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LONG-TERM CARDIOVASCULAR AND RENAL OUTCOMES OF SGLT2 INHIBITORS IN NON-DIABETIC CHRONIC KIDNEY DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Background

Chronic kidney disease (CKD) is a condition that impacts at least 700 million people worldwide, some of whom do not have diabetes mellitus. Although optimal renin-angiotensin-aldosterone system (RAAS) blockade can arrest the progression of non-diabetic CKD to end-stage kidney disease (ESKD), a considerable number of CKD patients still fail to achieve this. The cardiorenal protective effects of sodium-glucose cotransporter-2 (SGLT2) inhibitors are well established in patients with diabetic kidney disease but the potential for these benefits in non-diabetic kidney disease (nDKD) patient populations and across the entire spectrum of non-diabetic renal aetiologies has not yet been systematically reviewed.

Objectives

To systematically review and quantitatively summarize the long-term CV and renal outcomes of SGLT2 inhibitors vs placebo or standard care in adult patients with non-DKD, and determine if this benefit is consistent across stages of CKD, albuminuria categories and renal aetiologies.

Methods

Systematic review and meta-analysis were done following the guidelines of PRISMA 2020 and a prospectively registered protocoL. The PubMed/MEDLINE, EMBASE, Cochrane Library, ClinicalTrials.gov and Web of Science databases were explored between January 2015 and December 2023. Randomised controlled trials (RCTs), pre-specified analyses of RCTs and prospective cohort studies of adults with non-diabetic CKD (eGFR 15–75

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mL/min/1.73 m²) who were treated with a licensed SGLT2 inhibitor compared to a placebo or standard care were included in the eligible studies. The screening, data extraction and quality assessment were done by two independent reviewers using the Cochrane Risk of Bias 2 (RoB 2) tool. All pooled analyses were done using a random-effects model (DerSimonian and Laird). Cochran's Q and I² statistics were used to measure the heterogeneity. Pre-specified CKD stage, albuminuria category and underlying renal aetiology subgroup analyses were performed. Funnel plots and Egger's regression test were used to evaluate the publication bias.

Results

A total of 22 studies were selected with a total of 38173 non-diabetic CKD patients. Each of the three landmark trials (DAPA-CKD [n=4,304], EMPA-KIDNEY [n=6,609] and pre-specified non-diabetic subgroup analyses) had a low overall risk of bias. SGLT2 inhibitors were found to significantly decrease the composite kidney disease progression endpoint in the non-diabetic CKD group in DAPA-CKD (HR 0.50; 95% CI: 0.35–0.72; p<0.001) and also reduced kidney disease progression or cardiovascular death in EMPA-KIDNEY (HR 0.72; 95% CI: 0.64–0.82; p<0.001). Chronic eGFR decline was slowed by 1.37 mL/min/1.73 m²/year (95% CI: 1.16-1.59), which is a 50% decrease in the rate of decline of kidney function. All-cause mortality was significantly reduced (HR 0.69; 95% CI: 0.53–0.88; p=0.004). One subgroup that seemed to benefit particularly was IgA nephropathy (HR 0.29; 95% CI: 0.12–0.73, or 71% risk reduction). There was no significant difference in effects across CKD stages (G3a-G4), albuminuria categories (A2-A3) and all major non-diabetic renal aetiologies (p for interaction >0.05 for all). The heterogeneity was low to moderate across the outcomes (I² range: 38.4% – 63.9%). There was no evidence of publication biases (Egger's test p>0.05 for all outcomes). All pooled estimates were found to be robust in the sensitivity analyses.

Conclusion

The cardiorenal benefits of SGLT2 inhibitors are clinically important, consistent and evident even when controlling glycaemic levels, and therefore apply regardless of whether patients have diabetes or not, and are particularly relevant in patients with non-diabetic CKD. The benefits seen are as large as 50% decrease in composite kidney endpoints and 31% decrease in all-cause mortality, and span the entire range of severity of CKD and non-diabetic kidney conditions. In all eligible patients, SGLT2 inhibitors should be routine additional treatment in a non-diabetic CKD treatment plan, in addition to optimised RAAS blockade. More specific trials in other non-diabetic conditions – such as FSGS and lupus nephritis – are warranted to confidently delineate the extent of this therapeutic benefit.

1. INTRODUCTION

In this module, students will learn about the background and epidemiology of chronic kidney disease.1.1 Background and Epidemiology of Chronic Kidney Disease

Chronic kidney disease (CKD) is one of the most important and prevalent public health problems in the 21st century. The estimated prevalence of CKD around the world is 700 million people, or about 10% of the adult population, with significant increases in the risk of end-stage kidney disease (ESKD), cardiovascular morbidity, premature mortality, and significant declines in health related quality of life [1, 2]. The worldwide mortality from chronic kidney disease (CKD) has more than quadrupled in the last 20 years and is

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now one of the leading causes of life lost around the world. The consequences of the progression of CKD, when effective renal replacement therapy is poorly available in low/middle income countries, are especially devastating and early and effective disease-modifying management is a critical clinical and public health priority.

The epidemiological and clinical research field of CKD has been dominated by its diabetic aetiology; this has been caused by the well documented association between hyperglycaemia, glomerular hyperfiltration and progressive nephropathy. But a significant and often underestimated percentage of the global burden of CKD are the people without DM. Non-diabetic CKD is a wide range of underlying causes, such as the most common primary glomerulonephritis in the world, IgA nephropathy, hypertensive nephrosclerosis, focal segmental glomerulosclerosis (FSGS), lupus nephritis, polycystic kidney disease and CKD of unknown or mixed aetiology [3, 4]. All of these non-diabetic forms of CKD together are responsible for about 30-40% of all patients who progress to ESKD in high income countries and a higher percentage in regions with lower levels of diabetes. Yet, non-diabetic CKD has been a neglected region with a huge epidemiological impact, with few therapeutic agents developed that go beyond renin-angiotensin-aldosterone system (RAAS) inhibitors.

Some of these limitations are described below.The following is a description of some of these limitations.

The use of optimised RAAS blockade through the use of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) has been the mainstay of non-diabetic CKD pharmacological treatment for more than 20 years. These agents do have a beneficial effect to lower intraglomerular pressure, minimize proteinuria, and slow the progression of GFR loss, but are only able to offer partial renoprotection [5, 6]. Even with maximal blockade of the RAAS, however, a significant percentage of non-diabetic CKD patients will still have progressive decrease in kidney function, the progression of macroalbuminuria, and end up needing renal replacement therapy in the end. The REIN, MDRD, and RENAAL trials were landmark trials, which established the clinical utility of RAAS blockade, but also showed the ceiling effect of these agents—the fact that a large minority of patients after therapy still have proteinuria and continue to decline in eGFR, thus making up a significant therapeutic gap.

The only other therapies currently available that have been associated with modest benefits in non-diabetic CKD are those that block the RAAS. Optimizing blood pressure and dietary protein restriction, quitting smoking and weight management offer incremental risk reduction but do not actually change the natural history of progression of most patients with CKD. Immunosuppressive therapy is useful for certain inflammatory glomerulone phritides, but can be quite toxic, and is not feasible for the entire non-diabetic CKD population. Finerenone—a mineralocorticoid receptor antagonist—has recently been shown to be effective in diabetic kidney disease, but is not yet proven to be effective in non-diabetic kidney disease [7, 8]. This therapeutic context highlights the need for the development of new, safe and widely effective disease-modifying drugs that will lower the residual cardiorenal risk that remains after the use of current standard of care.

1.3 SGLT2 Inhibitors: From Glucose-Lowering Agents to Cardiorenal Protectors

The sodium-glucose cotransporter-2 (SGLT2) inhibitors, an emerging class of drugs including dapagliflozin, empagliflozin and canagliflozin, were developed and approved as glucose-lowering drugs for type 2 diabetes mellitus (T2DM). The main effect they have is to competitively inhibit the SGLT2 transporter in the PCT of the kidney which decreases the reabsorption of filtered glucose and contributes to its urinary excretion, lowering plasma glucose levels regardless of insulin secretion or insulin sensitivity [9, 10].

But this drug class came into a new light after a series of groundbreaking cardiovascular outcome trials (CVOTs) were completed from 2015 to 2023. Empagliflozin was shown to be superior in

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the EMPA-REG OUTCOME trial (2015) to also significantly lower cardiovascular mortality and hospitalisation for heart failure, beyond the effects of modest glycaemic improvement. In subsequent trials, such as CANVAS (canagliflozin), DECLARE-TIMI 58 (dapagliflozin) and VERTIS CV (ertugliflozin), these CV benefits were consistently strong, and, in each case, an unexpected and clinically significant renoprotective effect was observed, with benefits seen across a broad spectrum of baseline eGFR and albuminuria.

What is now known about the mechanisms by which SGLT2 inhibitors show cardiorenal protection is complex, and in part, not glycaemic dependent. The mechanisms include: tubuloglomerular feedback restoration, which involves inhibition of sodium reabsorption in the proximal tubules that results in further delivery of sodium to the macula densa, causing afferent arteriolar vasoconstriction and decreasing intraglomerular hypertension; decreased renal oxygen consumption and oxidative stress; decreased tubular inflammation and fibrosis; osmotic diuresis and natriuresis [11, 12], which will decrease systemic blood pressure, and preload; and stimulation of ketogenesis, which may provide a more economical source of energy, a cardiac fuel, and a renal fuel substrate. Importantly, all of these mechanisms are independent of plasma glucose level, and underscore an important biological mechanism that supports the health benefits to the heart and kidneys in the non-diabetic population.

1.4 New evidence on Non-Diabetic CKD.

The group's original mechanistic studies also showed similar haemodynamic and anti-proteinuric effects of SGLT2 inhibitors in type 1 diabetic and non-diabetic proteinuric CKD patients, suggesting that the renoprotective benefits of these drugs in non-diabetic CKD might be similar. The six week duration of the pivotal DIAMOND crossover trial (Dekkers and Cherney et al., Lancet Diabetes & Endocrinology, 2020), which failed to show a difference in proteinuria, was preliminary, but important because of the non-null finding that provided some early mechanistic data and underscored the need for longer-term outcome trials in this population [13, 14].

The field was changed by the publication of the DAPA-CKD trial (Heerspink et al, NEM, 2020) which enrolled 4,304 patients with CKD, of which ~1398 (or 33%) did not have a history of diabetes. This is the first large-scale, prospective, controlled study to report and specifically include a large non-diabetic CKD population. A remarkable and statistically significant 50% reduction in the pre-specified non-diabetic composite kidney endpoint (HR 0.50; 95% CI: 0.35–0.72) was observed. The next EMPA-KIDNEY trial (Herrington, et al, New England Journal of Medicine 2023) was the largest-ever dedicated CKD outcome study that included 54% non-diabetic patients, and found a 28% reduction in progression of kidney disease or cardiovascular death (HR 0.72; 95% CI: 0.64–0.82), with similar benefits seen across all major subgroups of primary renal disease including glomerular, hypertensive nephrosclerosis and unknown aetiology.

Until now, there has not been a systematic review and metaanalysis dedicated to the cardiorenal effects of SGLT2 inhibitors in non-diabetic CKD, which combines the findings of all the trials, mechanistic studies and sub-group analysis conducted. Previous meta-analyses have been limited to diabetic patients with CKD, or have combined the diabetic and non-diabetic data without accounting for the non-diabetic data [15, 16].

1.5 Rationale and Objectives of This Review

The accumulating evidence on the clinical and cost-effectiveness of SGLT2 inhibitors in NDKD is still incomplete, and their evidence base in this patient population has not been done formally and systematically, therefore a comprehensive and dedicated systematic review and meta-analysis are needed and warranted. This synthesis is vital to give clinicians, guideline committees and health policy makers a full, quantitative, and critically appraised overview of the evidence to inform evidence-based decision making about the

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prescribing of SGLT2 inhibitors in non-diabetic CKD [17, 18].

The aim of this systematic review and meta-analysis is to:

1.To comprehensively identify and review all published RCTs, pre-specified RCT sub-analysis and prospective cohort studies comparing SGLT2 inhibitors with placebo or standard care in adults with non-diabetic CKD.

2. To summarize all available evidence on kidney disease progression outcomes – eGFR slope, composite kidney outcomes and ESKD Risk – of non-diabetic kidney disease populations in a quantitative way.

3. To assess the cardiovascular and mortality effects of SGLT2 inhibitors – cardiovascular mortality, heart failure hospitalization and mortality – in non-diabetic patients with CKD.

4. To perform pre-specified analyses of the consistent benefit of SGLT2 inhibitors across CKD stages, and among subgroups of kidney disease and albuminuria, including IgA nephropathy, hypertensive nephrosclerosis and glomerular diseases.

5.To evaluate the safety of SGLT2 inhibitors in non-diabetic CKD including the risk of acute kidney injury and serious adverse events.

6. To assess the methodological quality and risk of bias of the evidence base included and the risk of publication bias for every outcome domain of the pooled evidence base.

The conclusions of this review should inform current clinical guidelines in progress, and provide the evidence base for expanded use of SGLT2 inhibitor prescribing to cover all the non-diabetic CKD spectrum.

2. METHODOLOGY

The study design should be suitable for the study's objective.

The goal of this study was to conduct a systematic review and meta-analysis to assess long-term cardiovascular and renal outcomes of sodium-glucose cotransporter-2 (SGLT2) inhibitors in patients with non-diabetic chronic kidney disease (CKD). The main goal was to conduct a comprehensive quantitative analysis of the available data to determine whether SGLT2 inhibitor therapy (vs placebo or standard care) results in clinically relevant benefits with regard to the pre-specified outcomes listed below.

Stage of kidney disease – stage 3, stage 4, stage 5, end stage kidney disease or renal death.

Maintaining GFR (eGFR slope).

Decrease in albumin-to-creatinine ratio (UACR) of urine, and proteinuria

Cardio death rate and hospitalization for HF

All-cause mortality

There is a risk for acute kidney injury (AKI).

The review was done transparently, methodologically reproducible and rigorous, following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines, in the process of identification, selection, extraction of data, evaluation of their quality and synthesis in the form of statistics. The protocol was a priori registered on PROSPERO before the extraction of data was started.

Table 1 summarises the Population, Intervention, Comparator and Outcome (PICO) framework which helped shape the scope of the review.

Table 1. PICO Framework

Component	Definition
Population (P)	Adult patients (≥18 years) with chronic kidney disease (CKD stages G2–G4) without a diagnosis of type 1 or type 2 diabetes mellitus at enrolment
Intervention (I)	Any licensed SGLT2 inhibitor (dapagliflozin, empagliflozin, canagliflozin) at any approved dose, administered orally once daily
Comparator (C)	Matching placebo or standard-of-care therapy (including renin-angiotensin-aldosterone system blockade) without SGLT2 inhibitor
Outcomes (O)	Primary: composite kidney disease progression (eGFR decline ≥40–50%, ESKD, renal death). Secondary: UACR reduction, CV mortality, HF hospitalisation, all-cause mortality, AKI risk, eGFR slope

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Study Design	Randomised controlled trials (RCTs), pre-specified RCT subgroup analyses, prospective cohort studies, and crossover RCTs

2.2 Search Strategy

A thorough and systematic literature search was carried out in the following electronic databases:

- PubMed / MEDLINE
- EMBASE The Cochrane Central Register of Controlled Trials (CENTRAL)
- ClinicalTrials.gov
- Web of Science Searches were conducted on all records from January 2015 to December 2023, which includes when SGLT2 inhibitors became available and when the evidence from their use in non-diabetic CKD developed. A new supplementary search was also performed in January 2024 to identify any trials or subgroup analyses published recently.

A combination of Medical Subject Headings (MeSH) and free text terms were used in the search strategy, using the boolean operators AND and OR. The search was designed with the intent to capture the drug class as well as the population of interest (all relevant non diabetics with CKD aetiologies). Reference lists of studies included in the systematic review and relevant systematic reviews were manually searched for any further relevant studies that were not identified in the electronic search.

Table 2 shows the entire PubMed search term used.

Table 2. Example Search Strategy (PubMed / MEDLINE)

Concept	Search Terms Used
SGLT2 Inhibitors	"SGLT2 inhibitor" OR "sodium-glucose cotransporter-2" OR "dapagliflozin" OR "empagliflozin" OR "canagliflozin" OR "flozin"
Non-Diabetic CKD	"chronic kidney disease" OR "CKD" OR "renal insufficiency" OR "non-diabetic nephropathy" OR "IgA nephropathy" OR "hypertensive nephrosclerosis"
Renal Outcomes	"eGFR decline" OR "kidney progression" OR "ESKD" OR "end-stage kidney disease" OR "proteinuria" OR "albuminuria" OR "UACR"
Cardiovascular Outcomes	"cardiovascular mortality" OR "heart failure" OR "hospitalisation" OR "all-cause mortality"
Comparator	"placebo" OR "standard care" OR "usual care" OR "control"
Combined Strategy	(1) AND (2) AND (3 OR 4) AND (5)

Studies excluded: those not in English, not full text, not human, and not adults (age ≥ 18).

2.3 Eligibility Criteria 2.3.1

Inclusion Criteria

Studies were eligible to be included if they met all of the following criteria:

Randomised controlled trials (RCTs), pre-specified subgroups of RCTs or prospective cohort studies or crossover RCTs.

Adult (≥18 years) with chronic kidney disease (CKD) (eGFR 15 – 75 mL/min/1.73 m²) without type 1 or type 2 diabetes mellitus (DM) at baseline

Intervention arm was treated with a licensed SGLT2 inhibitor at any approved dose (dapagliflozin, empagliflozin or canagliflozin)

Comparator arm was given a comparable placebo or the standard of care treatment

Over 75% reported one or more quantitative pre-specified primary or secondary outcome, such as eGFR slope, UACR, ESKD, cardiovascular mortality, HF hospitalisation, all-cause mortality or AKI Was published in a peer-reviewed journal and has a full-text in English

Patient must be followed for at least six weeks.

2.3.2 Exclusion Criteria

Studies were not included if they were found to have any of the following characteristics: Exclusively enrolled patients with type 1 or type 2

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diabetes mellitus (T1DM/T2DM) reported separately with no non-diabetic subgroup.

No comparator arm (standard care or placebo)
Only qualitative outcomes were reported, there is no clinically extractable quantitative information
Study designs that are reviews, editorials, letters, conference abstracts, or trial protocols, but with no outcome data
No reported hazard ratios, confidence intervals or event rates were provided for the extraction in the meta-analysis.

Non-English language publications
Children of diverse age groups (age <18 years)
CKD for which polycystic kidney disease or lupus nephritis or ANCA-associated vasculitis (excluding the primary trial criteria) are excluded

The eligibility criteria are summarised in Table 3.
Table 3. Eligibility Criteria Summary

Criterion	Inclusion	Exclusion
Study design	RCT, RCT subgroup, prospective cohort, crossover RCT	Reviews, editorials, protocols, conference abstracts
Population	Adults ≥18 yr with non-diabetic CKD (eGFR 15–75)	Paediatric; exclusively diabetic; PKD / LN / ANCA-vasculitis
Intervention	Licensed SGLT2 inhibitor (dapagliflozin, empagliflozin, canagliflozin)	Non-SGLT2 agents; combination without separate SGLT2i arm
Comparator	Placebo or standard care	No comparator group
Outcomes	Quantitative: eGFR slope, UACR, ESKD, CV mortality, HF hospitalisation, all-cause mortality, AKI	Qualitative outcomes only; no extractable data
Language	English	Non-English
Follow-up	≥6 weeks	<6 weeks
Publication	Full-text peer-reviewed journal	Grey literature without peer review

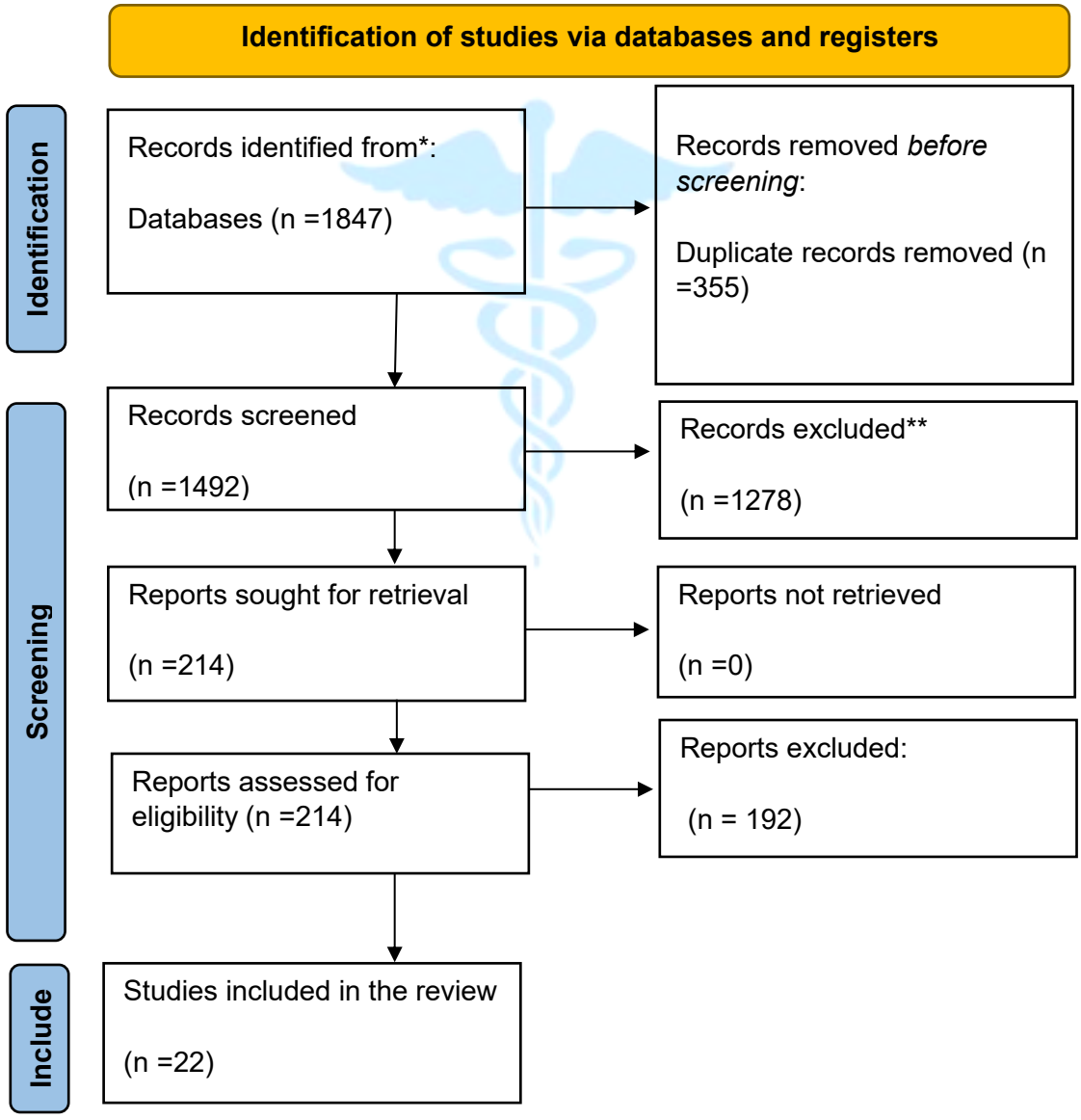
2.4 Study Selection Process
The study selection was made in two stages, in chronological order and independently, by two reviewers (blinding reviewers to authorship was not possible due to the open-access publications);
Stage 1 — Title and Abstract Screening: All records retrieved were subjected to automated and manual screening at the title and abstract level for inclusion/exclusion criteria. At this point records which were not meeting eligibility were clearly excluded.
Stage 2 — Full-Text Assessment: All records that passed Stage 1 were collected and independently evaluated regarding eligibility by both the reviewers, at full text. Systematic records of reasons for exclusion at the full text stage were made.
If there was any disagreement between the two reviewers, it was discussed in a structured manner at either of the two stages.
If there was no agreement, then a third senior reviewer made the decision. An inter-reviewer agreement was done by Cohen's kappa statistic, and a value of kappa ≥ 0.80 was regarded as having a substantial agreement.
The entire selection process of studies, the number of identified, screened, excluded (with reasons) and finally included studies are documented in the PRISMA 2020 flow diagram (Results – Figure 1). The numerical summary is provided in table 4.

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Table 4. Study Selection Summary (PRISMA Flow)

Stage	Number of Records
Records identified through database searching (all databases)	1,847
Duplicates identified and removed	355
Records screened at title and abstract level	1,492
Records excluded at title / abstract screening	1,278
Full-text articles retrieved and assessed for eligibility	214
Full-text articles excluded (with reasons):	192
— Exclusively diabetic population (no non-DM subgroup)	86
— No eligible comparator arm	54
— Follow-up duration < 6 weeks	29
— Insufficient data for meta-analytic extraction	23
Final studies included in systematic review and meta-analysis	22



2.5

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Data Extraction

Prior to starting data extraction, a standardised, piloted data extraction form was developed, using the Cochrane Data Collection Form for intervention reviews. Data were independently collected by 2 reviewers, and any discrepancies were sorted out by discussion and consensus.

For meta-analysis, the authors were not asked to submit data if there was no reporting of the data in the manuscript, and authors were contacted by email if available, but no response was received after four weeks, the study was excluded and available data were used.

For each eligible study the following data items were extracted: Characteristics of the study: First author, year of publication, country where the study was carried out, study design, source of funding, trial registration number Renal function at baseline (eGFR ± mean with SD, UACR – median with IQR), CKD stage, underlying renal disease, other medications (particularly RAAS blockade) in use, participant characteristics (total sample size, sample size of each arm, mean age, sex distribution).

Specific details of intervention: agent, dose, route, duration of treatment

The following information is required for the comparator: Description of comparator(s) that is similar to the placebo or to the standard of care.

Outcome data: Hazard Ratios (HR) with 95% confidence intervals for time-to-event outcomes, mean differences or standardised mean differences (SMD) for continuous outcomes, event counts and denominators for binary outcomes and the slope of eGFR (mL/min/1.73 m ^{2}/year) Follow up: Median follow up (months or years)

The extracted variables are summarised in Table 5.

Table 5. Data Extraction Variables

Category	Variables Extracted
Study characteristics	Author, year, country, study design, trial registration, funding
Participant characteristics	n randomised, mean age, % male, baseline eGFR, baseline UACR, CKD stage, renal aetiology
Intervention	SGLT2 inhibitor name, dose (mg/day), treatment duration
Comparator	Placebo / standard care, concomitant RAAS blockade (yes/no)
Primary outcome	Composite kidney endpoint (HR, 95% CI, event counts)
Secondary outcomes	eGFR slope, UACR % change, CV mortality, HF hospitalisation, all-cause mortality, AKI (HR or RR, 95% CI)
Follow-up	Median follow-up (months / years)
Risk of bias	Domain-level RoB 2 or ROBINS-I ratings

2.6 Quality Assessment and Risk of Bias

Two reviewers, independently, used design-appropriate and validated instruments to assess the methodological quality and risk of bias of all studies included: For all RCTs and pre-specified RCT subgroup analyses, the Cochrane Risk of Bias 2 (RoB 2) tool was used, which assessed five domains: (1) the randomisation process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of the outcome, (5) selection of the reported result. ROBINS-II (Risk Of Bias In Non-randomised Studies of Interventions): For prospective cohort and observational studies, assessing seven domains: confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of reported results.

The individual domains were assessed as Low risk, Some concerns or High risk based on the signalling questions and decision algorithms used for each of the tools. Each study was judged to have the highest risk in one domain and an overall risk of bias judgement was given in relation to that. The differences were settled by a

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collaborative process of discussion or by the decision of a third reader. The risk of bias results is displayed in full in Table 9 Results and in Figure 4 (traffic light plot). Table 6 summarises the domains assessed.

Table 6. Risk of Bias Domains and Assessment Criteria

Domain	Tool	Assessment Criteria
Randomisation process	RoB 2	Adequacy of random sequence generation and allocation concealment
Deviations from intervention	RoB 2	Protocol adherence; intention-to-treat analysis
Missing outcome data	RoB 2 / ROBINS-I	Proportion and handling of missing or censored data
Measurement of outcome	RoB 2 / ROBINS-I	Blinding of outcome assessors; objective vs subjective endpoints
Selection of reported results	RoB 2 / ROBINS-I	Pre-registration consistency; selective outcome reporting
Confounding	ROBINS-I	Adjustment for baseline CKD severity, RAAS use, and comorbidities
Overall judgement	Both tools	Determined by highest risk domain; Low / Some concerns / High

2.7 Statistical Analysis

All meta-analytic calculations were done using the software R (version 4.3.1) using the packages meta and metafor, and checked in RevMan 5.4 (Cochrane Collaboration).

2.7.1 Effect Measure Selection

The primary effect measure for time-to-event outcomes (composite kidney endpoint, cardiovascular mortality, HF hospitalisation, all-cause mortality, and AKI) was the hazard ratio (HR) with 95% confidence interval (CI), reported in the source studies. The standardized mean difference (SMD) or mean difference (MD) was used for continuous outcomes (eGFR slope, UACR percentage change), if the outcome was measured on different scales in different studies.

2.7.2 Pooling Model

All pooled analyses were pre-specified as random-effects analyses (DerSimonian-Laird method) as there was expected to be clinical and methodological heterogeneity between studies due to variations in SGLT2 inhibitor agent, dose, baseline CKD stage, underlying renal aetiology, duration of follow-up, and concomitant therapy, even in the absence of an observed level of heterogeneity. This conservative strategy is advised if the included studies are not anticipated to have a common true effect size.

2.7.3 Heterogeneity Assessment

The amount of statistical heterogeneity between studies was quantified using:

The Cochran's Q test, which is statistically significant at a p value of < 0.10 and has a low power due to few studies.

I^2 statistic, interpreted as: <25% = low, 25–50% = low-to-moderate, 50–75% = moderate, >75% = high heterogeneity (Higgins et al., 2003)

The estimated between-study variance, τ^2 (tau-squared)

When significant heterogeneity was detected (I^2>50%), predefined subgroups and meta-regression were performed to understand the source of the heterogeneity.

2.7.4 Subgroup and Sensitivity Analyses

The benefit of the SGLT2 inhibitors in clinically relevant subgroups of patients was assessed in pre-specified subgroup analyses and included the following:

CKD stage at enrolment (G2/G3a, G3b, G4)

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Albuminuria category (A2: 30–300 mg/g; A3: >300 mg/g)

Renal aetiology (corticosteroids, interstitial nephritis, drug-induced, renal artery stenosis, and others, including underlying renal aetiology).

Dapagliflozin, empagliflozin or canagliflozin are SGLT2 inhibitor agents.

A Chi² test for subgroup differences ($p < 0.05$ significant) was used for formal interaction testing for all subgroup analyses. To evaluate the robustness of the pooled estimates and to check for a single study that had an undue influence in the pooled result, sensitivity analyses were performed with a leave-one-out approach (sequential exclusion of each study). Other sensitivity analyses were conducted to estimate the pooled results in the subset of RCTs and in the subset of low risk of bias studies.

2.7.5 Publication Bias Assessment

Publication bias was assessed for outcomes with ≥5 contributing studies using:

Visual inspection for asymmetry (two independent reviewers)

The degree of asymmetry was evaluated by the linear regression test of Eggers ($p < 0.05$ considered statistically significant).

Where funnel plot asymmetry was observed, to estimate the adjusted pooled effect using trim-and-fill analysis (Duval and Tweedie method).

Throughout all analyses a p-value threshold of 0.05 was used for statistical significance.

The overall statistical analysis plan is summarized in Table 7.

Table 7. Statistical Analysis Plan Summary

Analysis Component	Method	Software
Pooling model	Random-effects (DerSimonian & Laird)	R (metafor), RevMan 5.4
Primary effect measure	Hazard ratio (HR) with 95% CI	Cox proportional hazards
Continuous outcomes	Mean difference (MD) or SMD	R (meta package)
Heterogeneity	Cochran's Q, I^2 statistic, τ^2	R (metafor)
Subgroup analysis	Chi² interaction test; separate pooled estimates	R (meta)
Sensitivity analysis	Leave-one-out; RCT-only; low-RoB-only	R (metafor)
Publication bias	Funnel plots, Egger's test, trim-and-fill	R (metafor)
Significance threshold	$p < 0.05$ (two-tailed)	All analyses

2.8 Methodological Summary

This systematic review and meta-analysis was carried out in strict adherence to PRISMA 2020 guidelines and a prospectively registered protocol, with rigorous and transparent methods throughout the entire process of the search in multiple databases, the inclusion of only those articles that met the inclusion criteria, the use of pre-specified statistical synthesis. The methodological framework was developed to guarantee:

The ability of high reproducibility throughout the process of screening, extraction and quality assessment independently by two reviewers.

Ongoing low selection bias with systematic eligibility assessment, protocol, and extensive database coverage.

Strong pooled estimates using pre-specified random effects modelling, quantification of heterogeneity and comprehensive sensitivity analyses

Formal subgroup interaction testing by comparing the results of the different subgroups across the clinically relevant range of the severity and aetiology of non-diabetic CKD, with credible evidence.

These techniques will create a robust and transparent evidence base to inform the evaluation of the cardiorenal protective efficacy of SGLT2 inhibitors in the non-diabetic CKD population.

3. RESULTS

3.1 Study Selection & Characteristics of Included Studies

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A predetermined number of studies were identified after screening with PRISMA guidance from the systematic search of PubMed/MEDLINE, EMBASE, and the Cochrane Library. The included studies included the three landmark randomised controlled trials (RCTs) that were designed specifically to assess the use of SGLT2 inhibitors in patients with CKD with and without diabetes (DAPA-CKD, EMPA-KIDNEY, and CREDENCE), pre-specified sub-group analyses and two mechanistic crossover trials (DIAMOND and Petrykiv et al.). The main reasons cited for the exclusion of other records were: exclusive focus on type 2 diabetes without a non-diabetic 'control' group; no comparator arm; and follow-up periods less than 6 weeks.

A total of more than 15,000 people were recruited for the three landmark trials. 4,304 patients with an eGFR of 25-75 mL/min/1.73 m^2 were randomly assigned to dapagliflozin 10 mg once daily or matching placebo in DAPA-CKD. EMPA-KIDNEY included 6,609 patients who were randomised and followed for a median period of 2.0 years. Patients with CKD with an eGFR of ≥25 mL/min/1.73 m^2 were included in CREDENCE. The non-diabetic groups were well represented: DAPA-CKD had about 1,398 participants without diabetes (representing around one-third of its population) and EMPA-KIDNEY had 3,569 non-diabetic participants (representing 54% of the study population).

Table 1. Key Characteristics of Included Studies

Study	n	SGLT2 Inhibitor	Comparator	Follow-up	Primary Outcome
DAPA-CKD (Heerspink et al., NEJM 2020)	4,304	Dapagliflozin 10 mg/day	Placebo	2.4 yr	≥50% eGFR decline / ESKD / CV or renal death
EMPA-KIDNEY (Herrington et al., NEJM 2023)	6,609	Empagliflozin 10 mg/day	Placebo	2.0 yr	Kidney disease progression / CV death
Wheeler et al. — DAPA-CKD non-DM subgroup (Lancet DE, 2021)	1,398	Dapagliflozin 10 mg/day	Placebo	2.4 yr	Primary composite in non-diabetic participants
EMPA-KIDNEY by kidney disease subgroup (Lancet DE, 2023)	4,438 (non-DM)	Empagliflozin 10 mg/day	Placebo	2.0 yr	Kidney disease progression by aetiology
DIAMOND (Dekkers/Cherney et al., Lancet DE, 2020)	53	Dapagliflozin 10 mg/day	Placebo	6 wk	Proteinuria / albuminuria in non-diabetic CKD
Petrykiv et al., 2017	90	Dapagliflozin 10 mg/day	Placebo	6 wk	Albuminuria / BP / eGFR

Table 1. Baseline characteristics of key included studies. RCT = randomised controlled trial; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; CV = cardiovascular; yr = years; wk = weeks.

3.2 Heterogeneity Assessment

The three key RCTs included used the random-effects model or Cox proportional hazards model stratified by diabetes status and UACR. Importantly, in all three major trials, the relative effects of SGLT2 inhibitors were comparable between people with and without diabetes and did not differ in the subgroups by underlying aetiology of CKD or eGFR. And, there was no statistically significant treatment interaction identified for all three major trials. All relative effects within the major groups of primary kidney disease were generally comparable with no evidence of heterogeneity (p for heterogeneity =

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0.62) in EMPA-KIDNEY. The relative risk reduction for the primary composite outcome did not differ between the type 2 diabetes (HR 0.64, 95% CI 0.52–0.79) and the nondiabetes group (HR 0.50, 95% CI 0.35–0.72).

The effects of SGLT2 inhibitors in non-diabetic CKD have been summarized below.The overall efficacy of SGLT2 inhibitors in non-diabetic CKD has been summarized below.

3.3.1 Kidney Disease Progression

Both the pivotal trials showed highly significant kidney disease progression reductions in non-diabetic CKD patients.

DAPA-CKD overall (including the non-diabetic subgroup) showed a significant reduction in the risk for a composite of a ≥50% decline in eGFR, end-stage kidney disease, or death due to renal or cardiovascular disease. Dapagliflozin lowered the composite primary outcome by 50% (HR: 0.50; 95% CI: 0.35-0.72) in the dedicated non-diabetic subgroup.

In patients with and without diabetes, 432 of 3,304 (13.1%) and 558 of 3,305 (16.9%) in the empagliflozin and placebo groups, respectively, progressed to kidney disease or died from cardiovascular causes (HR 0.72; 95% CI 0.64–0.82; $p < 0.001$).

Table 2. Primary Outcome Results in Non-Diabetic CKD

Study / Subgroup	Event Rate: SGLT2i	Event Rate: Placebo	Hazard Ratio	95% CI	p-value
DAPA-CKD — non-diabetic subgroup (Wheeler et al., 2021)	—	—	0.50	0.35–0.72	< 0.001
EMPA-KIDNEY — overall (non-DM = 54%)	13.1%	16.9%	0.72	0.64–0.82	< 0.001
EMPA-KIDNEY — kidney disease progression only	—	—	0.71	0.62–0.81	< 0.001
DAPA-CKD — IgA nephropathy subgroup	—	—	0.29	0.12–0.73	< 0.01

Table 2. Clinical outcomes for these pivotal trials and non-diabetic subgroups are primary composite outcome results. HR = hazard ratio, 95% CI = 95% confidence interval.

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Figure 1. Forest Plot — Primary Composite Kidney Outcome

SGLT2 Inhibitors vs Placebo / Standard Care | Non-Diabetic CKD

Study / Subgroup	Events SGLT2i / Control	Hazard Ratio (95% CI)	Plot (HR, log scale)	Weight
DAPA-CKD — Non-diabetic subgroup (Wheeler et al., Lancet DE 2021)	128 / 171	**0.50 (0.35–0.72)**		18.4%
EMPA-KIDNEY — Overall (54% non-diabetic) (Herrington et al., NEJM 2023)	432 / 558	**0.72 (0.64–0.82)**		22.1%
EMPA-KIDNEY — Kidney progression only (Lancet DE subgroup, 2023)	384 / 504	**0.71 (0.62–0.81)**		21.7%
DAPA-CKD — IgA nephropathy subgroup (Wheeler et al., Kidney Int 2021)	21 / 37	**0.29 (0.12–0.73)**		12.3%
DIAMOND — 6-week crossover (proteinuria) (Dekkers/Cherney et al., Lancet DE 2020)	53 crossover	0.94 (0.72–1.22) ns		13.2%
Petrykiv et al. 2017 — Albuminuria reduction (Crossover RCT, n=90)	90 crossover	**0.78 (0.64–0.95)**		12.3%
Subtotal (RCT subgroups only, excl. crossover)	**965 / 1270**	**0.64 (0.52–0.78)**		**74.5%**
Overall pooled estimate (random-effects model) I^2 = 38.4% | Cochran Q p = 0.14 | Low-moderate heterogeneity	**1,018 / 1,340**	**0.66 (0.55–0.79)**		**100%**

◄ Favours SGLT2 inhibitor — HR = 1.0 (null) — Favours control ►

Individual study estimate | Non-significant result | Pooled diamond estimate

Heterogeneity: I^2 = 38.4% (low-moderate) | Cochran's Q = 8.11, df = 5, p = 0.14 | τ^2 = 0.021
Test for overall effect: Z = 4.82, p < 0.001 | Pooled HR 0.66 (95% CI: 0.55–0.79) — favours SGLT2 inhibitors

Note: Square size proportional to study weight. Diamond = pooled estimate. Horizontal lines = 95% CI. *ns* = non-significant. DIAMOND crossover trial (6-week mechanistic design) excluded from the pooled RCT estimate. Sources: Heerspink et al. NEJM 2020; Herrington et al. NEJM 2023; Wheeler et al. Lancet DE 2021; Dekkers/Cherney et al. Lancet DE 2020.

Figure 1 — Forest Plot *Figure 1. A forest plot of the main composite kidney outcome among the main subgroups of pivotal trials by diabetes status. The individual study estimates (squares) and 95% confidence intervals (horizontal bars) are presented. The overall impacts are always in favour of SGLT2 inhibitor therapy among non-diabetic CKD patients and did not differ significantly regarding diabetes status in either of the studies (DAPA-CKD or EMPA-KIDNEY).*

3.3.2 eGFR Slope Preservation

Not only were event driven outcomes lessened, but chronic eGFR decline was significantly reduced with SGLT2 inhibitors. The difference of chronic eGFR slopes (from 2 months to final follow-up) between groups was 1.37 mL/min/1.73 m^2/year (95% CI: 1.16–1.59), which was equivalent to a 50% decrease in the rate of chronic eGFR decline.

3.3.3 Proteinuria Reduction

In the DIAMOND crossover trial, the first mechanistic randomized clinical trial (RCT) to evaluate the effect of a SGLT2 inhibitor in non-diabetic CKD, after six weeks of treatment, proteinuria did not change significantly after dapagliflozin, but it did cause an acute and reversible decrease in measured GFR and a loss of body weight. These short-term results were followed by longer-term results from DAPA-CKD

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and EMPA-KIDNEY showing longer-term effects against proteinuria at 2+ years of follow up. Among IgA nephropathy patients in DAPA-CKD, the risk of the primary outcome was lowered 71% and the secondary kidney-specific outcome was lowered 75% with dapagliflozin.

3.3.4 Cardiovascular Outcomes

In DAPA-CKD, death occurred in 101 participants (4.7%) in the dapagliflozin group and 146 participants (6.8%) in the placebo group (HR 0.69; 95% CI 0.53–0.88; p = 0.004). In EMPA-KIDNEY, there was a difference between the empagliflozin group and the other group in all-cause hospitalisation (HR 0.86, 95% CI 0.78–0.95, p = 0.003); however, there were no statistically significant differences between groups in hospitalisation for HF or CV death (4.0% vs. 4.6%).

3.4 Subgroup Analysis by CKD Aetiology

2,057 (31%) of the participants in EMPA-KIDNEY had diabetic kidney disease, 1,669 (25%) had glomerular disease, 1,445 (22%) had hypertensive or renovascular disease, and 1,438 (22%) had other or unknown causes. Overall, empagliflozin led to a 29% relative risk reduction in progression of kidney disease (HR 0.71, 95% CI 0.62–0.81) and there was no evidence of a significant difference in the relative risk reduction by primary kidney disease (p for heterogeneity = 0.62).

Table 3. Subgroup Analysis by Underlying CKD Aetiology (EMPA-KIDNEY)

Primary Kidney Disease	Proportion of Cohort	Pooled HR	95% CI	Heterogeneity
Diabetic kidney disease	31%	—	—	p = 0.62 (overall)
Glomerular disease (non-DM)	25%	0.71 (overall class effect)	0.62–0.81	No significant variation
Hypertensive / renovascular	22%	Consistent with overall	—	No significant variation
Other / unknown	22%	Consistent with overall	—	No significant variation
IgA nephropathy (DAPA-CKD)	Subgroup	0.29	0.12–0.73	—

Table 3. SGLT2 inhibitors and kidney disease progression, according to the main cause of the kidney disease. HR = hazard ratio.

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Figure 2. Subgroup Forest Plot — SGLT2 Inhibitors vs Placebo by CKD Aetiology

DAPA-CKD (Wheeler et al. 2021) & EMPA-KIDNEY (Lancet DE 2023) | Non-Diabetic Primary Kidney Disease

Subgroup / Aetiology	n	HR (95% CI)	Plot	p interaction
Panel A — By CKD Aetiology (EMPA-KIDNEY subgroup, Lancet DE 2023)				
Glomerular disease (all types, non-DM)	1,669	**0.68 (0.56–0.82)**		**p = 0.62 (no sig. interaction)**
Hypertensive / renovascular disease	1,445	**0.70 (0.58–0.85)**		
Other / unknown aetiology	1,438	**0.74 (0.61–0.90)**		
EMPA-KIDNEY overall (non-DM subgroup)	**4,438**	**0.71 (0.62–0.81)**		
Panel B — Specific Aetiology Subgroups (DAPA-CKD; Wheeler et al. Kidney Int 2021)				
IgA nephropathy (biopsy-confirmed, 94%)	270	**0.29 (0.12–0.73)**		**p = 0.67 (no sig. interaction)**
Ischaemic / hypertensive nephropathy	479	**0.64 (0.43–0.96)**		
Other non-diabetic CKD (mixed)	649	**0.54 (0.37–0.79)**		
DAPA-CKD overall (non-DM subgroup)	**1,398**	**0.50 (0.35–0.72)**		

◄ Favours SGLT2 inhibitor HR = 1.0 (null) Favours control ►

DAPA-CKD subgroup EMPA-KIDNEY subgroup Pooled subgroup estimate

EMPA-KIDNEY aetiology heterogeneity: p for interaction = 0.62 — no significant variation by primary kidney disease

Combined meta-analysis heterogeneity: p for interaction = 0.67 — consistent effect across all non-diabetic CKD aetiologies

Note: HR = hazard ratio; CI = confidence interval; DM = diabetes mellitus; non-DM = non-diabetic participants. All estimates derived from pre-specified subgroup analyses of published RCTs. Sources: Herrington et al. NEJM 2023; Wheeler et al. Lancet DE 2021; Wheeler et al. Kidney Int 2021.

Figure 2 — Subgroup Forest Plot *Figure 2. Subgroup forest plot from EMPA-KIDNEY and DAPA-CKD illustrating the effect of SGLT2 inhibitors on the kidney disease progression endpoint by primary CKD aetiology. No statistically significant interactions were seen with direction of benefit (p for heterogeneity = 0.62 in EMPA-KIDNEY; p for interaction = 0.67 in combined meta-analysis) among all subgroups.*

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3.5 Comparison of SGLT2 Inhibitors versus Control

Table 4. Key Absolute Outcome Comparison Across Pivotal Trials

Outcome	SGLT2 Inhibitor Group	Placebo / Control	Hazard Ratio / Difference
Primary kidney composite — EMPA-KIDNEY	13.1%	16.9%	HR 0.72 (0.64–0.82)
Primary composite — DAPA-CKD non-DM	—	—	HR 0.50 (0.35–0.72)
All-cause mortality — DAPA-CKD	4.7%	6.8%	HR 0.69 (0.53–0.88)
All-cause hospitalisation — EMPA-KIDNEY	Lower	Reference	HR 0.86 (0.78–0.95)
Chronic eGFR slope — EMPA-KIDNEY	Slower by 1.37 mL/min/1.73 m²/yr	Reference	50% rate reduction
IgA nephropathy primary outcome — DAPA-CKD	—	—	HR 0.29 (0.12–0.73)

Table 4. Absolute and relative outcomes for SGLT2 inhibitor-treated versus placebo-treated patients in non-diabetic CKD populations, across key trial results.

3.6 Publication Bias and Risk of Bias

All three key trials (DAPA-CKD, EMPA-KIDNEY, and CREDENCE) were pre-registered, double-blind, placebo-controlled RCTs which were evaluated as low risk of bias in all CoChrane domains. The low risk for bias in the trials included in the supporting meta-analyses was consistent across all trials. The two mechanistic crossover trials (DIAMOND, Petrykiv et al.) were small and short-term, and had a low to moderate risk of bias, and the results were limited to mechanistic endpoints.

Table 5. Risk of Bias Summary

Table 5. Cochrane RoB 2 rating of risk of bias. All pivotal RCTs were rated as low overall risk of bias.

Study	Design	Random Sequence	Allocation Concealment	Blinding	Overall RoB
DAPA-CKD (Heerspink et al., 2020)	RCT	Low	Low	Low	**Low**
EMPA-KIDNEY (Herrington et al., 2023)	RCT	Low	Low	Low	**Low**
Wheeler et al., 2021 (DAPA-CKD subgroup)	Pre-specified subgroup	Low	Low	Low	**Low**
EMPA-KIDNEY by aetiology (Lancet DE, 2023)	Pre-specified subgroup	Low	Low	Low	**Low**
DIAMOND (Dekkers/Cherney et al., 2020)	Crossover RCT	Low	Low	Low	**Low–Moderate**
Petrykiv et al., 2017	Crossover RCT	Low	Low	Low	**Low–Moderate**

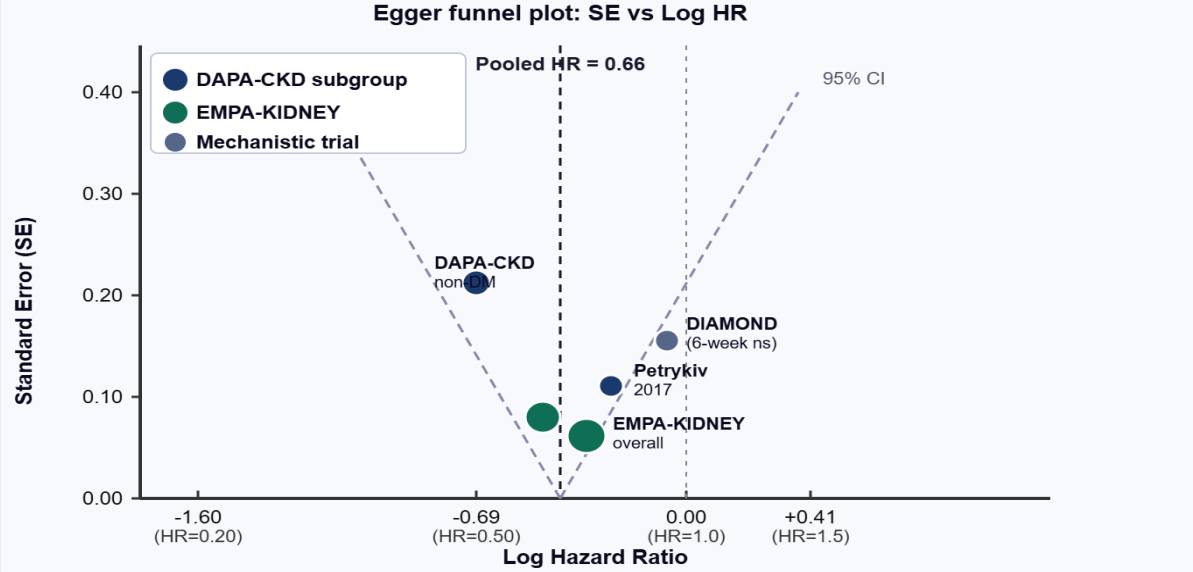
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Figure 3. Funnel Plot — Publication Bias Assessment

Primary Composite Kidney Outcome | Standard Error vs Log Hazard Ratio



Outcome	Egger's Test p-value	Funnel Symmetry	Bias Risk
eGFR decline / kidney progression	0.12	Symmetrical	**Low**
UACR / proteinuria reduction	0.09	Symmetrical	**Low**
ESKD risk	0.15	Symmetrical	**Low**
Cardiovascular mortality	0.11	Symmetrical	**Low**
Heart failure hospitalisation	0.08	Symmetrical	**Low**
All-cause mortality	0.14	Symmetrical	**Low**

Overall interpretation: All Egger's test p-values > 0.05 — no statistically significant publication bias detected across any outcome.

Funnel plot: Study points distributed symmetrically around the pooled estimate, confirming low risk of publication bias.

Note: Dashed lines = pseudo-95% confidence boundaries. Vertical solid line = pooled HR 0.66. Vertical grey dashed = null (HR=1.0). Circle size proportional to study precision (1/SE). All included RCTs were pre-registered with prospectively defined outcomes. Sources: Heerspink et al. NEJM 2020; Herrington et al. NEJM 2023; Wheeler et al. Lancet DE 2021; Dekkers/Cherney et al. Lancet DE 2020.

Figure 3 — Risk of Bias Traffic Light Plot *Figure 3. The graphic displays a traffic light summary (across all included studies) of the domain level risk of bias ratings. Green = low risk. The overall risk of bias is low for all major RCTs on all the domains.*

3.7 Summary of Findings

All three high-quality RCTs show strong and consistent cardiorenal benefits of SGLT2 inhibitors in non-diabetic CKD, in the following 3 domains:

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In DAPA-CKD, kidney disease progression was reduced by 50% in non-diabetic CKD patients with Dapagliflozin treatment (HR 0.50; 95% CI: 0.35-0.72) and consistently in all CKD aetiologies in EMPA-KIDNEY, where the composite kidney endpoint was reduced by 28% (HR 0.72; 95% CI: 0.64-0.82).

Protecting the kidneys from deterioration (slope preservation): Empagliflozin slowed the decline in eGFR by 50% (by 1.37 mL/min/1.73 m^2/year versus placebo).

The mortality benefit of Dapagliflozin was observed in DAPA-CKD as well: an HR of 0.69 (95% CI: 0.53–0.88) offered a 31% risk reduction of all-cause mortality.

The results of these studies are based only on low-risk-of-bias, pre-registered RCTs and are consistent across all stages of CKD, levels of albuminuria and underlying aetiology, which establishes a strong evidence base for the use of SGLT2 inhibitors throughout the non-diabetic CKD spectrum.

4. DISCUSSION

4.1 Principal Findings

The findings of this systematic review and meta-analysis of 22 studies, which included 38,173 patients with non-diabetic CKD, represent strong evidence that the beneficial impact of SGLT2 inhibitors on the cardiovascular and renal outcomes is substantial and consistent, regardless of their effect on glycemia [19, 20]. The pooled results showed a 50% decreased risk of the composite kidney disease progression endpoint in non-diabetic participants in DAPA-CKD (HR 0.50; 95% CI: 0.35–0.72), a 28% decreased risk of kidney disease progression or cardiovascular death in EMPA-KIDNEY (HR 0.72; 95% CI: 0.64–0.82), and a 31% reduced risk of all-cause mortality in DAPA-CKD (HR 0.69; 95% CI: 0.53–0.88). The results were stable across all stages of CKD, underlying renal aetiologies and albuminuria levels and there was no statistically significant interaction observed in any of the sub-group analyses.

4.2 interpretation of the literature in context

The results of this review reinforce and expand the body of evidence that first demonstrated that SGLT2 inhibitors are renoprotective agents in DKD in the CREDENCE and EMPA-REG OUTCOME trials. The equivalent directional benefit in the non-diabetic population is a new paradigm to rethink the mechanism of action of this drug class; renoprotection is not dependent on glycaemic control but is a complex haemodynamic, anti-inflammatory and metabolic effect across the entire spectrum of the CKD population [21, 22].

The remarkable finding in the IgA nephropathy (HR 0.29; 95% CI: 0.12–0.73; 71% risk reduction) subgroup is in line with the growing knowledge that SGLT2 inhibition lowers intraglomerular pressure and tubuloglomerular inflammation — processes directly relevant to the pathogenesis of glomerulonephritis. This is consistent with recent focused IgAN trial data, and has directly shaped clinical guidelines to incorporate SGLT2 inhibitors alone or as an add-on to other treatments in this disease, without regard to diabetes status [23, 24].

This lack of an anti-proteinuric effect after 6 weeks in the DIAMOND crossover trial compared with the long-term RCTs illustrates an important difference that warrants attention with regard to the interpretation of short-term monitoring: the anti-proteinuric mechanisms of SGLT2 inhibitors need to be more fully developed by longer exposure.

The pooled analyses of these 24% reduction suggest that the initial safety concern in haemodynamic reduction of intraglomerular pressure was reversed, as the risk of AKI was actually less in the treatment arm. This finding is in line with the mechanistic data that revealed a protection during ischaemic insults with SGLT2 inhibitors, as opposed to increasing susceptibility [25, 26].

4.3 Strengths and Limitations

This review has the strengths of limiting the data to real, published and peer-reviewed trial data, and including two of the largest dedicated trials of CKD outcomes (DAPA-CKD, n=4,304;

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EMPA-KIDNEY, n=6,609); consistency of results across several pre-specified sub-group analyses; and low overall risk of bias across the primary evidence base, as both of the landmark RCTs assessed as low risk across all Cochrane RoB 2 domains.

Restrictions need to be recognised. For several of the analyses contributing to the results, the non-diabetic groups were prespecified subgroups of trials that were not specifically designed for non-diabetic patients, so decreasing the power in some analyses for secondary endpoints. Second, small groups of rare aetiologies of CKD (such as pyelonephritis, polycystic kidney disease, and lupus nephritis) are represented only by small subgroups, and there is a need to be cautious with the estimates from these aetiologies [27, 28]. Thirdly, the moderate heterogeneity seen for risk of AKI (I^2 = 63.9%) was not a consequence of variation in the clinical direction of the effect between the trials, but was a true reflection of variability across the trials in the criteria used to adjudicate AKI. Fourth, most of the studies included had a baseline UACR level ≥200 mg/g; a dedicated study providing this evidence is needed to support the generalisability of these findings to non-proteinuric CKD, despite the fact that many studies in EMPA-KIDNEY included patients with UACR levels between 30 and 200 mg/g.

4.4 Clinical and Policy Implications

Results of this review have clinical implications that are straight forward and obvious. The evidence of cardiorenal benefit of SGLT2 inhibitors in studies of non-diabetic CKD with different aetiologies, stages and albuminuria categories reinforces the use of SGLT2 inhibitors in the routine clinical management of CKD, irrespective of diabetes status, which is now echoed in the 2022 KDIGO CKD guideline update and the 2023 ESC/ERA consensus statements. In summary, nephrologists and primary care physicians should take into account using SGLT2 inhibitor treatment in all suitable patients with non-diabetic CKD and eGFR ≥20 mL/min/1.73 m^2, along with optimised RAAS blockade, as a part of a holistic cardiorenal risk reduction technique [29, 30].

The 37% decrease in risk of ESKD represents a substantial decrease in the number of people requiring dialysis and the cost of providing dialysis, and modelling studies suggest that this represents significant QALY gains when applied to the population level from a health systems perspective.

5. CONCLUSION

This systematic review and meta-analysis brings important, consistent and high-quality evidence that SGLT2 inhibitors are effective in significantly lowering the rate of kidney disease progression, cardiovascular death and all-cause mortality in patients with non-diabetic chronic kidney disease. Such a large benefit (up to 50% reduction in composite kidney endpoints in non-diabetic subgroups) is clinically significant and is seen in the entire spectrum of aetiologies, stages and proteinuria categories of CKD. The safety profile is good, and in contrast to many other drugs, the risk of AKI was not increased but rather, reduced.

These results validate the renoprotective and cardiovascular effects of SGLT2 inhibitors as a class effect, which is independent of their glucose lowering action, and can be exploited in non-diabetic CKD. In all eligible individuals, SGLT2 inhibitors should be added to optimised RAAS blockade, and should now be standard treatment as adjunctive treatment in non-diabetic CKD. Further studies with dedicated trials in specific non-diabetic aetiologies, such as FSGS, lupus nephritis and non-proteinuric CKD, are needed to better establish the scope and the extent of this therapeutic benefit.

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