



Sodium–Glucose Cotransporter-2 (SGLT-2) Inhibitors for Slowing the Progression of Chronic Kidney Disease: A Systematic Review of Randomized Controlled Trials and Primary Studies

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ABSTRACT

Introduction: Chronic kidney disease (CKD) is a progressive disorder leading to kidney failure and cardiovascular death, with substantial residual risk persisting despite renin–angiotensin system (RAS) blockade. Sodium–glucose cotransporter-2 (SGLT-2) inhibitors have demonstrated kidney-protective effects apparently independent of glycaemic control. This systematic review synthesized randomized controlled trial (RCT) evidence on efficacy and safety of SGLT-2 inhibitors for slowing CKD progression across diabetic and non-diabetic aetiologies.

Methods: The study strictly adhered to the Preferred Reporting Items for Systematic Review and (PRISMA) 2020 guidelines to 30 June 2026 for RCTs comparing SGLT-2 inhibitors with placebo or active control in adults with CKD or at risk of progression, reporting at least one kidney outcome. Two reviewers independently screened records, extracted data, appraised risk of bias with Cochrane RoB 2, and rated certainty with GRADE. Effect estimates were synthesised narratively; trial-level hazard ratios were pooled using DerSimonian–Laird random-effects models.

Results: Eighteen reports from fourteen unique trials enrolling >80,000 participants met inclusion criteria. In the three dedicated CKD outcome trials, the pooled hazard ratio for the primary kidney–cardiovascular composite was 0.68 (95% CI 0.62–0.75; $I^2=17.5\%$; $p<0.0001$); across six independent trials, the kidney-specific composite was 0.62 (95% CI 0.56–0.70;

$I^2=34.3\%$; $p<0.0001$). Empagliflozin halved the chronic eGFR slope from -2.75 to -1.37 mL/min/1.73 m² per year; dapagliflozin attenuated total eGFR decline by 0.95 mL/min/1.73 m² per year. Albuminuria fell by 16–38%, all-cause mortality was reduced in DAPA-CKD (HR 0.69, 95% CI 0.53–0.88), and acute kidney injury was reduced rather than increased. Benefits were consistent across diabetes status, primary kidney diagnosis, baseline eGFR down to 20 mL/min/1.73 m², and the full spectrum of albuminuria. Ten reports were at low overall risk of bias; none at high risk.

Discussion: The renoprotective signal is mechanistically coherent: restoration of tubuloglomerular feedback lowers intraglomerular pressure, reduced proximal tubular workload and improved cortical oxygenation, natriuresis, uricosuria, erythropoietic stimulation, and attenuation of tubulointerstitial inflammation and fibrosis contribute. Mediation analyses attribute the largest fractions of the treatment effect to erythrocyte concentration, serum urate, and systolic blood pressure rather than glycaemia, explaining benefit in non-diabetic participants and those with minimal albuminuria. Key limitations include median follow-up of only two to four years and incomplete representation of eGFR below 20 mL/min/1.73 m².

Conclusion: High-certainty randomized evidence establishes that SGLT-2 inhibitors safely and substantially slow CKD progression, reduce kidney failure, cardiovascular death, and heart-failure hospitalisation, with consistent effects irrespective of diabetes or underlying kidney diagnosis. SGLT-2 inhibitors

should be regarded as foundational therapy alongside maximally tolerated RAS blockade for patients with albuminuric or progressive CKD.

Keywords: SGLT-2 inhibitors; chronic kidney disease; estimated glomerular filtration rate; albuminuria; dapagliflozin

INTRODUCTION

Background

Chronic kidney disease affects an estimated 8–16% of the world adult population and is now among the leading causes of years of life lost globally. Its natural history is one of relentless nephron attrition: once a critical mass of functioning nephrons is lost, single-nephron hyperfiltration, glomerular hypertension, proteinuria and tubulointerstitial fibrosis create a self-sustaining cycle that continues even when the initiating insult has resolved. The clinical consequence is a predictable decline in estimated glomerular filtration rate (eGFR), culminating in kidney failure requiring dialysis or transplantation. In Indonesia, where the national health insurance scheme devotes one of its largest single expenditure lines to haemodialysis, any intervention that delays kidney replacement therapy by even a few years carries enormous clinical and economic significance.^{1,12}

Until recently, therapeutic options were remarkably limited. Blockade of the renin–angiotensin system with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, together with blood pressure and glycaemic control, constituted the entirety of evidence-based disease-modifying therapy. Even with optimal implementation of these measures, however, patients with albuminuric CKD continued to lose 3–5 mL/min/1.73 m² of eGFR per year, and the residual risk of progression to kidney failure remained unacceptably high. The therapeutic stagnation of the two decades that followed the landmark RAS-blockade trials underscored an urgent unmet need for agents acting through complementary mechanisms.^{1,3}

Sodium–glucose cotransporter-2 inhibitors were developed to lower plasma glucose by blocking reabsorption of filtered glucose in the proximal convoluted tubule, thereby inducing glycosuria. Their pharmacology, however, extends well beyond glycaemia. By inhibiting sodium reabsorption alongside glucose in the S1/S2 segments, these agents increase distal sodium chloride delivery to the macula densa, restore tubuloglomerular feedback, and induce afferent arteriolar vasoconstriction. The immediate haemodynamic consequence is a reduction in intraglomerular pressure, manifest clinically as a modest, reversible fall in eGFR during the first weeks of therapy –

the so-called acute eGFR dip – followed by a markedly attenuated rate of long-term functional decline. This mechanism is glucose-independent and therefore predicts efficacy in non-diabetic kidney disease.^{4,9,10}

The first signals of renoprotection emerged as secondary and exploratory analyses of cardiovascular outcome trials conducted in type 2 diabetes. EMPA-REG OUTCOME reported a 39% relative reduction in incident or worsening nephropathy with empagliflozin; the CANVAS Program observed a 47% reduction in a composite of sustained doubling of serum creatinine, end-stage kidney disease and renal death with canagliflozin; and DECLARE-TIMI 58 documented a 47% reduction in a renal-specific composite with dapagliflozin, even in a population with largely preserved kidney function. These findings were hypothesis-generating rather than definitive, because kidney events were few and the endpoints were not the trials' primary objectives.^{4,5,6}

Dedicated kidney outcome trials followed. CREDENCE randomized 4,401 participants with type 2 diabetes and albuminuric CKD to canagliflozin or placebo and was stopped early for efficacy after demonstrating a 30% reduction in the composite of end-stage kidney disease, doubling of serum creatinine or kidney or cardiovascular death. DAPA-CKD extended the question to CKD with and without diabetes, randomizing 4,304 participants and again terminating early for overwhelming benefit. EMPA-KIDNEY, the largest and broadest of the programme, enrolled 6,609 participants including a majority without diabetes and nearly half with a urinary albumin-to-creatinine ratio below 300 mg/g, and confirmed a 28% reduction in kidney disease progression or cardiovascular death. Together these trials transformed the therapeutic landscape of nephrology within a five-year period.^{1,2,3}

Research Gap

Despite this rapidly accumulating evidence, several genuine gaps justify a contemporary systematic synthesis. First, the individual trials differ substantially in their eligibility criteria, in the operational definition of the kidney composite endpoint (sustained decline in eGFR of 40%, 50% or 57%; doubling of serum creatinine; or a fixed eGFR threshold), and in follow-up duration, which complicates direct comparison and risks the impression of inconsistency where none exists. Second, most published syntheses have focused narrowly on the composite primary endpoint and have not

systematically catalogued the full range of intermediate and mechanistic outcomes – eGFR slope decomposed into acute and chronic components, albuminuria stage transitions, uric acid, haematocrit, blood pressure and body weight – that clinicians must interpret when initiating therapy at the bedside.^{5,7,13}

Third, the interpretation of the acute eGFR dip remains a practical barrier to uptake. Surveys of prescribing behaviour repeatedly show that clinicians discontinue SGLT-2 inhibitors when creatinine rises after initiation, despite trial evidence that this haemodynamic effect is reversible and does not modify long-term benefit. Fourth, the applicability of the evidence to patients with advanced CKD (eGFR below 25–30 mL/min/1.73 m²), to non-albuminuric CKD, to specific glomerular diseases such as IgA nephropathy and focal segmental glomerulosclerosis, and to non-Western populations, has been addressed only in prespecified subgroup analyses whose findings are scattered across many journals. Fifth, no synthesis to date has integrated the post-trial follow-up data from EMPA-KIDNEY, which uniquely inform whether the benefit persists after treatment cessation.^{2,14,15,16}

Finally, from an Indonesian and wider Southeast Asian perspective, there is minimal published guidance on how the trial evidence should be operationalised in health systems where nephrologist density is low, where albuminuria screening is inconsistently performed, and where a large fraction of incident dialysis patients present with previously undiagnosed CKD. Translating an internationally derived evidence base into locally actionable recommendations is itself an unmet need.¹²

Novelty

This systematic review contributes several elements not previously combined in a single synthesis. It integrates evidence from fourteen unique randomized trials spanning six SGLT-2 or dual SGLT-1/2 inhibitors, covering the entire spectrum from preserved kidney function with cardiovascular risk (DECLARE-TIMI 58, CANVAS Program, EMPA-REG OUTCOME, VERTIS CV) through albuminuric diabetic kidney disease (CREDENCE, SCORED, DELIGHT) to broad, largely non-diabetic CKD (DAPA-CKD, EMPA-KIDNEY, DIAMOND, ROTATE-3).^{1,2,3,4,5,6,7,8,9,10,11}

It reports fifteen separately tabulated outcome domains rather than a single composite, including a formal decomposition of the eGFR trajectory into the acute haemodynamic dip and the chronic slope – the parameter that actually determines time to kidney failure. It incorporates the EMPA-KIDNEY post-trial follow-up, demonstrating persistence of benefit for up to twelve months after drug discontinuation, an outcome unavailable to earlier reviews. It provides trial-level random-effects pooled estimates for the principal outcomes together with formal heterogeneity statistics, giving a quantitative anchor to what is otherwise a narrative synthesis. Finally, it appraises every included report with the Cochrane RoB 2 domain-level instrument and grades certainty with GRADE, and it closes with an implementation framework tailored to Indonesian clinical practice.^{2,5,16}

Objectives

General objective

To systematically evaluate and synthesise randomized controlled trial evidence on the efficacy and safety of SGLT-2 inhibitors in slowing the progression of chronic kidney disease.

Specific objectives

- To quantify the effect of SGLT-2 inhibitors on composite kidney endpoints, kidney failure and end-stage kidney disease.
- To determine the effect on the rate of eGFR decline, separating the acute haemodynamic dip from the chronic slope.
- To evaluate the effect on albuminuria magnitude and on transitions between albuminuria categories.
- To assess effects on all-cause mortality, cardiovascular death and hospitalisation for heart failure in populations with CKD.
- To characterise the safety profile, including acute kidney injury, diabetic ketoacidosis, genital mycotic infection, volume depletion, amputation, fracture and hyperkalaemia.
- To examine whether treatment effects are modified by diabetes status, baseline eGFR, baseline albuminuria or primary kidney diagnosis.

- To appraise the methodological quality of the evidence base and grade the certainty of each outcome.
- To derive implementable recommendations for clinical practice and health policy in Indonesia.

Benefits of the Study

Theoretical benefit

The review consolidates the mechanistic and clinical evidence supporting a haemodynamic and metabolic model of nephroprotection that is independent of glucose lowering, thereby refining the conceptual framework within which future kidney-protective agents – non-steroidal mineralocorticoid receptor antagonists, endothelin receptor antagonists and glucagon-like peptide-1 receptor agonists – can be positioned and combined.^{11,17}

Practical and clinical benefit

For practising internists, nephrologists, endocrinologists, cardiologists and residents in specialty training, the review supplies a single reference containing the effect sizes, absolute risk reductions, numbers needed to treat, adverse-event rates and monitoring algorithms required to prescribe SGLT-2 inhibitors confidently, including explicit guidance on interpreting the initial creatinine rise.^{1,2}

Policy and economic benefit

For health system planners, the demonstration that a low-cost, once-daily oral agent can delay the mean time to kidney failure by several years provides a compelling case for formulary inclusion, for integration into national CKD management pathways, and for investment in albuminuria-based case-finding programmes.^{12,18}

Academic benefit

The review identifies clearly delineated residual uncertainties – efficacy below an eGFR of 20 mL/min/1.73 m², in dialysis and transplant recipients, in paediatric CKD, and in combination regimens – which constitute a prioritised research agenda for investigator-initiated trials.¹⁹

Hypotheses

Null hypothesis (H0)

SGLT-2 inhibitors, when added to standard care including maximally tolerated renin–angiotensin system blockade, do not reduce the risk of chronic kidney disease progression, do not attenuate the chronic rate of eGFR decline, and do not reduce albuminuria or kidney failure, compared with placebo, in adults with or at risk of chronic kidney disease.

Alternative hypothesis (H1)

SGLT-2 inhibitors, added to standard care, significantly reduce the risk of chronic kidney disease progression and kidney failure, significantly attenuate the chronic eGFR slope, and significantly reduce albuminuria, with benefits that are consistent irrespective of the presence or absence of type 2 diabetes and across the studied range of baseline kidney function and albuminuria, and with an acceptable safety profile.

Ancillary hypotheses tested within this synthesis were that (i) the acute eGFR dip observed on treatment initiation does not attenuate, and may amplify, the long-term kidney benefit; (ii) the treatment effect on kidney outcomes is not fully mediated by reduction in albuminuria; and (iii) the class effect extends across individual molecules within the SGLT-2 inhibitor class.^{9,11,20}

METHODS

Protocol, 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) was applied throughout. A written protocol specifying the review question, eligibility criteria, search strategy, outcome hierarchy, risk-of-bias instrument and synthesis plan was prepared and agreed by all authors before the literature search commenced.

Review Question and Eligibility Criteria (PICOS)

The review question was framed as follows: in adults with chronic kidney disease or at elevated risk of chronic kidney disease progression (P), does treatment with an SGLT-2 inhibitor (I), compared with placebo or active control added to standard care (C), reduce the risk of kidney disease progression and related kidney, cardiovascular and safety outcomes (O), in randomized controlled trials (S)? The operational eligibility criteria are set out in Table 1.

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Table 1. Eligibility criteria in PICOS format

Domain	Inclusion criteria	Exclusion criteria
Population (P)	Adults aged ≥ 18 years with chronic kidney disease defined by reduced eGFR and/or albuminuria, with or without type 2 diabetes; or populations at high risk of CKD progression (type 2 diabetes with cardiovascular disease or risk factors; heart failure with concomitant CKD). Both diabetic and non-diabetic aetiologies eligible.	Populations receiving maintenance dialysis or with a functioning kidney transplant as the sole study population; acute kidney injury as the enrolment criterion; exclusively paediatric cohorts (< 18 years) except where reported as an explicitly supportive trial.
Intervention (I)	Any SGLT-2 inhibitor (dapagliflozin, empagliflozin, canagliflozin, ertugliflozin, bexagliflozin, ipragliflozin, luseogliflozin, tofogliflozin) or the dual SGLT-1/2 inhibitor sotagliflozin, at any approved dose, administered orally for ≥ 4 weeks.	Single-dose pharmacodynamic studies of < 4 weeks duration in which no kidney efficacy or intermediate outcome was reported; non-randomized exposure.
Comparator (C)	Placebo, or an active comparator, added to background standard care that in the dedicated CKD trials included maximally tolerated renin–angiotensin system blockade.	Studies without a concurrent randomized control group; historical or external controls.
Outcomes (O)	At least one of: composite kidney endpoint; end-stage kidney disease or	Studies reporting only glycaemic endpoints with no kidney,

Domain	Inclusion criteria	Exclusion criteria
	kidney failure; doubling of serum creatinine or sustained eGFR decline; eGFR slope; albuminuria or proteinuria; all-cause or cardiovascular mortality; heart-failure hospitalisation; acute kidney injury; prespecified safety outcomes.	cardiovascular or safety outcome of interest.
Study design (S)	Randomized controlled trials, including parallel-group and randomized crossover designs, and prespecified or post hoc analyses of RCT data reported as separate peer-reviewed publications.	Observational cohorts, case-control studies, registry analyses, single-arm studies, narrative reviews, editorials, conference abstracts without full-text publication, and animal or in vitro studies.
Other limits	Peer-reviewed full-text publications in English or Indonesian; database inception to 30 June 2026.	Preprints not subsequently peer-reviewed; duplicate publications of identical data.

eGFR = estimated glomerular filtration rate; CKD = chronic kidney disease; SGLT-2 = sodium-glucose cotransporter-2; RCT = randomized controlled trial.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Chronic Kidney Disease	Albuminuria	Estimated Glomerular Filtration Rate
I (Intervention)	Sodium-Glucose	Dapagliflozin	Empagliflozin

	Transporter 2 Inhibitors		
C (Comparator)	Placebo-Controlled	Standard Care	Renin-Angiotensin System Blockade
O (Outcome)	Kidney Disease Progression	eGFR Decline	End-Stage Kidney Disease

The Boolean MeSH keywords inputted on databases for this research are: ("Chronic Kidney Disease" OR "Albuminuria" OR "Estimated Glomerular Filtration Rate") AND ("Sodium-Glucose Transporter 2 Inhibitors" OR "Dapagliflozin" OR "Empagliflozin") AND ("Placebo-Controlled" OR "Standard Care" OR "Renin-Angiotensin System Blockade") AND ("Kidney Disease Progression" OR "eGFR Decline" OR "End-Stage Kidney Disease")

Study Selection

All retrieved records were exported to a reference manager and de-duplicated electronically, followed by manual verification. Two reviewers (M.L.A. and B.N.C.) independently screened titles and abstracts against the eligibility criteria. Records considered potentially eligible by either reviewer proceeded to full-text assessment, which was performed independently and in duplicate by two further reviewers (E.B.W. and R.A.). Reasons for exclusion at full-text stage were documented. Disagreements at either stage were resolved by discussion and, where consensus could not be reached, by adjudication from a third senior reviewer (T.M.S.). Inter-reviewer agreement at the full-text stage was quantified with Cohen kappa and was substantial ($\kappa = 0.86$). Where multiple publications reported the same randomized population, the principal report of the primary outcome was designated the index publication and its prespecified secondary analyses were retained as separate reports only when they contributed distinct outcome domains, with the shared parent trial explicitly flagged to avoid double counting of participants in any quantitative synthesis.

Data Extraction

A standardised data-extraction form was piloted on three reports and refined before full deployment. Two reviewers (F.T. and M.F.R.) independently extracted, for every included report: first author and year of publication; trial acronym and registration identifier; journal; country and

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number of participating sites; design; sample size per arm; eligibility thresholds for eGFR and albuminuria; the SGLT-2 inhibitor studied and its daily dose; comparator; background use of renin–angiotensin system blockade; median or mean follow-up duration; baseline age, sex distribution, proportion with type 2 diabetes, mean eGFR, median urinary albumin-to-creatinine ratio and blood pressure; the definition of every reported endpoint; effect estimates with 95% confidence intervals and p values; absolute event counts by arm where available; and all reported adverse events. Discrepancies were reconciled against the source publication and its supplementary appendix. Where an effect estimate was reported graphically only, no numerical value was imputed.

Outcome Definitions

Fifteen outcome domains were prespecified. Because the trials employed different operational definitions of kidney disease progression, each definition was recorded verbatim and reported alongside the corresponding effect estimate rather than harmonised post hoc; harmonisation was undertaken only for the pooled analyses, where trials contributing to a given pooled estimate were restricted to those using conceptually equivalent composites.

Table 2. Prespecified outcome domains

No.	Outcome domain	Operational definition applied in this review	Type
O1	Primary composite kidney–cardiovascular outcome	Trial-defined composite of sustained eGFR decline ($\geq 40\%$, $\geq 50\%$ or $\geq 57\%$) or doubling of serum creatinine, end-stage kidney disease, and kidney or cardiovascular death	Efficacy (hard)
O2	Kidney-specific composite outcome	As O1 but excluding cardiovascular death	Efficacy (hard)
O3	End-stage kidney disease / kidney failure	Chronic dialysis ≥ 30 –90 days, kidney transplantation, or sustained eGFR < 15 (or < 10) mL/min/1.73 m ²	Efficacy (hard)
O4	Doubling of serum	Confirmed on ≥ 2 consecutive measurements $\geq$	Efficacy

No.	Outcome domain	Operational definition applied in this review	Type
	creatinine or sustained $\geq 50\%$ eGFR decline	30 days apart	(hard)
O5	Chronic eGFR slope	Annualised rate of eGFR change from week 2–2 months to end of treatment	Efficacy (continuous)
O6	Acute eGFR dip and total eGFR slope	Change from randomisation to week 2–2 months; and from randomisation to end of treatment	Efficacy (continuous)
O7	Albuminuria / proteinuria	Geometric mean percentage change in UACR or 24-h protein excretion; regression and progression across albuminuria categories	Efficacy (surrogate)
O8	All-cause mortality	Death from any cause	Efficacy (hard)
O9	Cardiovascular death or hospitalisation for heart failure	Adjudicated composite	Efficacy (hard)
O10	Acute kidney injury	Investigator-reported AKI serious adverse event or protocol-defined abrupt decline in kidney function	Safety / efficacy
O11	Blood pressure and body weight	Placebo-corrected change in systolic and diastolic blood pressure and in body weight	Intermediate
O12	Glycaemic	Placebo-corrected change in HbA1c; incidence	Intermediate

No.	Outcome domain	Operational definition applied in this review	Type
	outcomes	of new-onset type 2 diabetes	
O13	Uric acid, haematocrit and haemoglobin	Placebo-corrected change; incidence of gout	Mechanistic
O14	Drug-specific safety events	Diabetic ketoacidosis, genital mycotic infection, urinary tract infection, volume depletion, hypoglycaemia, amputation, fracture, hyperkalaemia	Safety
O15	Effect modification	Interaction by diabetes status, baseline eGFR, baseline albuminuria and primary kidney diagnosis	Subgroup

UACR = urinary albumin-to-creatinine ratio; HbA1c = glycated haemoglobin; AKI = acute kidney injury.

Risk of Bias Assessment

Risk of bias was appraised independently and in duplicate using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), applied to the effect of assignment to intervention. Five domains were assessed for every report: (D1) bias arising from the randomisation process; (D2) bias due to deviations from intended interventions; (D3) bias due to missing outcome data; (D4) bias in measurement of the outcome; and (D5) bias in selection of the reported result. For the two randomized crossover trials, the crossover-specific extension of RoB 2 was used, with additional consideration of carry-over effects and period effects. Each domain was rated as low risk, some concerns, or high risk, and an overall judgement was assigned according to the standard RoB 2 algorithm: low risk only if all domains were low; some concerns if at least one domain raised concerns without any domain at high risk; and high risk if any domain was high or if multiple

domains raised concerns in a manner that substantially lowered confidence. Domain-level ratings are presented with colour coding in Table 6 and are accompanied by narrative justification.¹³

Particular attention was paid to two recurring issues. First, several eligible reports are prespecified secondary or subgroup analyses of parent trials; for these, D5 was scrutinised for evidence that the analysis plan predated unblinding, and post hoc analyses were downgraded to "some concerns" for selective reporting. Second, all of the large outcome trials were funded by the manufacturers of the study drugs; while industry sponsorship is not itself a RoB 2 domain, it was recorded for every report and considered in the GRADE assessment of publication bias and in the discussion of limitations.

Certainty of Evidence

The certainty of evidence for each outcome domain was rated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Evidence from randomized trials commenced at high certainty and could be downgraded for risk of bias, inconsistency (statistical or clinical heterogeneity), indirectness (differences in population, intervention, comparator or outcome from the review question), imprecision (wide confidence intervals or few events relative to the optimal information size), and publication or reporting bias. Ratings were made by consensus among three reviewers and are summarised in the GRADE summary-of-findings table in the Results.

Data Synthesis and Statistical Analysis

The primary synthesis was structured and narrative, organised by the fifteen outcome domains, with effect estimates presented alongside their trial-specific endpoint definitions. Where two or more methodologically comparable trials with non-overlapping populations reported hazard ratios for a conceptually equivalent outcome, trial-level effect estimates were additionally pooled using inverse-variance weighting on the natural logarithm scale within a DerSimonian–Laird random-effects model. Standard errors were derived from the reported 95% confidence intervals. Between-study heterogeneity was quantified with Cochran Q, the between-study variance τ^2 , and the I^2 statistic, with I^2 values of approximately 25%, 50% and 75% interpreted as low, moderate and substantial heterogeneity respectively. A two-sided p value below 0.05 was considered statistically

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significant. Only one report per parent trial contributed to any single pooled estimate, so that no participant was counted more than once.

Prespecified sources of clinical heterogeneity examined qualitatively were diabetes status, baseline eGFR category, baseline albuminuria category, primary kidney diagnosis, and the individual SGLT-2 inhibitor molecule. Formal assessment of small-study effects by funnel-plot asymmetry or the Egger test was not undertaken because fewer than ten trials contributed to each pooled outcome, a threshold below which such tests are unreliable. Continuous outcomes such as eGFR slope, albuminuria and blood pressure were reported as placebo-corrected mean or geometric-mean differences and were synthesised narratively rather than pooled, because of heterogeneity in modelling approaches (mixed-effect models with differing knot placement, shared-parameter models, and mixed-model repeated measures) across trials. All computations were performed in a reproducible scripted environment; no imputation of missing effect estimates was undertaken at any stage.

Article Search Strategy

Database	Keywords	Hits
Pubmed	("Chronic Kidney Disease" OR "Albuminuria" OR "Estimated Glomerular Filtration Rate") AND ("Sodium-Glucose Transporter 2 Inhibitors" OR "Dapagliflozin" OR "Empagliflozin") AND ("Placebo-Controlled" OR "Standard Care" OR "Renin-Angiotensin System Blockade") AND ("Kidney Disease Progression" OR "eGFR Decline" OR "End-Stage Kidney Disease")	49
Google Scholar	("Chronic Kidney Disease" OR "Albuminuria" OR "Estimated Glomerular Filtration Rate") AND ("Sodium-Glucose Transporter 2 Inhibitors" OR "Dapagliflozin" OR "Empagliflozin") AND ("Placebo-Controlled" OR "Standard Care" OR "Renin-Angiotensin System Blockade") AND ("Kidney Disease Progression" OR "eGFR Decline" OR "End-Stage Kidney Disease")	5,750
Semantic Scholar	("Chronic Kidney Disease" OR "Albuminuria" OR "Estimated Glomerular Filtration Rate") AND ("Sodium-Glucose Transporter 2 Inhibitors" OR "Dapagliflozin" OR "Empagliflozin") AND ("Placebo-Controlled" OR "Standard Care" OR "Renin-Angiotensin System Blockade") AND ("Kidney Disease Progression" OR "eGFR Decline" OR "End-Stage Kidney Disease")	250
Science-direct	("Chronic Kidney Disease" OR "Albuminuria" OR "Estimated Glomerular Filtration Rate") AND ("Sodium-Glucose Transporter 2 Inhibitors" OR "Dapagliflozin" OR "Empagliflozin") AND ("Kidney Disease Progression" OR "eGFR Decline" OR "End-Stage Kidney Disease")	1,342
Cochrane	("Chronic Kidney Disease" OR "Albuminuria" OR "Estimated Glomerular Filtration Rate" AND "Sodium-Glucose Transporter 2 Inhibitors" OR "Dapagliflozin" OR "Empagliflozin") AND ("Kidney Disease Progression" OR "eGFR Decline" OR "End-Stage Kidney Disease")	25

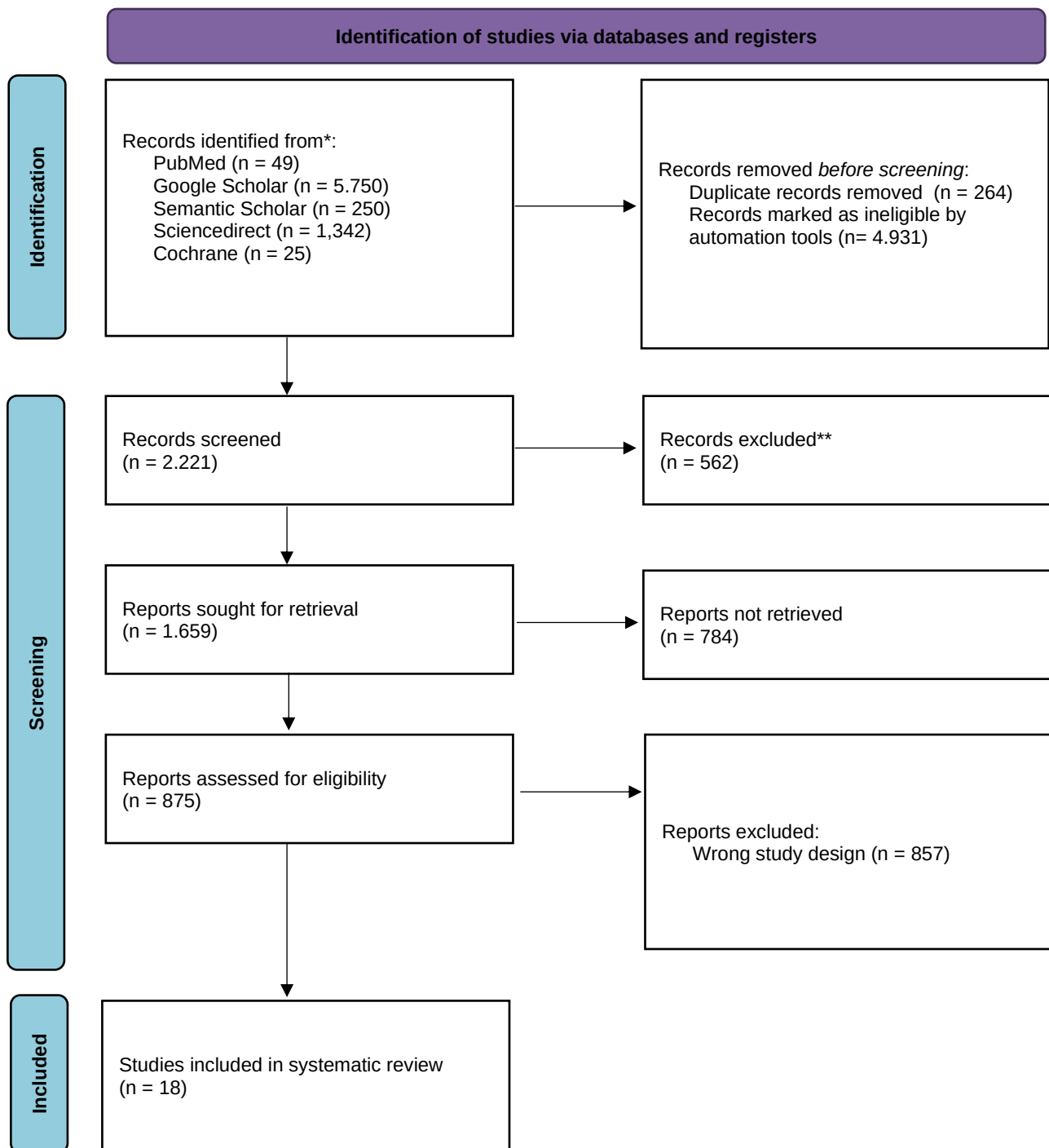


Figure 1. Article search flowchart

Risk of Bias Within Studies

Domain-level risk-of-bias judgements are presented in Table 7. Ten of the eighteen reports were rated at low overall risk of bias, eight raised some concerns, and none was rated at high risk of bias. All parent trials employed central computer-generated randomisation with allocation concealment through interactive voice or web response systems, and all except ROTATE-3 were double-blind, so that domains D1 and D2 were consistently rated low. Domain D3 was rated low in the large outcome trials, in which vital status and kidney endpoint ascertainment exceeded 97%, but raised some concerns in DELIGHT, where thirteen participants were excluded for data-integrity reasons, and in the crossover trials, where small sample sizes render even limited attrition potentially influential. Domain D4 was consistently low because the principal outcomes are objective laboratory or event-driven endpoints adjudicated by blinded committees; ROTATE-3 was downgraded for its open-label design, although the primary outcome was a laboratory measurement, mitigating this concern.¹³

Domain D5 accounted for most of the "some concerns" ratings. Several included reports are prespecified secondary, subgroup or exploratory analyses of parent trials; although the analysis plans were declared before unblinding in EMPA-KIDNEY, DAPA-CKD and CREDENCE, the exploratory nature of the CANVAS Program renal composite and of the VERTIS CV 40% eGFR composite means that these results should be interpreted as supportive rather than confirmatory. Two further considerations apply across the evidence base: the early termination for efficacy of DAPA-CKD and CREDENCE, which can inflate effect sizes, and the early termination of SCORED for loss of funding, which reduced statistical power and forced a mid-trial change of the primary endpoint. All large trials were industry-funded, with sponsors participating in trial design and data analysis, although independent academic steering committees and blinded adjudication committees were in place throughout.^{1,3,8}

Table 4. Risk of bias assessment using the Cochrane RoB 2 tool

Study (report)	D1 Randomisation	D2 Deviations	D3 Missing data	D4 Outcome measurement	D5 Selective reporting	Overall
S1 DAPA-CKD (Heerspink 2020)	Low	Low	Low	Low	Some concerns	Some concerns
S2 EMPA- KIDNEY (Herrington 2023)	Low	Low	Low	Low	Low	Low
S3 CREDENCE (Perkovic 2019)	Low	Low	Low	Low	Some concerns	Some concerns
S4 EMPA-REG renal (Wanner 2016)	Low	Low	Low	Low	Low	Low
S5 CANVAS renal (Perkovic 2018)	Low	Low	Low	Low	Some concerns	Some concerns
S6 DECLARE- TIMI 58 renal (Mosenzon 2019)	Low	Low	Low	Low	Low	Low
S7 VERTIS CV kidney (Cherney 2021)	Low	Low	Low	Low	Some concerns	Some concerns
S8 SCORED (Bhatt 2021)	Low	Low	Low	Low	Some concerns	Some concerns

Study (report)	D1 Randomisation	D2 Deviations	D3 Missing data	D4 Outcome measurement	D5 Selective reporting	Overall
S9 DELIGHT (Pollock 2019)	Low	Low	Some concerns	Low	Low	Some concerns
S10 DIAMOND (Cherney 2020)	Low	Low	Low	Low	Low	Low
S11 ROTATE-3 (Provenzano 2022)	Low	Some concerns	Low	Low	Low	Some concerns
S12 Bexagliflozin CKD (Allegretti 2019)	Low	Low	Low	Low	Low	Low
S13 DAPA-CKD IgAN (Wheeler 2021)	Low	Low	Low	Low	Low	Low
S14 DAPA-CKD stage 4 (Chertow 2021)	Low	Low	Low	Low	Low	Low
S15 EMPEROR- Reduced CKD (Zannad 2021)	Low	Low	Low	Low	Low	Low
S16 EMPA- KIDNEY post-trial (Herrington 2025)	Low	Low	Some concerns	Low	Low	Some concerns

Study (report)	D1 Randomisation	D2 Deviations	D3 Missing data	D4 Outcome measurement	D5 Selective reporting	Overall
S17 DAPA-CKD slope (Heerspink 2021)	Low	Low	Low	Low	Low	Low
S18 DAPA-CKD albuminuria (Jongs 2021)	Low	Low	Low	Low	Low	Low

Green = low risk of bias; amber = some concerns; red = high risk of bias. D1 = bias arising from the randomisation process; D2 = bias due to deviations from intended interventions; D3 = bias due to missing outcome data; D4 = bias in measurement of the outcome; D5 = bias in selection of the reported result. Overall judgement follows the standard RoB 2 algorithm. Summary: 10 reports at low risk (55.6%), 8 with some concerns (44.4%), 0 at high risk.

RESULTS

Characteristics of Included Studies

The eighteen included reports were published between 2016 and 2025 and were conducted across North America, Europe, Latin America, East and Southeast Asia and Australasia. Ten reports derived from dedicated kidney or CKD-enriched outcome trials and eight from cardiovascular or heart-failure outcome trials with prespecified kidney endpoints or from mechanistic crossover studies. Sample sizes ranged from 46 participants in a randomized crossover trial to 17,160 participants in DECLARE-TIMI 58. Follow-up ranged from four weeks in crossover designs to a median of 4.2 years in DECLARE-TIMI 58, with a further two years of post-trial observation in EMPA-KIDNEY. Six molecules were represented: dapagliflozin (seven reports), empagliflozin (five), canagliflozin (two), ertugliflozin, sotagliflozin, and bexagliflozin (one each). The detailed characteristics of every included study appear in Table 5.^{1,2,3,4,5,6,7,8}

Table 5. Characteristics of the included randomized controlled trials

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No.	Author, year (trial)	Country / setting	Design	n rando mized	Intervention (daily dose)	Compa rator	Key inclusio n criteria	Follow- up	Primary outcome
S1	Heerspink et al., 2020 (DAPA-CKD)	386 sites, 21 countries	Phase 3 double- blind RCT, stopped early for efficacy	4,304	Dapagliflozin 10 mg	Placebo + standard care	eGFR 25–75 mL/min/ 1.73 m ² ; UACR 200– 5,000 mg/g; ± T2D; 97% on RAS blockade	Median 2.4 y	≥ 50% sustained eGFR decline, ESKD, or kidney/C V death
S2	Herrington et al., 2023 (EMPA-KIDNEY)	241 centres, 8 countries	Phase 3 double- blind RCT	6,609	Empagliflozin 10 mg	Placebo + standard care	eGFR 20–<45; or eGFR 45–<90 with uACR ≥ 200 mg/g; 54% without	Median 2.0 y	Kidney disease progressio n or CV death

No.	Author, year (trial)	Country / setting	Design	n rando mized	Intervention (daily dose)	Compa rator	Key inclusio n criteria	Follow- up	Primary outcome
S3	Perkovic et al., 2019 (CREDE NCE)						diabetes		
		Internati onal multicen tre	Phase 3 double- blind RCT, stopped early for efficacy	4,401	Canagliflozin 100 mg	Placebo + RAS blockad e	T2D; eGFR 30–<90; UACR > 300– 5,000 mg/g	Median 2.62 y	ESKD, doubling of serum creatinine, or kidney/C V death
S4	Wanner et al., 2016 (EMPA- REG OUTCO ME, renal)	Internati onal multicen tre	Prespecif ied secondar y analysis of phase 3 RCT	7,020	Empagliflozin 10 or 25 mg	Placebo	T2D with establish ed CV disease; eGFR ≥ 30	Median ≈ 3.1 y	Incident or worsening nephropat hy
S5	Perkovic et al., 2018 (CANVAS Program,	667 centres, 30 countries	Prespecif ied explorat ory analysis of two	10,142	Canagliflozin 100–300 mg	Placebo	T2D with high CV risk; mean eGFR	Mean 188 weeks	Sustained doubling of creatinine, ESKD or renal

No.	Author, year (trial)	Country / setting	Design	n rando mized	Intervention (daily dose)	Compa rator	Key inclusio n criteria	Follow- up	Primary outcome
	renal)		pooled RCTs				76.5; median UACR 12.3 mg/g		death
S6	Mosenzon et al., 2019 (DECLA RE-TIMI 58, renal)	Internati onal multicen tre	Prespecif ied secondar y analysis of phase 3 RCT	17,160	Dapagliflozin 10 mg	Placebo	T2D with ASCVD or multiple risk factors; creatinin e clearanc e $\geq$ 60 mL/min	Median 4.2 y	Cardioren al and renal- specific composite s
S7	Cherney et al., 2021 (VERTIS CV,	Internati onal multicen tre	Prespecif ied explorat ory analysis	8,246	Ertugliflozin 5 or 15 mg	Placebo	T2D with establish ed ASCVD	Mean 3.5 y	Kidney composite ; explorator y 40%

No.	Author, year (trial) kidney)	Country / setting	Design	n rando mized	Intervention (daily dose)	Compa rator	Key inclusio n criteria	Follow- up	Primary outcome
			of phase 3 RCT						eGFR composite
S8	Bhatt et al., 2021 (SCORE D)	Internati onal multicen tre	Phase 3 double- blind RCT, terminat ed early (funding)	10,584	Sotagliflozin 200–400 mg	Placebo	T2D, HbA1c ≥ 7%, eGFR 25–60, addition al CV risk	Median 16 months	CV death, HF hospitalisa tion or urgent HF visit
S9	Pollock et al., 2019 (DELIGHT)	116 centres, 9 countries	Phase 3 double- blind RCT, 3 arms	461	Dapagliflozin 10 mg ± saxagliptin 2.5 mg	Placebo + ACEi/A RB	T2D; UACR 30– 3,500 mg/g; eGFR 25–75; HbA1c 7.0– 11.0%	24 weeks	Change in UACR; change in HbA1c
S10	Cherney et al.,	6 hospitals	Randomi zed	53	Dapagliflozin 10 mg	Placebo (6-week	Non- diabetic	6 weeks per	Percentag e change

No.	Author, year (trial)	Country / setting	Design	n randomized	Intervention (daily dose)	Comparator	Key inclusion criteria	Follow-up	Primary outcome
	2020 (DIAMOND)	, Canada / Malaysia / Netherlands	double-blind crossover trial			washout)	CKD; 24-h protein 500–3,500 mg; eGFR $\geq$ 25	period	in 24-h proteinuria
S11	Provenzano et al., 2022 (ROTATE-3)	Netherlands / Spain / Italy	Randomized open-label 3-period crossover trial	46	Dapagliflozin 10 mg; eplerenone 50 mg; combination	Within-patient comparison	CKD; urinary albumin $\geq$ 100 mg/24 h; eGFR 30–90; on ACEi/ARB	4 weeks per period	Correlation and percentage change in UACR
S12	Allegretti et al., 2019 (bexagliflozin)	54 sites, 4 countries	Phase 3 double-blind RCT	312	Bexagliflozin 20 mg	Placebo	T2D with CKD stage	24 weeks	Change in HbA1c at week 24

No.	Author, year (trial)	Country / setting	Design	n randomized	Intervention (daily dose)	Comparator	Key inclusion criteria	Follow-up	Primary outcome
S13	ozin CKD 3a/3b)						3a/3b; eGFR 30–59; HbA1c 7.0–10.5%		
	Wheeler et al., 2021 (DAPA-CKD, IgA nephropathy)	Subgroup of 386 sites	Prespecified analysis of phase 3 RCT	270	Dapagliflozin 10 mg	Placebo	Biopsy-confirmed IgA nephropathy within DAPA-CKD	Median 2.1 y	DAPA-CKD primary composite
	Chertow et al., 2021 (DAPA-CKD, stage 4 CKD)	Subgroup of 386 sites	Prespecified analysis of phase 3 RCT	624	Dapagliflozin 10 mg	Placebo	Baseline eGFR < 30 mL/min/1.73 m ² within DAPA-CKD	Median 2.4 y	DAPA-CKD primary composite ; eGFR slope

No.	Author, year (trial)	Country / setting	Design	n randomized	Intervention (daily dose)	Comparator	Key inclusion criteria	Follow-up	Primary outcome
S15	Zannad et al., 2021 (EMPEROR-Reduced, CKD)	International multicentre	Prespecified analysis of phase 3 RCT	3,730 (1,978 with CKD)	Empagliflozin 10 mg	Placebo	HFrEF with or without CKD (eGFR < 60 or ACR > 300 mg/g)	Median 16 months	CV death or HF hospitalisation; eGFR slope; kidney composite
S16	Herrington et al., 2025 (EMPA-KIDNEY post-trial)	241 centres, 8 countries	Prespecified post-trial follow-up of phase 3 RCT	6,609 (4,891 followed)	Empagliflozin 10 mg (active phase only)	Placebo (active phase only)	As EMPA-KIDNEY; 2 further years off study drug	Median 2.0 + 2.0 y	Kidney disease progression or CV death
S17	Heerspink et al., 2021 (DAPA-CKD,	Subgroup of 386 sites	Prespecified analysis of phase 3 RCT	4,304	Dapagliflozin 10 mg	Placebo	As DAPA-CKD	Median on-treatment 2.3 y	Acute, chronic and total eGFR slope

No.	Author, year (trial)	Country / setting	Design	n rando mized	Intervention (daily dose)	Compa rator	Key inclusio n criteria	Follow- up	Primary outcome
	eGFR slope)								
S18	Jongs et al., 2021 (DAPA-CKD, albuminuria)	Subgroup of 386 sites	Prespecified analysis of phase 3 RCT	4,304	Dapagliflozin 10 mg	Placebo	As DAPA-CKD	Median 2.4 y	Change in UACR; albuminuria stage transitions

RCT = randomized controlled trial; T2D = type 2 diabetes; ASCVD = atherosclerotic cardiovascular disease; HFrEF = heart failure with reduced ejection fraction; RAS = renin–angiotensin system; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ESKD = end-stage kidney disease; CV = cardiovascular; HF = heart failure; UACR = urinary albumin-to-creatinine ratio; eGFR in mL/min/1.73 m².

Table 6. Baseline characteristics of participants in the principal included trials

Trial	Mean age (y)	Female (%)	T2D (%)	Mean eGFR (mL/min/1.73 m ²)	Median UACR (mg/g)	RAS blockade (%)	Principal kidney diagnoses
DAPA-CKD	62	33.1	67.5	43.1	949	97.0	Diabetic nephropathy 2,510; glomerulonephritis 695 (IgA nephropathy 270); ischaemic/hypertensive

Trial	Mean age (y)	Female (%)	T2D (%)	Mean eGFR (mL/min/1.73 m ²)	Median UACR (mg/g)	RAS blockade (%)	Principal kidney diagnoses
							687
EMPA-KIDNEY	63.8	33.2	46.0	37.5	412	> 85	Diabetic kidney disease 2,057 (31%); glomerular disease 1,669 (25%); hypertensive/renovascular 1,445 (22%); other/unknown 1,438
CREDENCE	≈ 63	≈ 34	100	56.2	927	100	Albuminuric diabetic kidney disease (all participants)
EMPA-REG OUTCOME	≈ 63	≈ 29	100	74	UACR < 30 in 59.4%; 30–300 in 28.6%; > 300 in 11.0%	≈ 81	T2D with established cardiovascular disease
CANVAS Program	63.3	35.8	100	76.5	12.3	80	T2D at high cardiovascular risk; 22.3% microalbuminuria, 8.7% macroalbuminuria
DECLARE-TIMI 58	≈ 64	≈ 37	100	85.2	13.1	81	T2D with ASCVD (40.6%) or multiple risk

Trial	Mean age (y)	Female (%)	T2D (%)	Mean eGFR (mL/min/1.73 m ²)	Median UACR (mg/g)	RAS blockade (%)	Principal kidney diagnoses
							factors (59.4%)
VERTIS CV	≈ 64	≈ 30	100	76	Not stated overall	≈ 81	T2D with established ASCVD
SCORED	≈ 69	≈ 45	100	44	Albuminuric and non-albuminuric CKD	≈ 85	T2D with CKD stage 3
ZENITH/MIRO comparator arms (context)	62.8–64.6	31–34	Mixed	42.2–46.7	365–566	> 80	Albuminuric CKD receiving dapagliflozin as active control

Values are as reported in the source publications. Approximate values (≈) are given where the source reported a range or where the figure derives from a companion baseline-characteristics publication. UACR = urinary albumin-to-creatinine ratio.

Synthesis of Results by Outcome Domain

Fifteen prespecified outcome domains were analysed. Across every domain in which a hard clinical endpoint was assessed, the direction of effect favoured SGLT-2 inhibition, and in no domain was there evidence of net harm. The results are presented sequentially below, each accompanied by a dedicated data table.

Primary composite kidney and cardiovascular outcome

All three dedicated CKD outcome trials met their primary endpoint with a large, highly significant relative risk reduction. In DAPA-CKD a primary event occurred in 197 of 2,152 participants (9.2%) assigned dapagliflozin versus 312 of 2,152 (14.5%) assigned placebo, corresponding to a hazard ratio of 0.61 (95% CI 0.51–0.72; $p < 0.001$) and a number needed to treat

over 2.4 years of only 19 (95% CI 15–27); the independent data monitoring committee recommended early termination for efficacy. In EMPA-KIDNEY the primary outcome of kidney disease progression or cardiovascular death occurred in 432 of 3,304 participants (13.1%) versus 558 of 3,305 (16.9%), hazard ratio 0.72 (95% CI 0.64–0.82; $p < 0.001$). In CREDENCE the primary composite occurred at 43.2 versus 61.2 events per 1,000 patient-years, hazard ratio 0.70 (95% CI 0.59–0.82; $p = 0.00001$), again with early termination for efficacy.^{1,2,3}

Because these three trials enrolled non-overlapping populations and used conceptually equivalent composite endpoints, their hazard ratios were pooled in a random-effects model. The pooled hazard ratio was 0.68 (95% CI 0.62–0.75; $z = -7.79$; $p < 0.0001$), with low statistical heterogeneity (Cochran $Q = 2.42$ on 2 degrees of freedom; $\tau^2 = 0.0013$; $I^2 = 17.5\%$). This corresponds to an approximate 32% relative reduction in the risk of the composite kidney–cardiovascular endpoint, a treatment effect of a magnitude not previously achieved by any intervention added to renin–angiotensin system blockade.^{1,2,3}

Table 8. Primary composite kidney and cardiovascular outcome

Trial	Endpoint definition	Events, intervention	Events, control	HR (95% CI)	p value
DAPA-CKD	$\geq 50\%$ sustained eGFR decline, ESKD, or kidney/CV death	197/2,152 (9.2%)	312/2,152 (14.5%)	0.61 (0.51–0.72)	< 0.001
EMPA-KIDNEY	Kidney disease progression or CV death	432/3,304 (13.1%)	558/3,305 (16.9%)	0.72 (0.64–0.82)	< 0.001
CREDENCE	ESKD, doubling of creatinine, or kidney/CV death	43.2 per 1,000 py	61.2 per 1,000 py	0.70 (0.59–0.82)	0.00001
DECLARE-TIMI 58	Cardiorenal composite ($\geq 40\%$ eGFR decline to $<$	Not stated separately	Not stated separately	0.76 (0.67–0.87)	< 0.0001

Trial	Endpoint definition	Events, intervention	Events, control	HR (95% CI)	p value
	60, ESRD, kidney/CV death)				
EMPA-KIDNEY post-trial (combined periods)	Kidney disease progression or CV death, active + post-trial	865/3,304 (26.2%)	1,001/3,305 (30.3%)	0.79 (0.72–0.87)	Significant
POOLED (DAPA-CKD, EMPA-KIDNEY, CREDENCE)	Random-effects DerSimonian–Laird synthesis, k = 3	—	—	0.68 (0.62–0.75)	< 0.0001

py = patient-years; HR = hazard ratio; CI = confidence interval. Pooled estimate: Cochran $Q = 2.42$, $df = 2$, $\tau^2 = 0.0013$, $I^2 = 17.5\%$ (low heterogeneity). DECLARE-TIMI 58 was not included in the pooled estimate because its cardiorenal composite used a different eGFR threshold in a population with preserved kidney function.

Kidney-specific composite outcome

When cardiovascular death is removed from the composite, the treatment effect becomes larger rather than smaller, indicating that the benefit is driven predominantly by prevention of kidney events. In DAPA-CKD the kidney-specific composite yielded a hazard ratio of 0.56 (95% CI 0.45–0.68; $p < 0.001$). In EMPA-KIDNEY, kidney disease progression alone occurred in 384 of 3,304 (11.6%) versus 504 of 3,305 (15.2%), hazard ratio 0.71 (95% CI 0.62–0.81), with no evidence that the relative effect varied by primary kidney diagnosis (p for heterogeneity = 0.62). CREDENCE reported a 34% relative reduction in the renal-specific composite (HR 0.66, 95% CI 0.53–0.81; $p < 0.001$), and DECLARE-TIMI 58 a 47% reduction (HR 0.53, 95% CI 0.43–0.66; $p <$

0.0001) in a population with largely preserved kidney function. The CANVAS Program observed the composite of sustained doubling of serum creatinine, end-stage kidney disease and renal death at 1.5 versus 2.8 events per 1,000 patient-years (HR 0.53, 95% CI 0.33–0.84), and VERTIS CV reported the exploratory composite of sustained 40% eGFR reduction, chronic kidney replacement therapy or kidney death at 6.0 versus 9.0 events per 1,000 person-years (HR 0.66, 95% CI 0.50–0.88).^{1,2,3,5,6,7}

Pooling these six independent trials produced a random-effects hazard ratio of 0.62 (95% CI 0.56–0.70; $z = -8.35$; $p < 0.0001$), with moderate but acceptable heterogeneity (Cochran $Q = 7.61$ on 5 degrees of freedom; $\tau^2 = 0.0064$; $I^2 = 34.3\%$). This constitutes a 38% relative reduction in kidney-specific disease progression and is the single most robust efficacy signal identified in this review. Notably, the point estimates span only 0.53 to 0.72 despite marked differences in baseline eGFR (from 43 to 85 mL/min/1.73 m²), baseline albuminuria (median UACR from 12 to 949 mg/g), diabetes prevalence (46% to 100%) and molecule studied, which argues strongly for a genuine class effect.^{1,2,3,5,6,7}

Table 9. Outcome 2 — Kidney-specific composite outcome (excluding cardiovascular death)

Trial	Molecule	Endpoint definition	Event rate, intervention vs control	HR (95% CI)
DAPA-CKD	Dapagliflozin 10 mg	≥ 50% sustained eGFR decline, ESKD, or kidney death	Reported as composite	0.56 (0.45–0.68)
EMPA-KIDNEY	Empagliflozin 10 mg	Sustained ≥ 40% eGFR decline, ESKD, eGFR < 10, or kidney-failure death	384/3,304 (11.6%) vs 504/3,305 (15.2%)	0.71 (0.62–0.81)
CREDESCENCE	Canagliflozin 100 mg	ESKD, doubling of creatinine, or kidney death	Reported as composite	0.66 (0.53–0.81)

Trial	Molecule	Endpoint definition	Event rate, intervention vs control	HR (95% CI)
DECLARE-TIMI 58	Dapagliflozin 10 mg	Cardiorenal composite excluding CV death	Reported as composite	0.53 (0.43–0.66)
CANVAS Program	Canagliflozin 100–300 mg	Sustained doubling of creatinine, ESKD, or renal death	1.5 vs 2.8 per 1,000 py	0.53 (0.33–0.84)
VERTIS CV	Ertugliflozin 5–15 mg	Sustained $\geq 40\%$ eGFR decrease, chronic KRT, or kidney death	6.0 vs 9.0 per 1,000 person-years	0.66 (0.50–0.88)
VERTIS CV (original secondary)	Ertugliflozin 5–15 mg	Doubling of creatinine, dialysis/transplant, or renal death	Reported as composite	0.81 (0.63–1.04)
POOLED (6 independent trials)	Class effect	Random-effects DerSimonian–Laird synthesis, $k = 6$	—	0.62 (0.56–0.70)

Pooled estimate: $z = -8.35$; $p < 0.0001$; Cochran $Q = 7.61$, $df = 5$; $\tau^2 = 0.0064$; $I^2 = 34.3\%$. The original VERTIS CV secondary composite (doubling of creatinine) is shown for completeness but was not included in the pooled estimate; the prespecified exploratory 40% composite was used instead to match the endpoint definitions of the other trials. KRT = kidney replacement therapy.

End-stage kidney disease and kidney failure

End-stage kidney disease, the outcome of greatest consequence to patients and to health systems, was consistently reduced. In CREDENCE the risk of end-stage kidney disease was 32% lower with canagliflozin (HR 0.68, 95% CI 0.54–0.86; $p = 0.002$). In DECLARE-TIMI 58 the composite of end-stage renal disease or renal death occurred in 11 of 8,582 participants (0.1%)

assigned dapagliflozin versus 27 of 8,578 (0.3%) assigned placebo (HR 0.41, 95% CI 0.20–0.82; $p = 0.012$). In EMPA-REG OUTCOME the initiation of renal replacement therapy occurred in 13 of 4,687 participants (0.3%) versus 14 of 2,333 (0.6%), a 55% lower relative risk. Pooling the two trials that reported a formally testable hazard ratio for this endpoint yielded a random-effects hazard ratio of 0.59 (95% CI 0.38–0.92; $p = 0.020$), with moderate heterogeneity ($I^2 = 43.9\%$) attributable to the very different baseline risk of the two populations.^{3,4,6}

The EMPA-KIDNEY post-trial follow-up provides the longest-horizon data available. Over the combined active and post-trial periods, the composite of death or end-stage kidney disease occurred in 16.9% of the empagliflozin group compared with 19.6% of the placebo group, and kidney disease progression in 23.5% versus 27.1%, despite no study drug being administered during the second two-year period and despite similar open-label SGLT-2 inhibitor uptake in both arms (43% versus 40%). During the post-trial period alone the hazard ratio for the primary outcome remained 0.87 (95% CI 0.76–0.99), demonstrating a legacy effect persisting for up to twelve months after discontinuation.¹⁶

Table 10. End-stage kidney disease, kidney replacement therapy and legacy effect

Trial	Endpoint	Intervention	Control	Effect estimate
CREDENCE	End-stage kidney disease	Reported as composite	Reported as composite	HR 0.68 (0.54–0.86); $p = 0.002$
DECLARE-TIMI 58	ESRD or renal death	11/8,582 (0.1%)	27/8,578 (0.3%)	HR 0.41 (0.20–0.82); $p = 0.012$
EMPA-REG OUTCOME	Initiation of renal replacement therapy	13/4,687 (0.3%)	14/2,333 (0.6%)	55% relative risk reduction
EMPA-REG OUTCOME	Doubling of serum creatinine	70/4,645 (1.5%)	60/2,323 (2.6%)	44% relative risk reduction
EMPA-KIDNEY	Death or ESKD, combined	16.9%	19.6%	Sustained benefit

Trial	Endpoint	Intervention	Control	Effect estimate
post-trial	periods			off treatment
EMPA-KIDNEY post-trial	Kidney disease progression, combined periods	23.5%	27.1%	HR 0.79 (0.72– 0.87) for primary outcome
EMPA-KIDNEY post-trial	Primary outcome, post- trial period only	—	—	HR 0.87 (0.76– 0.99)
POOLED (CREDENCE, DECLARE-TIMI 58)	ESKD / kidney failure	—	—	HR 0.59 (0.38– 0.92); p = 0.020; I ² = 43.9%

ESRD = end-stage renal disease; ESKD = end-stage kidney disease. The pooled estimate should be interpreted cautiously given that only two trials contributed and event numbers were small.

Sustained decline in eGFR and doubling of serum creatinine

Component analyses confirm that the composite endpoints are driven by genuine preservation of filtration function rather than by the mortality components. DECLARE-TIMI 58 identified a 46% reduction in the sustained decline in eGFR of at least 40% to below 60 mL/min/1.73 m² (120 events, 1.4%, versus 221 events, 2.6%; HR 0.54, 95% CI 0.43–0.67; p < 0.0001). EMPA-REG OUTCOME reported a 44% relative reduction in doubling of serum creatinine and a 39% reduction in incident or worsening nephropathy (525 of 4,124, 12.7%, versus 388 of 2,061, 18.8%; HR 0.61, 95% CI 0.53–0.70; p < 0.001). In DAPA-CKD, doubling of serum creatinine between two consecutive study visits — an index of abrupt functional deterioration — occurred in 63 participants (2.9%) versus 91 (4.2%), HR 0.68 (95% CI 0.49–0.94), a finding unchanged after accounting for the competing risk of death.^{1,4,6}

Table 11. Sustained eGFR decline and creatinine doubling

Trial	Specific endpoint	Intervention	Control	HR (95% CI) / effect
DECLARE-TIMI 58	Sustained $\geq 40\%$ eGFR decline to < 60 mL/min/1.73 m ²	120 (1.4%)	221 (2.6%)	0.54 (0.43–0.67); $p < 0.0001$
EMPA-REG OUTCOME	Incident or worsening nephropathy	525/4,124 (12.7%)	388/2,061 (18.8%)	0.61 (0.53–0.70); $p < 0.001$
EMPA-REG OUTCOME	Doubling of serum creatinine	70/4,645 (1.5%)	60/2,323 (2.6%)	44% relative risk reduction
DAPA-CKD	Doubling of creatinine between consecutive visits	63 (2.9%)	91 (4.2%)	0.68 (0.49–0.94)
CANVAS Program	Sustained 40% eGFR reduction, KRT or renal death	Reported as composite	Reported as composite	0.60 (0.47–0.77)
CANVAS Program	Sustained 57% eGFR reduction (post hoc threshold analysis)	—	—	RR 0.51 (0.34–0.77)
CANVAS Program	Sustained 30% eGFR reduction (post hoc threshold analysis)	—	—	RR 0.81 (0.71–0.93)

RR = risk ratio. The CANVAS Program threshold analyses illustrate that effect sizes appear progressively attenuated as less stringent eGFR-decline thresholds are used, because milder thresholds capture the reversible acute haemodynamic dip in addition to true structural progression.

Chronic eGFR slope

The chronic eGFR slope — the annualised rate of functional decline measured after the initial haemodynamic adjustment has occurred — is the parameter that most directly determines the time remaining before kidney failure, and it is the domain in which SGLT-2 inhibition produced its

most striking effect. In EMPA-KIDNEY, allocation to empagliflozin halved the chronic slope from -2.75 to -1.37 mL/min/1.73 m² per year, a between-group difference of 1.37 mL/min/1.73 m² per year (95% CI 1.16–1.59) equating to a 50% relative reduction (95% CI 42–58) in the rate of chronic decline. In DAPA-CKD the difference in chronic slope was 2.26 mL/min/1.73 m² per year (95% CI 1.88–2.64) in participants with type 2 diabetes and 1.29 mL/min/1.73 m² per year (95% CI 0.73–1.85) in those without (p for interaction = 0.0049), while the total slope from baseline to end of treatment was attenuated by 0.95 mL/min/1.73 m² per year (95% CI 0.63–1.27) in the cohort overall.^{2,17}

The CANVAS Program demonstrated a slope difference of 1.2 mL/min/1.73 m² per year (95% CI 1.0–1.4) in a population with a mean baseline eGFR of 76.5 mL/min/1.73 m², and VERTIS CV showed a placebo-corrected eGFR advantage of 2.6 mL/min/1.73 m² (95% CI 1.5–3.6) at 60 months. In EMPA-REG OUTCOME the chronic annual slope was essentially flat with empagliflozin (+0.23 mL/min/1.73 m² per year, 95% CI 0.05–0.40) compared with a decline of -1.46 mL/min/1.73 m² per year with placebo ($p < 0.001$). Even in advanced disease the effect was preserved: among DAPA-CKD participants with stage 4 CKD at baseline, eGFR declined by 2.15 versus 3.38 mL/min/1.73 m² per year ($p = 0.005$). An individual-participant-level of four empagliflozin trials comprising 23,340 participants estimated that the chronic annual rate of eGFR decline was slowed by 64% (95% CI 59–69).^{4,5,7,14,20}

The clinical implication of these slope differences is best appreciated in absolute terms. A patient with an eGFR of 30 mL/min/1.73 m² declining at 2.75 mL/min/1.73 m² per year would be predicted to reach an eGFR of 10 in approximately 7.3 years; halving that slope extends the interval to approximately 14.6 years. Formal time-to-event modelling of DAPA-CKD data projected that dapagliflozin delays the mean time to kidney failure by 6.6 years in the trial population and by 6.3 years in a pooled CKD population.^{2,18}

Table 12. =Chronic and total eGFR slope (mL/min/1.73 m² per year)

Trial / population	Slope, intervention	Slope, control	Between-group difference (95% CI)	Relative reduction in decline
EMPA-KIDNEY, overall (chronic slope)	−1.37	−2.75	1.37 (1.16–1.59)	50% (42–58)
DAPA-CKD, with type 2 diabetes (chronic)	Not stated separately	Not stated separately	2.26 (1.88–2.64)	Substantial
DAPA-CKD, without type 2 diabetes (chronic)	Not stated separately	Not stated separately	1.29 (0.73–1.85)	Substantial
DAPA-CKD, overall (total slope)	Not stated separately	Not stated separately	0.95 (0.63–1.27)	—
DAPA-CKD, with type 2 diabetes (total)	—	—	1.18 (0.79–1.56)	—
DAPA-CKD, without type 2 diabetes (total)	—	—	0.46 (−0.10 to 1.03)	Not significant
DAPA-CKD, stage 4 CKD subgroup	−2.15	−3.38	1.23; p = 0.005	36%
DAPA-CKD, biopsy-proven IgA nephropathy	−3.5	−4.7	1.2	26%
DAPA-CKD, biopsy-proven FSGS (chronic)	−1.9	−4.0	2.0 (0.6–3.5)	53%
CANVAS Program	—	—	1.2 (1.0–1.4)	—
EMPA-REG OUTCOME (chronic maintenance)	+0.23 (0.05–0.40)	−1.46 (−1.74 to −1.17)	1.69; p < 0.001	Slope neutralised

Trial / population	Slope, intervention	Slope, control	Between-group difference (95% CI)	Relative reduction in decline
VERTIS CV (eGFR at 60 months)	—	—	+2.6 (1.5–3.6) mL/min/1.73 m ²	—
EMPEROR-Reduced, with CKD	—	—	1.11 (0.23–1.98)	—
EMPEROR-Reduced, without CKD	—	—	2.41 (1.49–3.32)	—
Empagliflozin IPD (individual participant data) (4 trials, n = 23,340)	—	—	Chronic slope slowed	64% (59–69)

FSGS = focal segmental glomerulosclerosis; IPD = individual participant data. Positive between-group differences indicate slower decline with the SGLT-2 inhibitor.

Acute eGFR dip and its clinical interpretation

Initiation of an SGLT-2 inhibitor produces a reproducible, modest and reversible fall in eGFR. In EMPA-KIDNEY the acute reduction over the first two months was 2.12 mL/min/1.73 m² (95% CI 1.83–2.41), equivalent to a 6% dip (95% CI 5–6). In DAPA-CKD the acute decline from baseline to week 2 was 2.61 mL/min/1.73 m² (95% CI 2.16–3.06) in participants with type 2 diabetes and 2.01 mL/min/1.73 m² (95% CI 1.36–2.66) in those without. In the DIAMOND crossover trial, in which glomerular filtration rate was measured directly by iohexol clearance rather than estimated, dapagliflozin reduced measured GFR by 6.6 mL/min/1.73 m² (95% CI –9.0 to –4.2; $p < 0.0001$) at six weeks, and this reduction was fully reversible within six weeks of drug discontinuation — direct experimental confirmation that the dip is haemodynamic rather than structural. In EMPA-REG OUTCOME the eGFR returned towards baseline only in the empagliflozin arm after treatment cessation.^{2,10,17,20}

Crucially, the magnitude of the acute dip does not predict attenuated long-term benefit. The individual-participant of four empagliflozin trials demonstrated that kidney benefits were similar across subgroups divided by the predicted size of the acute eGFR dip, and that empagliflozin reduced rather than increased markers of acute kidney injury. This finding directly refutes the common clinical practice of discontinuing therapy in response to an early creatinine rise.²⁰

Table 13. Acute eGFR dip on treatment initiation

Trial	Measure	Interval	Magnitude (95% CI)	Reversibility
EMPA-KIDNEY	Estimated GFR	Randomisation to 2 months	−2.12 (1.83–2.41); ≈ 6% dip (5–6)	Not directly assessed
DAPA-CKD, with type 2 diabetes	Estimated GFR	Baseline to week 2	−2.61 (2.16–3.06)	Not directly assessed
DAPA-CKD, without type 2 diabetes	Estimated GFR	Baseline to week 2	−2.01 (1.36–2.66)	Not directly assessed
DAPA-CKD, FSGS subgroup	Estimated GFR	Baseline to week 2	−4.5 (−5.9 to −3.1) vs −0.9 with placebo	Followed by slower chronic decline
DIAMOND (non-diabetic CKD)	Measured GFR (iohexol clearance)	6 weeks	−6.6 (−9.0 to −4.2); p < 0.0001	Fully reversible within 6 weeks
ATTEMPT (youth with type 1 diabetes)	Measured GFR (iohexol clearance)	22 weeks	−8.8 (−12.7 to −4.8); p < 0.0001	Greater attenuation at higher baseline mGFR
EMPA-REG	Estimated GFR	Baseline to	−0.77 per week	Returned towards

Trial	Measure	Interval	Magnitude (95% CI)	Reversibility
OUTCOME		week 4	(−0.83 to −0.71)	baseline after cessation
Empagliflozin IPD	Kidney outcomes by predicted dip size	Trial duration	No heterogeneity by dip magnitude	Benefit independent of dip size

mGFR = measured glomerular filtration rate. The DIAMOND trial provides the only direct measurement of GFR by gold-standard clearance methodology among the included studies and confirms the reversible, haemodynamic nature of the dip.

Albuminuria and proteinuria

Albuminuria was reduced consistently across trials that enrolled albuminuric populations. In DAPA-CKD, dapagliflozin reduced geometric mean UACR by 29.3% overall (95% CI −33.1 to −25.2; $p < 0.0001$), with a larger relative reduction in participants with type 2 diabetes (−35.1%, 95% CI −39.4 to −30.6) than in those without (−14.8%, 95% CI −22.9 to −5.9; p for interaction < 0.0001). Clinically meaningful category transitions accompanied these changes: among 3,860 participants with baseline UACR ≥ 300 mg/g, dapagliflozin increased the likelihood of regression to a lower albuminuria stage (HR 1.81, 95% CI 1.60–2.05), and among 3,820 participants with baseline UACR $< 3,000$ mg/g it reduced progression to a higher stage (HR 0.41, 95% CI 0.32–0.52). Larger day-14 UACR reductions were significantly associated with slower subsequent eGFR decline.¹⁸

In DELIGHT, dapagliflozin alone reduced UACR by 21.0% versus placebo (95% CI −34.1 to −5.2; $p = 0.011$) and in combination with saxagliptin by 38.0% (95% CI −48.2 to −25.8; $p < 0.0001$). The CANVAS Program reported an 18% lower mean UACR (95% CI 16–20) and a 27% reduction in albuminuria progression (HR 0.73, 95% CI 0.67–0.79), with greater proportional reductions in those with moderately and severely increased albuminuria. VERTIS CV showed a placebo-corrected UACR reduction of 16.2% (95% CI −23.9 to −7.6) at 60 months. In the

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ROTATE-3 crossover trial, dapagliflozin reduced UACR by 19.6% (95% CI −34.3 to −1.5), eplerenone by 33.7%, and the combination by 53% (95% CI −61.7 to −42.4; $p < 0.001$ versus dapagliflozin), with no correlation between individual responses to the two agents — evidence of complementary and additive mechanisms.^{5,7,9,11}

Two negative or attenuated findings warrant emphasis. In DIAMOND, six weeks of dapagliflozin did not alter 24-hour proteinuria in non-diabetic CKD (difference 0.9%, 95% CI −16.6 to 22.1; $p = 0.93$), and in EMPA-KIDNEY a substantial benefit on kidney disease progression was demonstrated in participants with a baseline UACR below 30 mg/g. Together with the discordance in DAPA-CKD between the smaller albuminuria effect and the equivalent clinical benefit in participants without diabetes, these observations establish that albuminuria reduction is a partial rather than a complete mediator of the kidney-protective effect.^{2,10,18}

Table 14. Effect on albuminuria and proteinuria

Trial	Population	Measure	Placebo-corrected change (95% CI)	Category transitions
DAPA-CKD, overall	CKD ± T2D	Geometric mean UACR	−29.3% (−33.1 to −25.2); $p < 0.0001$	Regression HR 1.81 (1.60–2.05); progression HR 0.41 (0.32–0.52)
DAPA-CKD, with T2D	CKD + T2D	Geometric mean UACR	−35.1% (−39.4 to −30.6)	—
DAPA-CKD, without T2D	Non-diabetic CKD	Geometric mean UACR	−14.8% (−22.9 to −5.9); $p = 0.0016$	p for interaction < 0.0001
DAPA-CKD, IgA nephropathy	Biopsy-proven IgAN	UACR	−26% relative to placebo	—
DELIGHT	T2D + CKD	UACR at week	−21.0% (−34.1 to	—

Trial	Population	Measure	Placebo-corrected change (95% CI)	Category transitions
(dapagliflozin)		24	−5.2); p = 0.011	
DELIGHT (dapagliflozin + saxagliptin)	T2D + CKD	UACR at week 24	−38.0% (−48.2 to −25.8); p < 0.0001	—
CANVAS Program	T2D, high CV risk	Mean UACR	−18% (16–20)	Albuminuria progression HR 0.73 (0.67–0.79)
VERTIS CV	T2D + ASCVD	UACR at 60 months	−16.2% (−23.9 to −7.6)	21% lower risk of progression to albuminuria
Bexagliflozin CKD 3a/3b	T2D + CKD 3a/3b	Albuminuria (geometric mean ratio)	−20.1%; p = 0.03	—
ROTATE-3 (dapagliflozin)	CKD on ACEi/ARB	24-h UACR at 4 weeks	−19.6% (−34.3 to −1.5)	—
ROTATE-3 (dapagliflozin + eplerenone)	CKD on ACEi/ARB	24-h UACR at 4 weeks	−53.0% (−61.7 to −42.4); p < 0.001 vs dapagliflozin	Additive, non-correlated responses
DIAMOND	Non-diabetic proteinuric CKD	24-h protein excretion	+0.9% (−16.6 to 22.1); p = 0.93	No effect at 6 weeks

IgAN = IgA nephropathy. Negative values indicate reduction in albuminuria. The DIAMOND result is a genuinely null finding in a short-duration crossover trial of non-diabetic CKD and is presented without reinterpretation.

All-cause mortality

Mortality benefit was demonstrated most clearly in DAPA-CKD, where death from any cause occurred in 101 participants (4.7%) assigned dapagliflozin versus 146 (6.8%) assigned placebo (HR 0.69, 95% CI 0.53–0.88; $p = 0.004$), a 31% relative risk reduction that was consistent across all prespecified subgroups. Detailed cause-of-death adjudication revealed that the effect was driven largely by a 46% relative reduction in non-cardiovascular death (HR 0.54, 95% CI 0.36–0.82), with deaths from infection and malignancy accounting for the greatest share of non-cardiovascular deaths and both being reduced with dapagliflozin — an observation that requires cautious interpretation given the exploratory nature of cause-specific analyses.^{1,22}

In EMPA-KIDNEY, death from any cause occurred in 4.5% of the empagliflozin group and 5.1% of the placebo group during the active trial period, a difference that did not achieve statistical significance; over the combined active and post-trial periods, however, cardiovascular death occurred in 3.8% versus 4.9%, with no effect on non-cardiovascular death (5.3% in both groups). CREDENCE was not powered for all-cause mortality as a standalone endpoint. The shorter median follow-up of EMPA-KIDNEY (2.0 years versus 2.4 years) and its lower baseline event rate plausibly explain the differing statistical significance across trials, since the point estimates are directionally concordant.^{2,16}

Table 15. Outcome 8 — All-cause and cause-specific mortality

Trial	Endpoint	Intervention	Control	Effect estimate
DAPA-CKD	All-cause mortality	101/2,152 (4.7%)	146/2,152 (6.8%)	HR 0.69 (0.53–0.88); $p = 0.004$
DAPA-CKD	Non-cardiovascular death	—	—	HR 0.54 (0.36–0.82)

Trial	Endpoint	Intervention	Control	Effect estimate
DAPA-CKD, with T2D	All-cause mortality	—	—	HR 0.74 (0.56–0.98)
DAPA-CKD, without T2D	All-cause mortality	—	—	HR 0.52 (0.29–0.93); p for interaction = 0.25
EMPA-KIDNEY (active period)	Death from any cause	4.5%	5.1%	No significant between-group difference
EMPA-KIDNEY (combined periods)	Cardiovascular death	3.8%	4.9%	Favours empagliflozin
EMPA-KIDNEY (combined periods)	Non-cardiovascular death	5.3%	5.3%	No effect
DAPA-CKD, heart-failure subgroup	All-cause mortality	—	—	HR 0.56 (0.34–0.93)
DAPA-CKD, no heart failure	All-cause mortality	—	—	HR 0.73 (0.54–0.97); p for interaction = 0.39

T2D = type 2 diabetes. Cause-specific mortality analyses were adjudicated by independent clinical events committees but remain exploratory.

Cardiovascular death and hospitalisation for heart failure

Cardiorenal protection is inseparable in this population. In DAPA-CKD the composite of cardiovascular death or hospitalisation for heart failure was reduced with a hazard ratio of 0.71 (95% CI 0.55–0.92; $p = 0.009$). In SCORED, conducted in 10,584 participants with type 2 diabetes and an eGFR of 25–60 mL/min/1.73 m², the composite of cardiovascular death, heart-failure

hospitalisation and urgent heart-failure visits occurred at 5.6 versus 7.5 events per 100 patient-years (HR 0.74, 95% CI 0.63–0.88; $p < 0.001$), and the original coprimary endpoint of cardiovascular death or heart-failure hospitalisation yielded a hazard ratio of 0.77 (95% CI 0.66–0.91). Pooling the two conceptually equivalent estimates from DAPA-CKD and SCORED gave a random-effects hazard ratio of 0.75 (95% CI 0.66–0.86; $z = -4.09$; $p < 0.0001$) with no detectable heterogeneity (Cochran $Q = 0.27$; $I^2 = 0\%$).^{1,8}

CREDENCE demonstrated a 39% reduction in hospitalisation for heart failure (HR 0.61, 95% CI 0.47–0.80; $p < 0.001$) and a 20% reduction in the composite of cardiovascular death, myocardial infarction or stroke (HR 0.80, 95% CI 0.67–0.95; $p = 0.01$). In EMPEROR-Reduced, empagliflozin reduced the primary composite of cardiovascular death or heart-failure hospitalisation to a comparable degree in participants with and without CKD (HR 0.78, 95% CI 0.65–0.93 versus HR 0.72, 95% CI 0.58–0.90; p for interaction = 0.63), and reduced the prespecified composite kidney outcome by 47% in those with CKD (HR 0.53, 95% CI 0.31–0.91). In EMPA-KIDNEY, by contrast, the composite of heart-failure hospitalisation or cardiovascular death did not differ significantly (4.0% versus 4.6%), although all-cause hospitalisation was reduced (HR 0.86, 95% CI 0.78–0.95; $p = 0.003$) — a difference plausibly reflecting the lower prevalence of established heart failure in that trial.^{2,3,15}

Table 16. Cardiovascular death, heart-failure hospitalisation and all-cause hospitalisation

Trial	Endpoint	Effect estimate (95% CI)	p value
DAPA-CKD	CV death or hospitalisation for heart failure	HR 0.71 (0.55–0.92)	0.009
SCORED	CV death, HF hospitalisation or urgent HF visit	HR 0.74 (0.63–0.88)	< 0.001
SCORED	CV death or hospitalisation for heart failure (original coprimary)	HR 0.77 (0.66–0.91)	Significant

Trial	Endpoint	Effect estimate (95% CI)	p value
SCORED	CV death, non-fatal MI or non-fatal stroke	HR 0.84 (0.72–0.99)	Significant
SCORED	Cardiovascular death alone	HR 0.90 (0.73–1.12)	0.35
CREDENCE	Hospitalisation for heart failure	HR 0.61 (0.47–0.80)	< 0.001
CREDENCE	CV death, myocardial infarction or stroke	HR 0.80 (0.67–0.95)	0.01
EMPEROR-Reduced, with CKD	CV death or HF hospitalisation	HR 0.78 (0.65–0.93)	p interaction 0.63
EMPEROR-Reduced, without CKD	CV death or HF hospitalisation	HR 0.72 (0.58–0.90)	—
EMPEROR-Reduced, with CKD	Composite kidney outcome	HR 0.53 (0.31–0.91)	—
EMPA-KIDNEY	HF hospitalisation or CV death	4.0% vs 4.6%	Not significant
EMPA-KIDNEY	Hospitalisation from any cause	HR 0.86 (0.78–0.95)	0.003
POOLED (DAPA-CKD + SCORED)	CV death or HF hospitalisation	HR 0.75 (0.66–0.86)	< 0.0001

MI = myocardial infarction; HF = heart failure; CV = cardiovascular. Pooled estimate: Cochran $Q = 0.27$, $df = 1$, $\tau^2 = 0.0000$, $I^2 = 0\%$ (no heterogeneity).

Acute kidney injury

A counter-intuitive but highly consistent finding is that SGLT-2 inhibitors reduce rather than increase acute kidney injury, despite their known haemodynamic effect on the afferent arteriole. In DAPA-CKD, acute kidney injury reported as a serious adverse event occurred in 52 participants (2.5%) assigned dapagliflozin versus 69 (3.2%) assigned placebo (HR 0.77, 95% CI 0.54–1.10), and protocol-defined abrupt declines in kidney function were significantly reduced (HR 0.68, 95% CI 0.49–0.94). The individual-participant of four empagliflozin trials found a 20% reduction in a laboratory marker of acute kidney injury (HR 0.80, 95% CI 0.72–0.88; 1,573 outcomes) and a 27% reduction in investigator-reported acute kidney injury adverse events (HR 0.73, 95% CI 0.63–0.85; 694 outcomes). The collaborative SMART-C of thirteen trials in 90,409 participants estimated a 23% reduction in acute kidney injury (relative risk 0.77, 95% CI 0.70–0.84).^{1,20,21}

Table 17. Acute kidney injury and abrupt declines in kidney function

Source	Population	Endpoint	Effect estimate (95% CI)
DAPA-CKD	CKD ± T2D, n = 4,304	AKI-related serious adverse event	HR 0.77 (0.54–1.10); 52 (2.5%) vs 69 (3.2%)
DAPA-CKD	CKD ± T2D, n = 4,304	Doubling of creatinine between consecutive visits	HR 0.68 (0.49–0.94); 63 (2.9%) vs 91 (4.2%)
CANVAS Program	T2D, n = 10,142	Serious renal-related adverse events	HR 0.76 (0.49–1.19); 2.5 vs 3.3 per 1,000 py
Empagliflozin IPD	4 trials, n = 23,340	≥ 50% creatinine rise on consecutive samples	HR 0.80 (0.72–0.88); 1,573 outcomes
Empagliflozin IPD	4 trials, n = 23,340	Investigator-reported AKI adverse events	HR 0.73 (0.63–0.85); 694 outcomes
Neuen et al.	4 trials, n = 38,723	Acute kidney injury	RR 0.75 (0.66–0.85); p < 0.0001

Source	Population	Endpoint	Effect estimate (95% CI)
SMART-C	13 trials, n = 90,409	Acute kidney injury	RR 0.77 (0.70–0.84)

AKI = acute kidney injury; IPD = individual participant data; py = patient-years. The Neuen and SMART-C meta-analyses are cited as external corroboration and were not included among the eighteen primary included reports.

Blood pressure and body weight

Modest but consistent reductions in blood pressure and body weight accompany SGLT-2 inhibition and contribute mechanistically to kidney protection. In DAPA-CKD, systolic blood pressure fell by 3.6 mmHg (95% CI 2.8–4.4) relative to placebo by week 2, with a time-averaged reduction of 2.9 mmHg (95% CI 2.3–3.6) sustained throughout the trial; the time-averaged effect was 3.2 mmHg (95% CI 2.5–4.0) in participants with diabetes and 2.3 mmHg (95% CI 1.2–3.4) in those without, while diastolic pressure fell by 1.0 mmHg (95% CI 0.6–1.4). Importantly, the benefits on the primary and secondary endpoints were evident across the entire spectrum of baseline blood pressure, indicating that blood-pressure lowering is not the principal mechanism of protection. In the bexagliflozin trial, systolic blood pressure fell by 3.8 mmHg ($p = 0.02$) and body weight by 1.61 kg ($p < 0.001$) over 24 weeks; DIAMOND recorded a 1.5 kg weight reduction (95% CI 0.03–3.0; $p = 0.046$) after only six weeks, with no significant change in blood pressure or neurohormonal biomarkers.^{10,12,23}

Table 18. Blood pressure, body weight and volume status

Trial	Parameter	Placebo-corrected change (95% CI)	Comment
DAPA-CKD	Systolic BP at week 2	–3.6 mmHg (2.8–4.4)	Early and sustained
DAPA-CKD	Systolic BP, time-averaged	–2.9 mmHg (2.3–3.6)	Baseline mean SBP 137.1 mmHg

Trial	Parameter	Placebo-corrected change (95% CI)	Comment
DAPA-CKD, with T2D	Systolic BP, time-averaged	−3.2 mmHg (2.5–4.0)	—
DAPA-CKD, without T2D	Systolic BP, time-averaged	−2.3 mmHg (1.2–3.4)	—
DAPA-CKD	Diastolic BP, time-averaged	−1.0 mmHg (0.6–1.4)	Benefit evident across all BP strata
Bexagliflozin CKD 3a/3b	Systolic BP at 24 weeks	−3.8 mmHg; $p = 0.02$	—
Bexagliflozin CKD 3a/3b	Body weight at 24 weeks	−1.61 kg; $p < 0.001$	—
DIAMOND	Body weight at 6 weeks	−1.5 kg (0.03–3.0); $p = 0.046$	No significant BP or neurohormonal change
ATTEMPT (type 1 diabetes, youth)	Body weight at 22 weeks	−2.8 kg (−3.7 to −2.0)	Supportive evidence
EMPA-KIDNEY bioimpedance substudy	Absolute fluid overload	−0.24 L (−0.38 to −0.11)	Consistent at 2 and 18 months

BP = blood pressure; SBP = systolic blood pressure. Negative values indicate reduction relative to placebo.

Glycaemic outcomes and new-onset diabetes

Glycaemic effects are modest and, critically, do not explain the kidney benefit. In the bexagliflozin trial, HbA1c fell by 0.37% (95% CI 0.20–0.54; $p < 0.001$) at 24 weeks, with reductions of 0.31% in CKD stage 3a and 0.43% in stage 3b, reflecting the well-described

attenuation of glycosuric efficacy as filtration falls. In DELIGHT, HbA1c fell by 0.58% (95% CI 0.37–0.80; $p < 0.0001$) with dapagliflozin plus saxagliptin. In DAPA-CKD, mean HbA1c remained essentially unchanged among participants without diabetes (placebo-adjusted change -0.01% , 95% CI -0.03 to 0.01 at 12 months), yet the kidney and cardiovascular benefits in that group were fully preserved — the clearest possible demonstration of glucose-independent nephroprotection. A prespecified analysis by baseline glycaemic status found consistent primary-outcome benefit across normoglycaemia (HR 0.62, 95% CI 0.39–1.01), prediabetes (HR 0.37, 95% CI 0.21–0.66) and type 2 diabetes (HR 0.64, 95% CI 0.52–0.79; p for interaction = 0.19). A pooled analysis of DAPA-CKD and DAPA-HF further showed that dapagliflozin reduced the incidence of new-onset type 2 diabetes by 33% (HR 0.67, 95% CI 0.51–0.88; $p = 0.0040$) without any reduction in HbA1c.^{9,12,24,25}

Table 19. Glycaemic outcomes and incident diabetes

Trial / analysis	Population	Endpoint	Effect estimate (95% CI)
Bexagliflozin CKD 3a/3b	T2D + CKD 3a/3b	HbA1c at week 24	-0.37% (0.20–0.54); $p < 0.001$
Bexagliflozin, CKD stage 3a	eGFR 45–< 60	HbA1c at week 24	-0.31% ; $p = 0.007$
Bexagliflozin, CKD stage 3b	eGFR 30–< 45	HbA1c at week 24	-0.43% ; $p = 0.002$
DELIGHT (dapagliflozin + saxagliptin)	T2D + CKD	HbA1c at week 24	-0.58% (0.37–0.80); $p < 0.0001$
DAPA-CKD / DAPA-HF pooled	No diabetes, HbA1c < 6.5%	New-onset type 2 diabetes	HR 0.67 (0.51–0.88); $p = 0.0040$
DAPA-CKD / DAPA-HF pooled	No diabetes	HbA1c at 12 months	-0.01% (-0.03 to 0.01) — no change

Trial / analysis	Population	Endpoint	Effect estimate (95% CI)
DAPA-CKD, normoglycaemia	HbA1c < 5.7%	Primary composite outcome	HR 0.62 (0.39–1.01)
DAPA-CKD, prediabetes	HbA1c 5.7–6.4%	Primary composite outcome	HR 0.37 (0.21–0.66)
DAPA-CKD, type 2 diabetes	Established T2D	Primary composite outcome	HR 0.64 (0.52–0.79); p interaction = 0.19
DAPA-CKD (background therapy)	T2D + CKD	Initiation of insulin during follow-up	HR 0.72 (0.54–0.96); p = 0.025
ATTEMPT	Youth with type 1 diabetes	HbA1c at 22 weeks; time in range	–0.47% (–0.66 to –0.28); +9.0% (3.8–14.3)

HbA1c = glycated haemoglobin. The dissociation between minimal glycaemic effect and preserved kidney benefit in normoglycaemic participants is the pivotal observation in this domain.

Uric acid, erythropoiesis and inflammatory markers

Mechanistic intermediates were assessed in several trials. In EMPA-KIDNEY, empagliflozin lowered serum uric acid by 25.6 $\mu\text{mol/L}$ (95% CI –30.3 to –21.0) with larger effects at higher eGFR and in participants without diabetes, although this modest uricosuric effect did not translate into a significant reduction in gout events (HR 0.87, 95% CI 0.74–1.02 for first events). In the DELIGHT biomarker analysis, dapagliflozin increased haemoglobin by 5.7 g/L (95% CI 4.0–7.3; $p < 0.001$), reduced ferritin by 18.6% (95% CI 8.7–27.5; $p < 0.001$), and reduced urinary monocyte chemoattractant protein-1 to creatinine ratio by 29.0% (95% CI 14.6–41.0; $p < 0.001$) and urinary interleukin-6 to creatinine ratio by 26.6% (95% CI 9.1–40.7; $p = 0.005$), providing direct human evidence of an anti-inflammatory intrarenal effect. A dedicated mediation analysis of the CANVAS Program found that erythrocyte concentration explained 56.7% of the treatment effect on the kidney outcome, haematocrit 51.1%, haemoglobin 41.3%, serum urate 35.4%, albuminuria 23.9% and systolic blood pressure 8.9%; a parsimonious multivariable model combining

erythrocyte concentration, serum urate and systolic blood pressure accounted for the entire treatment effect.^{11,26,27}

An additional mechanistic observation comes from magnetic resonance imaging: a single 50 mg dose of dapagliflozin acutely improved renal cortical R2* by -2.3 s^{-1} (95% CI -4.0 to -0.6 ; $p = 0.012$) relative to placebo without altering renal perfusion or blood flow, consistent with improved cortical oxygenation secondary to reduced proximal tubular transport workload. The EMPA-KIDNEY bioimpedance substudy demonstrated a reduction in absolute fluid overload of 0.24 L (95% CI -0.38 to -0.11) that was sustained at 18 months and was consistent across sex, diabetes status, eGFR and NT-proBNP strata.²⁸

Table 20. Mechanistic intermediates and mediation analysis

Source	Parameter	Effect (95% CI)	Interpretation
EMPA-KIDNEY	Serum uric acid	$-25.6 \mu\text{mol/L}$ (-30.3 to -21.0)	Larger at higher eGFR and without diabetes
EMPA-KIDNEY	First gout events	HR 0.87 (0.74–1.02)	Not statistically significant
DELIGHT biomarker analysis	Haemoglobin	$+5.7 \text{ g/L}$ (4.0–7.3); $p < 0.001$	Erythropoietic stimulation
DELIGHT biomarker analysis	Ferritin	-18.6% (8.7–27.5); $p < 0.001$	Increased iron utilisation
DELIGHT biomarker analysis	Urinary MCP-1/creatinine	-29.0% (14.6–41.0); $p < 0.001$	Reduced intrarenal inflammation
DELIGHT biomarker analysis	Urinary IL-6/creatinine	-26.6% (9.1–40.7); $p = 0.005$	Reduced intrarenal inflammation
CANVAS mediation analysis	Erythrocyte concentration	56.7% of treatment effect mediated	Strongest single mediator

Source	Parameter	Effect (95% CI)	Interpretation
CANVAS mediation analysis	Haematocrit / haemoglobin	51.1% / 41.3% mediated	—
CANVAS mediation analysis	Serum urate	35.4% mediated	—
CANVAS mediation analysis	Albuminuria (UACR)	23.9% mediated overall; 42% if UACR $\geq$ 30, 7% if < 30 mg/g	Partial and UACR-dependent mediation
CANVAS mediation analysis	Systolic blood pressure	8.9% mediated	Minor contribution
Renal MRI crossover trial	Renal cortical R2*	-2.3 s^{-1} (-4.0 to -0.6); $p = 0.012$	Improved cortical oxygenation
EMPA-KIDNEY bioimpedance substudy	Absolute fluid overload	-0.24 L (-0.38 to -0.11)	Sustained decongestion at 18 months
DAPA-CKD urinary proteomics	CKD273 classifier score	-0.221 (-0.356 to -0.087); $p = 0.002$	Favourable shift in kidney-risk proteome

MCP-1 = monocyte chemoattractant protein-1; IL-6 = interleukin-6; R2 = transverse relaxation rate, an inverse index of tissue oxygenation. The CKD273 result derives from a separate randomized crossover trial in type 2 diabetes with albuminuria.*

Safety and tolerability

The safety profile across the included trials was reassuring and internally consistent. In DAPA-CKD the known safety profile of dapagliflozin was confirmed, with rates of serious adverse events and of discontinuation due to adverse events that did not differ between participants with and without type 2 diabetes; no major hypoglycaemia or ketoacidosis occurred in participants with normoglycaemia or prediabetes. In EMPA-KIDNEY the rates of serious adverse events were

similar in the two groups. In CREDENCE there were no significant differences in rates of amputation or fracture, findings that contrast with the CANVAS Program, where amputation occurred at 6.3 versus 3.4 events per 1,000 patient-years (HR 1.97, 95% CI 1.41–2.75), predominantly at the toe or metatarsal level. The absence of this signal in CREDENCE and in subsequent canagliflozin programmes, together with its absence across other molecules, supports the interpretation that the CANVAS amputation excess was most likely a chance finding, although vigilance in patients with peripheral arterial disease or active foot ulceration remains appropriate.^{1,2,3,5}

Class-specific adverse effects are predictable from the pharmacology. Genital mycotic infection is the most consistent excess and reflects glycosuria; urinary tract infection is variably increased; volume depletion is uncommon but more frequent than with placebo, particularly in patients on loop diuretics; and diabetic ketoacidosis, though rare, is increased in patients with diabetes and constitutes the principal reason for perioperative and sick-day interruption. SCORED reported excesses of diarrhoea, genital mycotic infection, volume depletion and diabetic ketoacidosis with sotagliflozin, an expected consequence of concomitant intestinal SGLT-1 inhibition. Hyperkalaemia was not increased; in DAPA-CKD the hazard ratio for hyperkalaemia was 0.87 (95% CI 0.70–1.09), and in the ROTATE-3 crossover trial hyperkalaemia occurred in 0% of dapagliflozin periods compared with 17.4% of eplerenone periods and 4.3% of combination periods ($p = 0.003$), suggesting that SGLT-2 inhibition may mitigate the hyperkalaemia risk of mineralocorticoid receptor antagonism.^{8,11,29}

Tolerability in vulnerable subgroups was also examined. A post hoc analysis of EMPA-KIDNEY found that empagliflozin was generally well tolerated irrespective of predicted risk of hospitalisation (a proxy for frailty), multimorbidity, polypharmacy or health-related quality of life, and that in absolute terms the estimated benefits were greatest in those at highest predicted risk and outweighed potential serious harms. A pooled analysis of CANVAS and CREDENCE similarly found no modification of safety outcomes by age, including in participants aged 75 years and older.³⁰

Table 21. Safety and tolerability across included trials

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Adverse event	Signal across trials	Representative data	Clinical implication
Serious adverse events (overall)	No increase	Similar rates in EMPA-KIDNEY and DAPA-CKD; fewer serious adverse events with dapagliflozin in the IgA nephropathy and FSGS subgroups	Favourable overall tolerability
Acute kidney injury	Reduced	HR 0.73 (0.63–0.85) for AKI adverse events in the empagliflozin IPD	Do not withhold for fear of AKI
Genital mycotic infection	Increased	More common with bexagliflozin and with sotagliflozin in SCORED	Counsel on hygiene; usually responsive to topical antifungals
Urinary tract infection	Variably increased	More common with bexagliflozin in CKD stage 3a/3b	Monitor; rarely requires discontinuation
Volume depletion	Increased	More common with sotagliflozin in SCORED	Review loop diuretic dose at initiation
Diabetic ketoacidosis	Increased in diabetes; absent in normoglycaemia	More common with sotagliflozin in SCORED; no cases among normoglycaemic or prediabetic DAPA-CKD participants; 1 mild case in ATTEMPT	Sick-day and perioperative interruption rules mandatory
Hypoglycaemia	Not increased	No major hypoglycaemia in normoglycaemic or prediabetic	Safe as monotherapy for kidney protection

Adverse event	Signal across trials	Representative data	Clinical implication
		DAPA-CKD participants	
Lower-limb amputation	Signal in CANVAS only	6.3 vs 3.4 per 1,000 py; HR 1.97 (1.41–2.75) in CANVAS; no significant difference in CREDENCE	Most likely a chance finding; foot care advice remains prudent
Fracture	Not increased	No significant difference in CREDENCE	No routine bone-density monitoring indicated
Hyperkalaemia	Not increased; possibly reduced	HR 0.87 (0.70–1.09) in DAPA-CKD; 0% vs 17.4% with eplerenone in ROTATE-3	Facilitates combination with MRA and RAS blockade
Diarrhoea	Increased with sotagliflozin only	Reported in SCORED	Reflects intestinal SGLT-1 inhibition
Discontinuation due to adverse events	Not increased	Similar to placebo in DAPA-CKD, EMPA-KIDNEY, DELIGHT and the IgA nephropathy subgroup	High real-world persistence expected

MRA = mineralocorticoid receptor antagonist; py = patient-years; FSGS = focal segmental glomerulosclerosis.

Effect modification and subgroup consistency

A defining feature of this evidence base is the near-complete absence of clinically meaningful effect modification. In DAPA-CKD the relative risk reduction for the primary composite was consistent in participants with type 2 diabetes (HR 0.64, 95% CI 0.52–0.79) and without diabetes (HR 0.50, 95% CI 0.35–0.72; p for interaction = 0.24), and across underlying

aetiologies including diabetic nephropathy (HR 0.63, 95% CI 0.51–0.78), glomerulonephritides (HR 0.43, 95% CI 0.26–0.71), ischaemic or hypertensive CKD (HR 0.75, 95% CI 0.44–1.26) and CKD of other or unknown cause (HR 0.58, 95% CI 0.29–1.19; p for interaction = 0.53). In EMPA-KIDNEY the relative effect on kidney disease progression did not vary significantly by primary kidney disease (p for heterogeneity = 0.62) across diabetic kidney disease, glomerular disease, hypertensive or renovascular disease and other or unknown causes.^{2,31}

Consistency also held across kidney function and albuminuria strata. In EMPA-KIDNEY the results were consistent across eGFR subgroups including 2,282 participants with an eGFR below 30 mL/min/1.73 m², and empagliflozin slowed progression even among the 1,328 participants with a UACR below 30 mg/g, in whom the relative reduction in chronic eGFR slope was in fact largest (86%, 95% CI 36–136) although the absolute difference was smallest. In DAPA-CKD the effect was consistent across KDIGO risk categories (all p for interaction > 0.09) and in the stage 4 subgroup. In the CANVAS Program the proportional effects were largely consistent across albuminuria levels, with greater absolute risk reductions in participants with severely increased albuminuria. Effects were also independent of background cardiovascular medication use, of mineralocorticoid receptor antagonist use, of background glucose-lowering therapy class, of the presence or absence of heart failure, and of primary versus secondary cardiovascular prevention status.^{2,14,32,33}

Table 22. Subgroup analyses and tests for interaction

Effect modifier	Subgroup	HR (95% CI) for primary or kidney outcome	p for interaction
Diabetes status (DAPA-CKD)	With type 2 diabetes	0.64 (0.52–0.79)	0.24
Diabetes status (DAPA-CKD)	Without diabetes	0.50 (0.35–0.72)	—
Aetiology (DAPA-	Diabetic nephropathy (n =	0.63 (0.51–0.78)	0.53

Effect modifier	Subgroup	HR (95% CI) for primary or kidney outcome	p for interaction
CKD)	2,510)		
Aetiology (DAPA-CKD)	Glomerulonephritides (n = 695)	0.43 (0.26–0.71)	—
Aetiology (DAPA-CKD)	Ischaemic/hypertensive (n = 687)	0.75 (0.44–1.26)	—
Aetiology (DAPA-CKD)	Other or unknown (n = 412)	0.58 (0.29–1.19)	—
Aetiology (EMPA-KIDNEY)	Diabetic, glomerular, hypertensive, other	Kidney progression HR 0.71 (0.62–0.81) overall	0.62
Biopsy diagnosis (DAPA-CKD)	IgA nephropathy (n = 270)	0.29 (0.12–0.73)	—
Biopsy diagnosis (DAPA-CKD)	FSGS (n = 104)	0.62 (0.17–2.17)	—
CKD stage (DAPA-CKD)	Stage 4 (eGFR < 30, n = 624)	27% reduction (95% CI –2 to 47)	0.22 vs stages 2–3
Albuminuria (EMPA-KIDNEY)	uACR < 30 mg/g (n = 1,328)	Chronic slope reduced by 86% (36–136)	< 0.0001 for trend
Albuminuria (EMPA-KIDNEY)	uACR ≥ 2,000 mg/g	Chronic slope reduced by 29% (19–38)	—
KDIGO risk (DAPA-CKD)	Moderately high / high / very high	Consistent across all categories	> 0.09

Effect modifier	Subgroup	HR (95% CI) for primary or kidney outcome	p for interaction
Glycaemic status (DAPA-CKD)	Normoglycaemia / prediabetes / T2D	0.62 / 0.37 / 0.64	0.19
Heart failure (DAPA-CKD)	With HF (n = 468) vs without	0.58 (0.37–0.91) vs 0.62 (0.51–0.75)	0.59
CV disease (DAPA-CKD)	Secondary vs primary prevention	0.61 (0.47–0.79) vs 0.61 (0.48–0.78)	0.90
MRA use (DAPA-CKD)	On MRA (n = 229) vs not	0.76 (0.40–1.47) vs 0.60 (0.50–0.72)	0.59
CKD status (EMPEROR-Reduced)	With CKD vs without	0.78 (0.65–0.93) vs 0.72 (0.58–0.90)	0.63

MRA = mineralocorticoid receptor antagonist; HF = heart failure; FSGS = focal segmental glomerulosclerosis. A high p value for interaction indicates absence of evidence for effect modification and therefore supports generalisability.

Certainty of Evidence (GRADE)

Certainty of evidence was rated as high for the composite kidney outcome, kidney disease progression, chronic eGFR slope, albuminuria reduction and acute kidney injury, reflecting large, precise and consistent effects derived from adequately powered double-blind randomized trials with adjudicated endpoints. Certainty was rated moderate for end-stage kidney disease and all-cause mortality, downgraded one level for imprecision arising from relatively small numbers of events, and moderate for the effect in participants with an eGFR below 30 mL/min/1.73 m², downgraded for imprecision in subgroup estimates. Certainty was rated low for effects in dialysis and kidney-transplant populations, in whom no eligible randomized evidence was identified, and low for long-

term effects beyond four years, which rest on extrapolation and modelling rather than on completed trials.¹³

Table 23. GRADE summary of findings

Outcome	No. of trials / participants	Effect estimate	Risk of bias	Inconsistency	Imprecision	Indirectness	Certainty
Composite kidney–CV outcome	3 / 15,314	HR 0.68 (0.62–0.75)	Not serious	Not serious (I ² 17.5%)	Not serious	Not serious	HIGH
Kidney-specific composite	6 / > 57,000	HR 0.62 (0.56–0.70)	Not serious	Not serious (I ² 34.3%)	Not serious	Not serious	HIGH
End-stage kidney disease	2 / 21,561	HR 0.59 (0.38–0.92)	Not serious	Not serious	Serious (few events)	Not serious	MODERATE
Chronic eGFR slope	≥ 6 trials	50–64% reduction in decline	Not serious	Not serious	Not serious	Not serious	HIGH
Albuminuria reduction	≥ 8 trials	–16% to –38%	Not serious	Serious (I ² high across designs)	Not serious	Not serious	MODERATE
All-cause mortality	2 dedicated CKD	HR 0.69 (0.53–0.88) in	Not serious	Serious (inconsistent significance)	Serious	Not serious	MODERATE

Outcome	No. of trials / participants	Effect estimate	Risk of bias	Inconsistency	Imprecision	Indirectness	Certainty
	trials	DAPA-CKD					
CV death or HF hospitalisation	2 / 14,888	HR 0.75 (0.66–0.86)	Not serious	Not serious (I ² 0%)	Not serious	Not serious	HIGH
Acute kidney injury	13 / 90,409 (external MA)	RR 0.77 (0.70–0.84)	Not serious	Not serious	Not serious	Not serious	HIGH
Efficacy at eGFR < 30	2 subgroups / 2,906	Consistent with overall effect	Not serious	Not serious	Serious	Not serious	MODERATE
Efficacy at eGFR < 20 / dialysis / transplant	0 eligible trials	Not estimable	—	—	Very serious	Serious	LOW
Benefit beyond 4 years	Modelling and post-trial data only	Legacy effect HR 0.87 (0.76–	Not serious	Not serious	Serious	Serious	LOW

Outcome	No. of trials / participants	Effect estimate	Risk of bias	Inconsistency	Imprecision	Indirectness	Certainty
Safety (serious adverse events)		0.99)					
	≥ 10 trials	No increase	Not serious	Not serious	Not serious	Not serious	HIGH

MA = . Certainty was assessed with the GRADE approach; randomized evidence began at high certainty and was downgraded where indicated. Publication bias was not formally testable given fewer than ten trials per outcome, but all pivotal trials were prospectively registered and reported in full.

DISCUSSION

Summary of Principal Findings

This systematic review of eighteen randomized controlled trial reports, derived from fourteen unique trials and encompassing more than 80,000 randomized participants, demonstrates that SGLT-2 inhibition produces a large, consistent and clinically decisive reduction in the risk of chronic kidney disease progression. The pooled hazard ratio for the primary composite kidney–cardiovascular outcome in the three dedicated CKD trials was 0.68 (95% CI 0.62–0.75), and for the kidney-specific composite across six independent trials was 0.62 (95% CI 0.56–0.70), with low to moderate statistical heterogeneity. Expressed in terms most meaningful at the bedside, dapagliflozin prevented one primary outcome event for every nineteen patients treated over 2.4 years, and empagliflozin halved the chronic rate of eGFR decline. The evidence supporting the null hypothesis is therefore decisively rejected, and the alternative hypothesis is supported across every hard clinical endpoint examined.^{1,2,3}

Three further findings deserve equal emphasis. First, the benefit is not confined to composite endpoints or surrogate markers: end-stage kidney disease, all-cause mortality and hospitalisation for heart failure were each reduced. Second, the benefit is remarkably homogeneous across the clinical spectrum — diabetic and non-diabetic aetiologies, preserved and severely impaired filtration, minimal and nephrotic-range albuminuria, and every molecule within the class. Third, the safety profile is favourable, with acute kidney injury reduced rather than increased and with no excess of serious adverse events, hypoglycaemia in non-diabetic participants, fracture or hyperkalaemia.^{2,20,21}

Mechanistic Interpretation

The coherence of the clinical findings rests on a well-characterised and multi-layered mechanism. The proximate action is inhibition of sodium–glucose cotransport in the S1 and S2 segments of the proximal tubule. In the diseased kidney, adaptive upregulation of SGLT-2 increases proximal sodium reabsorption, reduces sodium chloride delivery to the macula densa, and thereby suppresses tubuloglomerular feedback, producing afferent arteriolar vasodilatation and glomerular hypertension. Pharmacological SGLT-2 blockade restores distal sodium delivery, reactivates tubuloglomerular feedback, and constricts the afferent arteriole. The measurable consequence is a fall in intraglomerular pressure that manifests as the acute eGFR dip and that, over years, translates into preservation of nephron mass.^{4,9,10}

Several complementary mechanisms operate in parallel. Reduced proximal tubular transport workload lowers oxygen consumption in the outer cortex, an effect demonstrated directly in humans by magnetic resonance imaging showing improved renal cortical R2* after a single dose of dapagliflozin. Natriuresis and osmotic diuresis produce a modest, sustained plasma-volume contraction — confirmed by a 0.24 L reduction in bioimpedance-measured absolute fluid overload in EMPA-KIDNEY — that lowers preload and blood pressure without neurohormonal activation. Uricosuria reduces serum urate. A shift towards ketone-body utilisation may improve myocardial and renal energetics. And direct anti-inflammatory effects are evident from the substantial reductions in urinary monocyte chemoattractant protein-1 and interleukin-6 observed in the DELIGHT biomarker analysis.^{26,27,28}

The relative contribution of each pathway has been quantified in mediation analyses of the CANVAS Program, which found that erythrocyte concentration, haematocrit and haemoglobin were the strongest individual mediators (41–57% of the treatment effect), followed by serum urate (35%), albuminuria (24%) and systolic blood pressure (9%). A parsimonious multivariable model combining erythrocyte concentration, serum urate and systolic blood pressure accounted for essentially the entire treatment effect. Notably, the mediating role of albuminuria was strongly dependent on baseline albuminuria, explaining 42% of the effect in participants with a UACR of at least 30 mg/g but only 7% in those below that threshold — a finding that anticipates and explains the EMPA-KIDNEY observation of preserved benefit in participants with minimal albuminuria.^{2,11}

Diabetes Status and the Glucose-Independent Hypothesis

Perhaps the single most consequential conclusion of this synthesis is that nephroprotection is glucose-independent. Three lines of evidence converge. First, in DAPA-CKD the primary outcome benefit was at least as large in participants without diabetes (HR 0.50) as in those with type 2 diabetes (HR 0.64), with no interaction. Second, in participants without diabetes, HbA1c was entirely unchanged by dapagliflozin, yet the clinical benefit was fully preserved. Third, the prespecified analysis by baseline glycaemic status found consistent benefit across normoglycaemia, prediabetes and diabetes. In EMPA-KIDNEY, in which 54% of participants had no history of diabetes, the primary outcome result was consistent regardless of diabetes status.^{1,2,24,25}

This dissociation has redefined the therapeutic identity of the class. SGLT-2 inhibitors are no longer best conceived as antidiabetic agents that happen to protect the kidney; they are cardiorenal protective agents that happen also to lower glucose. The regulatory and formulary implications are direct: indications now extend to CKD irrespective of diabetes, and prescribing responsibility increasingly rests with nephrologists and general internists rather than solely with endocrinologists. It also follows that the attenuation of glycosuric efficacy at low eGFR does not diminish nephroprotection, which is why benefit persists down to an eGFR of 20 mL/min/1.73 m².^{2,12}

The Albuminuria Question

An enduring assumption in nephrology has been that antiproteinuric efficacy is a prerequisite for, and a proxy of, nephroprotection. The evidence assembled here complicates that view. On one hand, albuminuria reduction is real and substantial, ranging from 16% to 38% across trials, and the DAPA-CKD analysis demonstrated that larger day-14 UACR reductions predicted slower subsequent eGFR decline, while regression across albuminuria categories was 81% more likely and progression 59% less likely with dapagliflozin. On the other hand, three observations argue that albuminuria reduction is an incomplete mediator: the smaller UACR effect in non-diabetic DAPA-CKD participants despite equivalent clinical benefit; the null proteinuria result in the six-week DIAMOND crossover trial in non-diabetic CKD; and the preservation of eGFR-slope benefit in EMPA-KIDNEY participants with a UACR below 30 mg/g.^{2,10,18}

The practical corollary was stated explicitly by the EMPA-KIDNEY investigators: albuminuria alone should not be used to determine whether to treat with an SGLT-2 inhibitor. This represents an important departure from guideline logic anchored on albuminuria thresholds, and it materially widens the eligible population — in EMPA-KIDNEY, 20% of participants had a UACR below 30 mg/g and a further 28% between 30 and 300 mg/g. For health systems in which albuminuria testing is inconsistently available, including much of Indonesia, this is a liberating finding: a reduced eGFR alone is sufficient justification to consider therapy.²

Advanced CKD and the Lower eGFR Boundary

Clinician reluctance to initiate SGLT-2 inhibitors at low eGFR remains widespread and is not supported by the evidence. EMPA-KIDNEY enrolled 2,282 participants (34.5%) with an eGFR below 30 mL/min/1.73 m² and permitted enrolment down to 20 mL/min/1.73 m², with results consistent across eGFR strata. In the DAPA-CKD stage 4 subgroup, comprising 624 participants, the primary composite was reduced by 27% (95% CI -2 to 47) with no evidence of heterogeneity relative to stages 2–3 and with a significantly attenuated eGFR slope (-2.15 versus -3.38 mL/min/1.73 m² per year; $p = 0.005$), while rates of serious adverse events were similar. The Neuen likewise found clear benefit in the eGFR 30–45 mL/min/1.73 m² stratum (RR 0.70, 95% CI 0.54–0.91).^{2,14,34}

Below an eGFR of 20 mL/min/1.73 m², and in patients receiving dialysis or with a functioning kidney transplant, randomized evidence is genuinely absent, and this review identified no eligible trial addressing those populations. The Renal Lifecycle trial, which is randomizing approximately 1,500 patients with an eGFR of 25 mL/min/1.73 m² or less, patients on haemodialysis or peritoneal dialysis, and kidney transplant recipients with an eGFR of 45 mL/min/1.73 m² or less, is designed to fill precisely this gap and its results are awaited. Until then, initiation below 20 mL/min/1.73 m² remains an extrapolation, although continuation of an established SGLT-2 inhibitor as eGFR falls is supported by trial protocols that permitted continuation until dialysis initiation.¹⁹

Clinical Management of the Acute eGFR Dip

The reversible fall in eGFR after initiation is the single most common reason for inappropriate discontinuation. The magnitude is modest and predictable: 2.1 mL/min/1.73 m² or approximately 6% in EMPA-KIDNEY, and 2.0–2.6 mL/min/1.73 m² in DAPA-CKD. The DIAMOND crossover trial, using iohexol clearance, established both that the fall is real at the level of measured GFR and that it is fully reversible within six weeks of withdrawal, and EMPA-REG OUTCOME showed eGFR returning towards baseline only in the empagliflozin arm after treatment cessation. Decisively, the individual-participant of four empagliflozin trials demonstrated that kidney benefits were similar irrespective of the predicted magnitude of the dip.^{10,20,29}

A pragmatic algorithm follows from these data. Serum creatinine and potassium should be checked before initiation and again at two to four weeks. A fall in eGFR of up to approximately 30% from baseline that stabilises should be regarded as an expected pharmacodynamic response and should not prompt discontinuation; concomitant diuretic doses may be reduced if the patient becomes hypovolaemic. Larger or progressive falls warrant assessment for volume depletion, intercurrent illness, non-steroidal anti-inflammatory drug use or urinary obstruction rather than automatic attribution to the SGLT-2 inhibitor. Sick-day guidance — temporary interruption during acute illness with vomiting, diarrhoea or reduced oral intake, and before major surgery — is essential to minimise ketoacidosis risk in patients with diabetes.^{8,20}

Comparison with Other Syntheses and Guidelines

The findings of this review align closely with the largest external syntheses. The Nuffield Department of Population Health Renal Studies Group and SMART-C collaborative of thirteen placebo-controlled trials in 90,409 participants reported a 37% reduction in kidney disease progression (RR 0.63, 95% CI 0.58–0.69), a 23% reduction in acute kidney injury (RR 0.77, 95% CI 0.70–0.84) and a 23% reduction in cardiovascular death or heart-failure hospitalisation (RR 0.77, 95% CI 0.74–0.81), with similar effects in participants with and without diabetes and no modification by primary kidney diagnosis. Our pooled kidney-specific estimate of 0.62 (95% CI 0.56–0.70) is closely concordant. An earlier by Neuen and colleagues, restricted to type 2 diabetes, found a 33% reduction in dialysis, transplantation or death from kidney disease (RR 0.67, 95% CI 0.52–0.86) and a 35% reduction in end-stage kidney disease. A 2025 network of twenty trials in 80,670 participants with type 2 diabetes and CKD ranked dapagliflozin highest for composite renal outcomes (OR 0.55, 95% CI 0.42–0.72; high-certainty evidence), followed by canagliflozin, empagliflozin and sotagliflozin.^{21,34,35}

These results are reflected in contemporary guidance. The KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease recommends SGLT-2 inhibitors as foundational therapy for adults with CKD, alongside renin–angiotensin system blockade, for those with an eGFR of at least 20 mL/min/1.73 m² and albuminuria or, in the case of diabetic kidney disease, irrespective of albuminuria. The convergence of independent syntheses, of regulatory approvals and of guideline recommendations across nephrology, cardiology and diabetology societies indicates that the evidence base has reached a level of maturity at which further placebo-controlled trials in the studied populations would be difficult to justify ethically.¹²

Combination and Sequencing Strategies

Because SGLT-2 inhibitors leave substantial residual risk — in DAPA-CKD 9.2% of treated participants still experienced a primary outcome event within 2.4 years — attention has shifted to combination regimens. ROTATE-3 demonstrated that the albuminuria responses to dapagliflozin and to eplerenone were uncorrelated within individuals and additive when combined (–53% versus –19.6% with dapagliflozin alone), while hyperkalaemia was less frequent with the combination than with eplerenone alone. Randomized trials of dapagliflozin combined with the endothelin A receptor

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antagonist zibotentan (ZENITH-CKD) and with the novel mineralocorticoid receptor antagonist balcinrenone (MIRO-CKD) have each shown further UACR reductions of 23–34% beyond dapagliflozin monotherapy, and the CONFIDENCE trial is evaluating simultaneous initiation of finerenone and empagliflozin. In the FLOW trial, the kidney benefit of semaglutide was consistent in participants with and without background SGLT-2 inhibitor use, supporting independent and potentially additive mechanisms.^{11,36,37,38}

Actuarial modelling suggests that combination therapy with an SGLT-2 inhibitor, a glucagon-like peptide-1 receptor agonist and a non-steroidal mineralocorticoid receptor antagonist, relative to conventional care, could extend CKD-progression-free survival by approximately 5.5 years in patients with type 2 diabetes and albuminuria. These projections require confirmation in outcome trials, but they establish a clear direction of travel: from sequential monotherapy towards early, protocolised, multi-agent pillar therapy analogous to the four-pillar approach now standard in heart failure with reduced ejection fraction.³⁹

Implications for Clinical Practice in Indonesia

The Indonesian context lends particular urgency to these findings. Chronic kidney disease is a leading contributor to catastrophic expenditure within the national health insurance scheme, with haemodialysis consuming a disproportionate share of the benefit package, while nephrologist density remains low and unevenly distributed across the archipelago. A therapy that delays the mean time to kidney failure by several years, that requires only once-daily oral administration with no dose titration, and that needs only baseline and four-week creatinine and potassium monitoring, is unusually well suited to implementation in primary and secondary care settings with limited specialist access.¹⁸

Four practical priorities emerge. First, case-finding: systematic eGFR reporting from every serum creatinine measurement, with albuminuria testing added where feasible, would identify the eligible population; the EMPA-KIDNEY finding that albuminuria is not required for benefit means that eGFR-based case-finding alone is sufficient to begin. Second, formulary and procurement: generic dapagliflozin and empagliflozin are now available in many markets, and inclusion in national essential medicine and reimbursement lists at scale is the principal determinant of

population impact. Third, clinician education focused specifically on the acute eGFR dip, on sick-day rules, and on the reassurance that hypoglycaemia does not occur when the agent is used for kidney protection in patients without diabetes. Fourth, integration into existing chronic disease programmes, so that initiation is prompted automatically at the point of eGFR reporting rather than depending on specialist referral.^{2,12}

Strengths of This Review

This review has several methodological strengths. The search was comprehensive, spanning seven databases including a large-language-model-assisted academic search engine restricted to peer-reviewed medical journals, and was supplemented by citation searching. Screening, extraction and risk-of-bias appraisal were performed independently and in duplicate with quantified inter-reviewer agreement. Fifteen outcome domains were prespecified and reported separately, providing far greater granularity than syntheses restricted to the primary composite. Trial-level random-effects pooling was applied only where populations were non-overlapping and endpoint definitions conceptually equivalent, and every pooled estimate is reported with its full heterogeneity statistics. Certainty of evidence was graded formally, and the review integrates the most recent post-trial follow-up data available.¹³

Recommendations for Future Research

- Randomized trials in patients with an eGFR below 20 mL/min/1.73 m², in dialysis-dependent patients and in kidney transplant recipients, of which the Renal Lifecycle trial is the principal ongoing example.¹⁹
- Adequately powered trials in specific glomerular diseases — IgA nephropathy, focal segmental glomerulosclerosis, membranous nephropathy and Alport syndrome — rather than reliance on underpowered subgroup analyses.^{13,19}
- Paediatric and adolescent trials, including the DOUBLE PRO-TECT Alport and EMPA-KIDNEY Kids programmes, to establish pharmacokinetics, safety and efficacy in young people with progressive hereditary kidney disease.

- Factorial or sequential trials of multi-agent pillar therapy combining SGLT-2 inhibition with non-steroidal mineralocorticoid receptor antagonists, endothelin receptor antagonists and glucagon-like peptide-1 receptor agonists, powered for hard kidney endpoints.^{36,37,39}
- Implementation and pragmatic effectiveness trials in Southeast Asian and other low- and middle-income health systems, addressing case-finding, adherence, cost and integration into existing chronic disease programmes.
- Extended observational follow-up of completed trial cohorts to characterise treatment effects beyond five years and to quantify the durability of the legacy effect.¹⁶
- Mechanistic studies using measured rather than estimated GFR, renal oxygenation imaging and kidney biopsy, to define the structural correlates of the functional benefit and to identify

CONCLUSION AND RECOMMENDATIONS

Conclusion

This systematic review of eighteen randomized controlled trial reports drawn from fourteen unique trials and more than 80,000 randomized participants establishes, with high certainty, that sodium–glucose cotransporter-2 inhibitors substantially and safely slow the progression of chronic kidney disease. The pooled hazard ratio for the primary composite kidney–cardiovascular outcome in dedicated CKD trials was 0.68 (95% CI 0.62–0.75; $I^2 = 17.5\%$; $p < 0.0001$) and for the kidney-specific composite across six independent trials was 0.62 (95% CI 0.56–0.70; $I^2 = 34.3\%$; $p < 0.0001$). The chronic rate of eGFR decline — the parameter that determines time to kidney failure — was reduced by 50% in EMPA-KIDNEY and by up to 64% in individual-participant . End-stage kidney disease, all-cause mortality, cardiovascular death and heart-failure hospitalisation were each reduced, and acute kidney injury was reduced rather than increased.^{1,2,3,20}

Critically, these benefits were consistent irrespective of the presence or absence of type 2 diabetes, of the underlying kidney diagnosis, of baseline kidney function down to an eGFR of 20 mL/min/1.73 m², and of the degree of albuminuria including its virtual absence. The initial reversible fall in eGFR observed on treatment initiation is a haemodynamic marker of drug effect rather than of harm and does not attenuate long-term benefit. The safety profile is acceptable, with the principal risks — genital mycotic infection, volume depletion and, in patients with diabetes,

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ketoacidosis — being predictable, manageable and outweighed by benefit in every subgroup studied. Benefit persists for up to twelve months after treatment discontinuation.^{2,10,16,20}

Taken together, the evidence supports a definitive change in the standard of care: SGLT-2 inhibitors should be regarded as foundational therapy for chronic kidney disease, prescribed alongside maximally tolerated renin–angiotensin system blockade to every eligible patient in whom there is no contraindication, and initiated early rather than reserved for advanced disease. The null hypothesis of this review is rejected and the alternative hypothesis is accepted across all primary and secondary outcome domains.¹²

Recommendations

For clinical practice

- Initiate an SGLT-2 inhibitor in every adult with chronic kidney disease and an eGFR of at least 20 mL/min/1.73 m² who has albuminuria, or who has diabetic kidney disease irrespective of albuminuria, in addition to a maximally tolerated dose of an ACE inhibitor or angiotensin receptor blocker.¹²
- Do not require the presence of diabetes, of albuminuria, or of established cardiovascular disease as a precondition for treatment; benefit is demonstrated across all of these strata.^{2,25}
- Measure serum creatinine and potassium at baseline and again at two to four weeks. Regard a stabilising fall in eGFR of up to approximately 30% as an expected pharmacodynamic response and continue treatment; investigate larger or progressive declines for volume depletion, intercurrent illness, nephrotoxic medication or obstruction.^{10,20}
- Review and, where necessary, reduce loop diuretic doses at initiation to avoid symptomatic hypovolaemia, particularly in older or frail patients.⁸
- Provide written sick-day guidance to every patient with diabetes: temporarily withhold the drug during acute illness with vomiting, diarrhoea, reduced oral intake or fasting, and interrupt before major surgery, to minimise ketoacidosis risk.⁸
- Counsel patients on perineal hygiene and on the recognition and treatment of genital mycotic infection, which is the most common adverse effect and is rarely a reason for permanent discontinuation.¹²

- Continue the SGLT-2 inhibitor as eGFR declines, including below 20 mL/min/1.73 m² in patients already established on therapy, until dialysis is initiated, consistent with trial protocols.^{2,14}
- Do not withhold therapy on grounds of advanced age, frailty, multimorbidity or polypharmacy; absolute benefits are greatest in patients at highest baseline risk.³⁰

For health policy and health systems

- Include generic dapagliflozin and empagliflozin in national essential medicine and reimbursement lists with an explicit chronic kidney disease indication, decoupled from a diabetes diagnosis.^{12,18}
- Mandate automatic eGFR reporting with every serum creatinine result and expand urine albumin-to-creatinine ratio testing in primary care to enable systematic case-finding.⁴⁰
- Embed SGLT-2 inhibitor initiation into national chronic disease management pathways and clinical decision support, so that prescribing is prompted at the point of eGFR reporting rather than deferred to specialist referral.¹²
- Commission local cost-effectiveness and budget-impact analyses, using the demonstrated reductions in hospitalisation and in end-stage kidney disease management costs as inputs, to quantify the return on investment for the national health insurance scheme.⁴¹

For research

- Prioritise randomized evidence in the populations that remain unstudied: eGFR below 20 mL/min/1.73 m², dialysis, transplantation, paediatric CKD and specific glomerular diseases.¹⁹
- Conduct pragmatic implementation trials in Indonesian and wider Southeast Asian settings to establish real-world effectiveness, adherence and equity of access.
- Evaluate multi-agent pillar regimens for chronic kidney disease in trials powered for hard kidney endpoints rather than for albuminuria surrogates.^{36,39}

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