgroup evidence bases in modern cardiovascular therapeutics.^{55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74}

Table 17. Prespecified subgroup analyses and tests for effect modification

Effect modifier examined	Trial(s)	Finding	Interaction p-value
Established ASCVD vs multiple risk factors	DECLARE-TIMI 58 (Cahn, 2021)	Consistent effect on CV death/HHF and renal outcome	0.99 and 0.72
Primary vs secondary CV prevention	CANVAS + CREDENCE (Sharma, 2024)	MACE HR 0.84 (0.76–0.94) consistent in both groups	0.86
Primary vs secondary prevention	CREDENCE (Mahaffey, 2019)	HR 0.68 (0.49–0.94) vs 0.85 (0.69–1.06)	0.25
Heart failure at baseline	CANVAS (Rådholm, 2018)	HR 0.61 (0.46–0.80) with HF vs 0.87 (0.72–1.06) without	0.021 (greater benefit with HF)
Baseline eGFR (<60 vs ≥60)	CANVAS (Neuen, 2018)	HR 0.70 (0.55–0.90) vs 0.92 (0.79–1.07)	0.08
Baseline eGFR strata	CREDENCE (Jardine, 2020)	Consistent renal and CV benefit down to eGFR 30	>0.11
Baseline eGFR strata	CANVAS + CREDENCE (Vaduganathan, 2024)	Total HF hospitalization benefit consistent	0.51
KDIGO risk category	CANVAS (Neuen, 2020)	Relative effect consistent; absolute benefit greater at higher risk	0.2 (trend); ARR trend 0.03

Effect examined	modifier	Trial(s)	Finding	Interaction p-value
Albuminuria category		CANVAS (Neuen, 2019)	Proportional effects consistent; absolute benefit greatest with UACR >300	Mostly consistent
Albuminuria and eGFR combined		CANVAS + CREDENCE (Sarraju, 2022)	CV death or HHF HR 0.70 (0.62–0.79) across all strata	>0.40
Chronic kidney disease at baseline		EMPEROR-Reduced (Zannad, 2021)	HR 0.78 (0.65–0.93) with CKD vs 0.72 (0.58–0.90) without	0.63
Chronic kidney disease at baseline		EMPEROR-Preserved (Sharma, 2023)	HR 0.80 (0.69–0.94) with CKD vs 0.75 (0.60–0.95) without	0.67
Baseline eGFR category		DELIVER (Mc Causland, 2023)	Primary outcome benefit not modified by eGFR category	0.16
Diabetes status		DAPA-HF (Petrie, 2020)	HR 0.75 (0.63–0.90) with T2DM vs 0.73 (0.60–0.88) without	0.80
Diabetes / glycaemic status		EMPEROR-Reduced (Anker, 2021)	HR 0.72 (0.60–0.87) with diabetes vs 0.78 (0.64–0.97) without	0.57
Baseline HbA1c (continuous)		EMPEROR-Reduced (Anker, 2021)	No modification of treatment effect	0.40
Baseline HbA1c category		DECLARE-TIMI 58 (Cahn, 2022)	Benefit preserved including HbA1c <7%	>0.05

Effect examined	modifier	Trial(s)	Finding	Interaction p-value
Diabetes status		DAPA-CKD (Wheeler, 2021)	HR 0.64 (0.52–0.79) with T2DM vs 0.50 (0.35–0.72) without	0.24
Sex		DECLARE-TIMI 58 (O'Donoghue, 2021)	CV death/HHF HR 0.84 women vs 0.83 men	0.90
Sex		EMPEROR-Preserved (Butler, 2022)	HR 0.75 women vs 0.81 men	0.54
Age category		EMPA-REG OUTCOME (Monteiro, 2019)	CV death benefit consistent; MACE greater in older	0.484 (CV death); 0.047 (MACE)
Age category		EMPEROR-Reduced (Filippatos, 2022)	Consistent across <65, 65–74 and ≥75 years	0.24 (trend)
Age category		CANVAS + CREDENCE (Siriwardana, 2025)	CV and kidney benefit consistent across age	>0.10
Duration of diabetes		CANVAS (Young, 2021)	MACE benefit consistent across duration strata	>0.17
Duration of diabetes		DECLARE-TIMI 58 (Bajaj, 2020)	CV death/HHF consistent; MACE greater in longer duration	0.76 and 0.004
Background renin–angiotensin blockade, beta-blocker, diuretic,		DECLARE-TIMI 58 (Oyama, 2022)	Cardiorenal benefit consistent regardless of background therapy	>0.05

Effect examined	modifier	Trial(s)	Finding	Interaction p-value
MRA				
Background guideline-directed HF therapy		EMPEROR-Reduced (Verma, 2021)	Benefit irrespective of triple therapy	0.77
Baseline systolic blood pressure		DECLARE-TIMI 58 (Furtado, 2022); EMPEROR-Preserved (Böhm, 2022)	HHF and renal benefit independent of baseline blood pressure	0.28 / 0.69
Peripheral artery disease		DECLARE-TIMI 58 (Bonaca, 2020)	CV death/HHF HR 0.86 with PAD vs 0.82 without	0.79
Ejection fraction		VERTIS CV (Cosentino, 2020)	Greater first-HHF benefit with EF ≤45% (HR 0.48, 0.30–0.76)	0.40 (prior HF)
Ejection fraction		DELIVER (Solomon, 2022)	Benefit consistent above and below EF 60%	Not significant

ASCVD = atherosclerotic cardiovascular disease; HHF = hospitalization for heart failure; MRA = mineralocorticoid receptor antagonist; PAD = peripheral artery disease; EF = ejection fraction; KDIGO = Kidney Disease: Improving Global Outcomes. Interaction p-values are those reported in the source publication.

DISCUSSION

Summary of Principal Findings

This systematic review of 21 randomized controlled trial reports representing 17 distinct trials and approximately 105,000 randomized participants demonstrates that SGLT2 inhibition significantly reduces the risk of cardiovascular events in patients with type 2 diabetes mellitus. Statistically significant pooled reductions were demonstrated in six of the principal outcome domains: three-point MACE by 11%, cardiovascular death by 15%, all-cause mortality by 20%,

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hospitalization for heart failure by 32%, the composite of cardiovascular death or heart failure hospitalization by 22%, and composite kidney outcomes by 35%. Each of these pooled estimates was significant at conventional thresholds, and three of them — MACE, heart failure hospitalization and the cardiovascular death or heart failure composite — exhibited complete absence of between-trial heterogeneity.^{1,3,5,7,9,11,13,15,16,19,20}

The central and most clinically instructive finding, however, is not simply that benefit exists but that it is unevenly distributed across the components of cardiovascular risk. A reproducible hierarchy of effect emerges, in which cardiorenal and heart failure endpoints are reduced substantially and uniformly, mortality endpoints are reduced moderately and heterogeneously, atherothrombotic coronary endpoints are affected only marginally and principally in high-risk coronary phenotypes, and cerebrovascular endpoints are not affected at all. This hierarchy is summarized in Table 21 and constitutes the organizing principle for interpretation of the entire evidence base.^{1,26,28}

Table 18. Hierarchy of treatment effect across cardiovascular outcome domains

Rank	Outcome domain	Pooled relative risk reduction	Heterogeneity (I ²)	Inference
1	Composite kidney outcome	35%	36%	Largest effect; cardiorenal axis
2	Hospitalization for heart failure	32%	0%	Uniform class effect
3	CV death or HF hospitalization	22%	0%	Uniform class effect
4	All-cause mortality	20%	61%	Risk-dependent
5	Cardiovascular death	15%	40%	Risk-dependent
6	Three-point MACE	11%	0%	Modest but

Rank	Outcome domain	Pooled relative risk reduction	Heterogeneity (I ²)	Inference
				consistent
7	Non-fatal myocardial infarction	≈20% for total events only	Not estimable	Confined to high-risk coronary phenotypes
8	Fatal or non-fatal stroke	None	Not estimable	No demonstrable effect

Relative risk reductions derive from the pooled random-effects estimates presented in Tables 6 to 13. I² values quantify between-trial heterogeneity.

Interpretation by Outcome Domain

The heart failure signal is the dominant and most reliable effect

The reduction in hospitalization for heart failure was demonstrated in every trial that reported it, with individual point estimates confined to the narrow interval 0.61 to 0.73 and an I² of precisely zero. This degree of consistency is unusual in cardiovascular therapeutics and is difficult to reconcile with anything other than a genuine, uniform pharmacological class effect. The dissociation observed within VERTIS CV is particularly informative: ertugliflozin failed to demonstrate superiority for MACE or for the cardiovascular death or heart failure composite, yet significantly reduced first heart failure hospitalization by 30% and total heart failure hospitalizations by 30%. A single trial thus internally demonstrates that the heart failure effect and any putative antiatherosclerotic effect are mechanistically separable.^{9,10}

The extension of this benefit across the entire ejection fraction spectrum, established by EMPEROR-Preserved and DELIVER, is of major clinical importance because heart failure with preserved ejection fraction had previously been refractory to essentially all disease-modifying therapy. Approximately half of the participants in each of these trials had diabetes, and in both the treatment effect was explicitly consistent irrespective of diabetes status. The relevance of this observation to the diabetic population is heightened by the fact that heart failure with preserved

ejection fraction is the phenotype most strongly associated with the metabolic and inflammatory milieu of type 2 diabetes.^{15,16}

The mortality signal is real but risk-dependent

The moderate heterogeneity observed for cardiovascular death (I^2 40.3%) and all-cause mortality (I^2 60.6%) requires careful interpretation and should not be construed as evidence of inconsistent drug efficacy. The distribution of individual estimates maps closely onto baseline absolute risk: the largest effects were observed in EMPA-REG OUTCOME, in which all participants had established atherosclerotic disease and the placebo cardiovascular death rate was 5.9% over 3.1 years, and in DAPA-CKD, in which all participants had albuminuric chronic kidney disease. The smallest effects were observed in DECLARE-TIMI 58, in which almost 60% of participants were enrolled for multiple risk factors rather than established disease and the background event rate was correspondingly low. Where the absolute event rate is low, even a preserved relative effect will produce a confidence interval crossing unity.^{1,5,19}

This interpretation is directly supported by the subgroup evidence. In DECLARE-TIMI 58 the reduction in cardiovascular death or heart failure hospitalization was quantitatively identical in the primary-prevention and secondary-prevention cohorts (interaction $p = 0.99$), and in the pooled CANVAS and CREDENCE dataset the MACE reduction was identical in primary and secondary prevention (interaction $p = 0.86$). Relative efficacy is constant; absolute benefit is not.^{55,56}

The absence of a stroke effect is mechanistically informative

The complete absence of benefit on stroke, with a total-event rate ratio of 1.10 in the prespecified EMPA-REG OUTCOME analysis, is the single most discriminating observation in the mechanistic debate. SGLT2 inhibition lowers systolic blood pressure by approximately 2 to 7 mmHg. On the basis of the classical antihypertensive literature, in which a 10 mmHg systolic reduction is associated with an approximate 27% reduction in stroke, a detectable stroke benefit would have been anticipated in trials of this size and duration. Its complete absence indicates that blood pressure reduction is not the operative mechanism, and that the class does not meaningfully modify cerebrovascular atherothrombosis or cardioembolic risk despite reducing incident atrial fibrillation.^{6,28,31}

Mechanistic Considerations

The pattern of effect described above is best explained by a haemodynamic, metabolic and antifibrotic mechanism operating at the level of the myocardium and the nephron, rather than by an antiatherosclerotic mechanism. The formal mediation analysis of EMPA-REG OUTCOME provides the strongest single line of evidence: changes in haematocrit and haemoglobin mediated 51.8% and 48.9% respectively of the reduction in cardiovascular death, whereas changes in glycated haemoglobin, fasting glucose and uric acid mediated at most 29.3%. Multivariable models incorporating haematocrit, fasting glucose, uric acid and urinary albumin-to-creatinine ratio accounted for 85.2% to 94.6% of the effect.²⁷

Direct imaging evidence corroborates this account. Empagliflozin produced regression of left ventricular mass on cardiac magnetic resonance within six months, accompanied by a significant rise in haematocrit. Canagliflozin reduced myocardial extracellular volume — a validated marker of diffuse interstitial fibrosis — by 3.67% relative to sitagliptin despite identical glycated haemoglobin reduction in both arms, demonstrating a glucose-independent antifibrotic action. Dapagliflozin improved myocardial flow reserve on positron emission tomography, indicating amelioration of coronary microvascular dysfunction. Haemodynamic studies demonstrated rapid improvement in left ventricular filling pressure, detectable from the first day of treatment and sustained, without change in cardiac index or systemic vascular resistance, providing a physiological explanation for the very early separation of heart failure event curves.^{21,51,52}

The renal mechanism is equally well characterized. Inhibition of proximal tubular sodium and glucose reabsorption increases distal sodium delivery to the macula densa, restoring tubuloglomerular feedback, constricting the afferent arteriole and relieving intraglomerular hypertension. This produces the characteristic acute reversible fall in estimated glomerular filtration rate followed by long-term preservation of the chronic slope, a pattern observed without exception across the programme. Because chronic kidney disease is among the most powerful multipliers of cardiovascular risk in diabetes, this renal action constitutes an indirect but substantial cardiovascular protective pathway.^{24,25,26,35}

Conversely, glycaemic improvement can be excluded as the principal mediator. The magnitude of glycated haemoglobin reduction achieved is modest, treatment effect is not modified by baseline glycated haemoglobin either as a categorical or a continuous variable, and full benefit is preserved in participants with prediabetes and normoglycaemia in whom empagliflozin did not lower glycated haemoglobin at all. This is the decisive refutation of the glucocentric hypothesis for this drug class.^{14,70}

Table 19. Proposed mechanisms of cardiovascular benefit and their consistency with the observed hierarchy of effect

Proposed mechanism	Supporting randomized evidence	Consistency with observed outcome hierarchy
Plasma volume contraction and haemoconcentration	Mediation analysis of EMPA-REG OUTCOME: haematocrit mediated 51.8% and haemoglobin 48.9% of the CV death benefit; multivariable models 94.6%. Haematocrit rose significantly in EMPA-HEART CardioLink-6 ($p = 0.0003$)	Strongly consistent: explains large HF effect and absence of stroke effect
Natriuresis and reduction in cardiac preload/afterload	Empagliflozin reduced E/e' (LV filling pressure) from day 1 without change in cardiac index or systemic vascular resistance	Consistent: rapid separation of HF event curves within 3 months
Regression of left ventricular hypertrophy	EMPA-HEART CardioLink-6: LV mass index -3.35 g/m^2 at 6 months on CMR	Consistent with structural reverse remodelling
Attenuation of myocardial interstitial	Canagliflozin reduced CMR extracellular volume by 3.67% vs sitagliptin at equal	Consistent: glucose-independent antifibrotic

Proposed mechanism	Supporting randomized evidence	Consistency with observed outcome hierarchy
fibrosis	glycaemic control	action
Improvement in coronary microvascular function	DAPAHEART: myocardial flow reserve 2.56 → 3.59 with dapagliflozin (p interaction = 0.001)	Consistent with modest MI benefit in coronary disease
Shift in myocardial substrate utilization	Empagliflozin reduced myocardial glucose uptake by 57% without change in free fatty acid uptake or oxygen consumption	Partially consistent; modest magnitude
Reduction in systemic inflammation	Dapagliflozin reduced plasma IL-1 β and preserved PBMC mitochondrial respiration over 12 months	Plausible contributory mechanism
Improvement in vascular function	Empagliflozin improved endothelium-independent vasodilation by 21% and reduced 24-h systolic BP by 5 mmHg	Weakly consistent; blood pressure alone cannot explain the absent stroke effect
Restoration of tubuloglomerular feedback	Acute reversible eGFR dip followed by preserved chronic slope in every trial; UACR reduced 16–18%	Strongly consistent: explains the dominant kidney effect
Uric acid lowering	VERTIS CV: uric acid -0.26 mg/dL; mediation 29–50%; gout composite HR 0.76	Contributory
Glycaemic improvement	HbA1c reduction of 0.5–0.9%; benefit preserved in normoglycaemic and non-diabetic participants; no modification by	Not consistent: benefit is glucose-independent

Proposed mechanism	Supporting randomized evidence	Consistency with observed outcome hierarchy
	baseline HbA1c	

CMR = cardiac magnetic resonance; LV = left ventricular; E/e' = ratio of early mitral inflow velocity to early diastolic mitral annular velocity; PBMC = peripheral blood mononuclear cell; IL-1 β = interleukin-1 beta; UACR = urinary albumin-to-creatinine ratio.

Class Effect Versus Molecule-Specific Effect

The evidence supports a predominantly class-wide effect with some quantitative variation between molecules. The complete absence of heterogeneity for heart failure hospitalization and for the cardiovascular death or heart failure composite, across trials of empagliflozin, dapagliflozin, canagliflozin, ertugliflozin and sotagliflozin, is incompatible with substantial molecule-specific differences on these endpoints. Comparative appraisal of the four principal cardiovascular outcome trials has attributed the apparent divergence in headline results principally to differences in baseline kidney filtration function and albuminuria — mean eGFR ranged from 85.2 mL/min/1.73 m² in DECLARE-TIMI 58 to 56.2 in CREDENCE, and median urinary albumin-to-creatinine ratio from 12.3 mg/g in CANVAS to 927 mg/g in CREDENCE — rather than to intrinsic pharmacological differences.⁴¹

Some molecule-level nuance nonetheless persists. The cardiovascular death benefit of empagliflozin in EMPA-REG OUTCOME has not been replicated in magnitude by any other agent, although the confidence intervals of the individual trials overlap substantially and the difference may reflect population selection rather than pharmacology. The dual SGLT1/2 inhibitor sotagliflozin demonstrated efficacy comparable to selective SGLT2 inhibitors on heart failure and composite cardiovascular endpoints, but carried an additional burden of diarrhoea and severe hypoglycaemia attributable to intestinal SGLT1 inhibition, indicating that dual inhibition confers no evident efficacy advantage while adding tolerability cost. Hypothesis H7 is therefore supported for efficacy but qualified for safety.^{1,17,18,41}

Comparison with the Existing Synthesis Literature

The present findings are directionally concordant with prior syntheses while adding outcome-level granularity. A previous meta-analysis restricted to kidney endpoints reported a 33% reduction in dialysis, transplantation or death from kidney disease, a 35% reduction in end-stage kidney disease and a 25% reduction in acute kidney injury, with an I^2 of 0% for the primary endpoint, closely paralleling the pooled kidney estimate of 0.65 derived here. A comparative appraisal of class effects across the four principal cardiovascular outcome trials reached the same conclusion regarding the primacy of baseline kidney function and albuminuria as determinants of absolute benefit.^{26,41}

Contemporary real-world evidence provides external validation. A Danish nationwide target trial emulation comparing SGLT2 inhibitors with dipeptidyl peptidase-4 inhibitors in 13,524 individuals with type 2 diabetes and cardiovascular disease found absolute three-year risk differences favouring SGLT2 inhibition of 2.8 percentage points for MACE, 5.1 for heart failure hospitalization and 3.1 for all-cause mortality — absolute benefits larger than the corresponding intention-to-treat estimates from the randomized trials, consistent with the effect of treatment adherence and with the higher baseline risk of unselected clinical populations. Notably, that analysis also detected a 2.4 percentage point reduction in stroke, a finding not corroborated by randomized data and most plausibly attributable to residual confounding.⁴⁶

An important consideration in applying trial evidence to practice concerns generalizability. A systematic review of eligibility across 1,703,519 unselected patients with type 2 diabetes found that the proportion meeting entry criteria was 49.5% for DECLARE-TIMI 58, 36.4% for the CANVAS Program, 19.0% for VERTIS CV and only 17.0% for EMPA-REG OUTCOME. The broad DECLARE-TIMI 58 population is therefore the most representative of routine clinical practice, which lends particular weight to that trial's demonstration that heart failure and kidney benefit are preserved even in primary prevention, while atherothrombotic benefit is not.^{48,55}

Effect Modification and Personalization of Therapy

The subgroup evidence base assembled in this review is unusually large and unusually consistent. Across more than thirty formal interaction tests, effect modification of clinical significance was identified in only two instances, and in both the direction favoured greater benefit

in higher-risk patients. Relative efficacy was preserved irrespective of established atherosclerotic disease, prevention setting, baseline eGFR down to 20–30 mL/min/1.73 m², albuminuria category, chronic kidney disease status, heart failure status, ejection fraction stratum, diabetes and glycaemic status, glycated haemoglobin including values below 7%, sex, age including participants aged 75 years and over, diabetes duration, systolic blood pressure including normotensive participants, peripheral artery disease, and background therapy with renin–angiotensin system inhibitors, beta-blockers, diuretics, mineralocorticoid receptor antagonists or sacubitril/valsartan.^{55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,73}

The clinical corollary is that the decision to prescribe should be driven by absolute risk rather than by any individual clinical characteristic, and that concerns commonly cited as reasons for withholding therapy — advanced age, impaired kidney function, normotension, well-controlled glycaemia, or maximal background heart failure therapy — are not supported by the randomized evidence. Analysis by KDIGO risk category in the CANVAS Program showed constant relative effects but significantly increasing absolute benefit with rising risk (trend $p = 0.03$), and pooled CANVAS and CREDENCE data demonstrated a constant 30% relative reduction in cardiovascular death or heart failure hospitalization across all eGFR and albuminuria strata. Table 23 translates these observations into a prioritized clinical framework.^{40,47}

Modelling of combination therapy extends this reasoning. In patients with type 2 diabetes and albuminuria, the projected combination of an SGLT2 inhibitor, a glucagon-like peptide-1 receptor agonist and a non-steroidal mineralocorticoid receptor antagonist was associated with a hazard ratio of 0.65 for MACE relative to conventional care, an absolute risk reduction of 4.4% over three years and a number needed to treat of 23, with an estimated gain of 3.2 MACE-free years and 2.4 additional years of overall survival for a patient commencing therapy at age 50. Prespecified analyses of the SOUL and FLOW trials found no evidence of heterogeneity in the benefit of semaglutide according to concomitant SGLT2 inhibitor use, and no safety interaction, supporting the combinability of these classes.^{42,75,76}

Table 20. Prioritized clinical framework for SGLT2 inhibitor prescribing in type 2 diabetes

Clinical phenotype	Best supporting trial evidence	Absolute benefit	Priority
T2DM with albuminuric CKD (UACR >300, eGFR 30–<90)	CREDENCE; DAPA-CKD	NNT 19–22 for the primary composite over 2.4–2.6 years	Highest
T2DM with heart failure with reduced ejection fraction	DAPA-HF; EMPEROR-Reduced	NNT 21 over 18 months for worsening HF or CV death	Highest
T2DM with heart failure with preserved or mildly reduced EF	EMPEROR-Preserved; DELIVER	NNT 31–33 over 2.0–2.3 years	High
T2DM with recent hospitalization for worsening heart failure	SOLOIST-WHF	25.3 fewer events per 100 patient-years	High (initiate before discharge)
T2DM with established ASCVD, particularly prior myocardial infarction	EMPA-REG OUTCOME; DECLARE-TIMI 58 prior-MI subgroup	NNT 35 over 3 years for CV death or HHF; ARR 2.6% for MACE with prior MI	High
T2DM with CKD without albuminuria	EMPA-KIDNEY; SCORED	NNT 27 over 2 years	High
T2DM with multiple risk factors but no established ASCVD, HF or CKD	DECLARE-TIMI 58 primary-prevention cohort	HHF HR 0.64 (0.46–0.88); renal HR 0.51 (0.37–0.69)	Moderate; benefit concentrated on HF and kidney
T2DM with well-	DECLARE-TIMI 58	Benefit preserved; no	Treat on risk,

Clinical phenotype	Best supporting trial evidence	Absolute benefit	Priority
controlled HbA1c (<7%) and cardiorenal disease	HbA1c analysis	interaction by baseline HbA1c	not on glycaemia

NNT = number needed to treat; ARR = absolute risk reduction; ASCVD = atherosclerotic cardiovascular disease; UACR = urinary albumin-to-creatinine ratio; HHF = hospitalization for heart failure.

Safety Profile and the Balance of Benefit and Risk

The safety profile is dominated by two predictable, manageable and generally non-serious effects: genital mycotic infection, an obligate consequence of glucosuria that is readily treated and rarely leads to permanent discontinuation, and diabetic ketoacidosis, which although consistently increased in relative terms remains very rare in absolute terms and is largely preventable through sick-day guidance, avoidance of prolonged fasting and perioperative interruption of therapy. Neither of these effects offsets the magnitude of cardiorenal benefit demonstrated in this review.^{1,5,37}

The amputation question warrants explicit resolution because it has been a principal driver of therapeutic inertia. The near-doubling of amputation risk observed in the CANVAS Program was not reproduced in CREDENCE, which enrolled a population at substantially higher baseline amputation risk and found no significant difference, nor in DECLARE-TIMI 58, in which amputation and limb ischaemic events were balanced with no interaction by peripheral artery disease status, nor in VERTIS CV. Contemporary consolidated appraisal of the canagliflozin programme concludes that the amputation and fracture signals of CANVAS appear to have been spurious chance findings. The regulatory boxed warning that followed the CANVAS publication has since been removed. Careful foot examination remains prudent, but the evidence does not support withholding therapy on this basis.^{3,7,38,43}

Several safety findings are actively reassuring and are frequently under-appreciated. Acute kidney injury is reduced rather than increased, by 25% in pooled analysis of four cardiovascular

outcome trials, a counterintuitive but robust finding that should reframe clinical anxiety regarding the initial eGFR dip. Major hypoglycaemia is reduced, including in patients receiving insulin or sulphonylureas. Hyperkalaemia and the need for potassium binders are reduced in mineralocorticoid receptor antagonist users, facilitating the retention of guideline-directed heart failure therapy. Fractures, malignancies and urinary tract infections are not increased, and fewer bladder cancers occurred with dapagliflozin. Blinded withdrawal studies further demonstrated that benefit persists after years of treatment and dissipates rapidly on discontinuation, underscoring the importance of therapeutic continuity.^{26,37,72,73}

Clinical and Guideline Implications

The findings of this review support a reconceptualization of SGLT2 inhibitors from glucose-lowering agents with incidental cardiovascular benefit to organ-protective agents with incidental glucose-lowering activity. Three practical consequences follow. First, initiation should be indexed to cardiorenal risk rather than to glycated haemoglobin, since benefit is preserved at glycated haemoglobin below 7% and is not modified by baseline glycaemia. Second, the agent should be positioned early rather than as a late add-on, since benefit is independent of diabetes duration, of the number of background glucose-lowering agents and of insulin use, and since pooled analysis of the canagliflozin programme suggests that earlier treatment confers consistent cardiorenal benefit. Third, therapy should be continued through the initial eGFR decline and through intercurrent illness wherever safe, since discontinuation results in rapid loss of benefit.^{64,70,72}

The evidence also supports initiation in the acute and peri-discharge setting. In SOLOIST-WHF, sotagliflozin was commenced before discharge in 48.8% of participants and a median of two days after discharge in the remainder, and benefit was consistent regardless of timing; post-hoc analysis of participants who began study drug on or before discharge demonstrated a 46% reduction in cardiovascular death or heart failure events at 90 days and a 61% reduction in all-cause mortality at 90 days. In DELIVER, dapagliflozin was equally effective and equally safe when initiated during or shortly after a heart failure hospitalization. The traditional practice of deferring initiation to the outpatient setting is therefore not evidence-based.^{17,44}

Implications for Indonesia and Comparable Health Systems

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Several features of the Indonesian clinical context render these findings particularly consequential. Type 2 diabetes in Indonesia frequently presents late, with a high prevalence of established nephropathy and undiagnosed heart failure at first specialist contact — precisely the phenotypes in which the absolute benefit demonstrated in this review is greatest and the number needed to treat lowest. Access to renal replacement therapy is constrained and constitutes a major cost burden on the national health insurance scheme, so that a 35% reduction in composite kidney outcomes and a 32% relative reduction in end-stage kidney disease carry disproportionate system-level value.^{7,19,20,26}

Because hospitalization is the dominant driver of direct medical cost in diabetic cardiovascular disease, the consistent reductions in all-cause hospitalization — 11% in EMPA-REG OUTCOME, 14% in EMPA-KIDNEY, and 17% in the total-events analysis — provide an economic argument that is independent of the mortality argument. Where budget constraints preclude universal prescribing, the prioritized framework in Table 23 offers a rational, evidence-anchored basis for allocation, directing therapy first to patients with albuminuric chronic kidney disease and to those with heart failure of any ejection fraction. Implementation should be accompanied by structured patient education regarding genital hygiene, sick-day rules and the avoidance of prolonged fasting, which is of particular relevance during Ramadan.^{2,20,28}

Strengths of This Review

- Comprehensive, multi-database search with independent duplicate screening, extraction and appraisal, and substantial inter-reviewer agreement ($\kappa = 0.87$).
- Outcome-stratified architecture reporting thirteen discrete domains, exposing the internal structure of the treatment effect rather than obscuring it within a single composite.
- Integration within one appraisal framework of the classical cardiovascular outcome trials, the dedicated heart failure trials across the full ejection fraction spectrum, and the dedicated kidney outcome trials, with explicit annotation of diabetes prevalence and of every treatment-by-diabetes interaction test.^{12,14,15,16,19,22}

- Uniform random-effects generic inverse-variance synthesis of adjudicated hazard ratios with formal quantification of heterogeneity for every pooled domain, permitting the internal consistency of the class effect to be tested rather than assumed.
- Systematic verification of every cited reference through the Consensus academic search engine restricted to peer-reviewed medical literature, with a persistent verification link supplied for each entry, providing a fully auditable evidentiary chain.
- Formal application of the Cochrane RoB 2 instrument at domain level and of the GRADE framework at outcome level, with transparent justification for every downgrade.

Directions for Future Research

Several questions remain open. Direct head-to-head randomized comparison between individual SGLT2 inhibitors has not been undertaken, and the ongoing ENVELOP trial, which will randomize 2,862 participants with type 2 diabetes to enavogliflozin versus dapagliflozin or empagliflozin with a composite cardiorenal primary endpoint, will provide the first such comparison. The optimal position of SGLT2 inhibition relative to metformin in early type 2 diabetes remains unresolved and is being addressed by the register-based SMARTTEST trial, which randomized 2,072 participants with diabetes of less than four years' duration to dapagliflozin or metformin.^{80,81}

Populations systematically excluded from the trials appraised here — patients with eGFR below 20 to 25 mL/min/1.73 m², patients receiving maintenance dialysis, and kidney transplant recipients — are being addressed by the Renal Lifecycle trial. Further priorities include the definitive characterization of the atrial fibrillation effect using prospective rhythm monitoring rather than adverse-event ascertainment; the elucidation of mechanisms underlying benefit in heart failure with preserved ejection fraction, where mechanistic randomized studies have demonstrated improvements in exercise capacity, left atrial function and diastolic reserve; and the generation of cost-effectiveness and implementation data from South-East Asian populations, since almost all existing economic evaluation derives from high-income health systems with different unit costs and different baseline event rates.^{82,83,84}

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

This systematic review of 21 randomized controlled trial reports representing 17 distinct trials and approximately 105,000 randomized participants establishes that SGLT2 inhibitor therapy significantly and reproducibly reduces the risk of cardiovascular events in adults with type 2 diabetes mellitus. Pooled random-effects estimates demonstrated statistically significant reductions in three-point major adverse cardiovascular events (HR 0.89, 95% CI 0.84–0.94; $p < 0.0001$), cardiovascular death (HR 0.85, 95% CI 0.77–0.93; $p < 0.001$), all-cause mortality (HR 0.80, 95% CI 0.70–0.91; $p < 0.001$), hospitalization for heart failure (HR 0.68, 95% CI 0.61–0.76; $p < 0.0001$), the composite of cardiovascular death or heart failure hospitalization (HR 0.78, 95% CI 0.75–0.82; $p < 0.0001$) and composite kidney outcomes (HR 0.65, 95% CI 0.59–0.71; $p < 0.0001$). All seven prespecified hypotheses were supported.^{1,3,5,7,9,11,13,15,16,19,20}

The benefit is not uniformly distributed across the components of cardiovascular risk. It is greatest and most homogeneous for kidney and heart failure endpoints, intermediate and risk-dependent for mortality endpoints, modest for coronary atherothrombotic endpoints and absent for stroke. The complete absence of between-trial heterogeneity for heart failure hospitalization and for the cardiovascular death or heart failure composite, observed across five distinct molecules and across populations ranging from primary prevention to advanced chronic kidney disease, establishes cardiorenal protection as a genuine and uniform class property rather than a molecule-specific phenomenon.^{26,41}

Relative efficacy is preserved across every clinically relevant subgroup examined, including advanced age, impaired kidney function, normotension, well-controlled glycaemia, absence of diabetes, and maximal background guideline-directed therapy, whereas absolute benefit scales steeply with baseline cardiorenal risk. Certainty of evidence is high for the principal heart failure and kidney outcome domains and for three-point MACE, and moderate for the mortality domains. The safety profile is acceptable and dominated by manageable genital mycotic infection and by rare diabetic ketoacidosis; the isolated amputation signal of the CANVAS Program was not replicated in any subsequent trial and is now best regarded as a chance finding.^{3,7,26,38,43}

SGLT2 inhibitors should therefore be regarded as foundational organ-protective therapy in type 2 diabetes mellitus rather than as glucose-lowering agents alone, and should be positioned alongside renin–angiotensin system blockade and statin therapy as a core component of cardiorenal risk reduction in this population.⁴²

Recommendations

For clinical practice

- Initiate an SGLT2 inhibitor in every patient with type 2 diabetes and established atherosclerotic cardiovascular disease, heart failure of any ejection fraction, or chronic kidney disease, irrespective of glycated haemoglobin and irrespective of the adequacy of existing glycaemic control.^{1,7,15,16,19}
- Accord highest priority to patients with albuminuric chronic kidney disease and to patients with heart failure with reduced ejection fraction, in whom the number needed to treat is lowest (19 to 22 over approximately 2.5 years).^{7,11,19}
- Initiate therapy during or immediately after hospitalization for worsening heart failure rather than deferring to the outpatient setting, since benefit accrues within 30 to 90 days of initiation.^{17,44}
- Anticipate and do not react to the initial fall in estimated glomerular filtration rate; it is haemodynamic, reversible, prognostically benign under active therapy, and followed by long-term preservation of kidney function.^{35,71}
- Do not withhold therapy on grounds of advanced age, eGFR down to 20 to 25 mL/min/1.73 m², normotension, glycated haemoglobin below 7%, peripheral artery disease, or maximal background heart failure therapy, none of which modifies relative efficacy.^{59,61,62,63,67,68}
- Counsel all patients on genital hygiene, on sick-day rules including temporary discontinuation during acute intercurrent illness, dehydration or prolonged fasting, and on perioperative interruption, in order to minimize the risk of genital mycotic infection and of euglycaemic diabetic ketoacidosis.^{5,37}
- Maintain therapy long term and avoid unnecessary interruption, since benefit persists for years but dissipates rapidly following withdrawal.⁷²

- Perform regular foot examination as part of routine diabetes care, while recognizing that the randomized evidence taken as a whole does not support withholding therapy because of amputation concern.^{7,38,43}

For health policy

- Ensure formulary availability and affordable access to at least one SGLT2 inhibitor within national health insurance schemes, prioritizing the high-absolute-benefit phenotypes defined in Table 23.^{42,47}
- Incorporate cardiorenal risk stratification — comprising estimated glomerular filtration rate, urinary albumin-to-creatinine ratio and natriuretic peptide measurement where available — into routine diabetes care pathways, since these variables identify the patients in whom absolute benefit is greatest.^{40,47}
- Recognize the reduction in all-cause hospitalization as a system-level economic outcome when conducting health-technology assessment, independent of the mortality benefit.^{2,20,28}

For future research

- Conduct head-to-head randomized comparisons between individual SGLT2 inhibitors with adequately powered cardiorenal endpoints.⁸¹
- Define the role of SGLT2 inhibition as first-line therapy in early type 2 diabetes relative to metformin.⁸⁰
- Extend randomized evidence to populations excluded from the existing programme, including advanced chronic kidney disease, maintenance dialysis and kidney transplantation.⁸²
- Characterize the atrial fibrillation effect using prospective rhythm monitoring rather than adverse-event ascertainment.^{6,31}
- Generate cost-effectiveness and implementation evidence from South-East Asian and other middle-income populations, in which baseline event rates, unit costs and health-system structures differ materially from those of the high-income settings in which existing economic analyses were conducted.⁴⁸

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