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Effect of Metformin versus Sodium Glucose Cotransporter-2 Inhibitors in Diabetic Patients with Chronic Kidney Disease: A Systematic Review

Qasim Hussain Mohsen ALHulyami[1], Arwa Ahmed Abdulkareem Alhajji[2], Mohammed Fahad Abdulwahab Almomen[3], Mustafa Ahmed Aish BuSaleh[4], Bandar Hamdan Mohaimeed Alnefaie[5], Narjes Ali Nasser AL Shawareb[6], Mona Ali Alwaif[7]

Background:

Diabetic chronic kidney disease carries high risks of kidney failure and cardiovascular events, and clinicians frequently weigh metformin-based care against sodium–glucose cotransporter 2 inhibitor therapy for renoprotection.

Methods:

PubMed was searched from inception to August 2025 (English-language, human studies) for trials and cohort studies in adults with diabetes and chronic kidney disease evaluating metformin strategies and/or sodium–glucose cotransporter 2 inhibitors. Studies reporting kidney progression and cardiovascular or mortality outcomes were narratively synthesized (no meta-analysis).

Results:

Six studies were included: three randomized trials (n=4,304; n=4,401; n=6,609) and three population-based cohort studies (n=1,450; n=45,545; n=4,278). Sodium–glucose cotransporter 2 inhibitors reduced composite kidney outcomes in trials (hazard ratios 0.61 [95% confidence interval 0.51–0.72], 0.70 [0.59–0.82], and 0.72 [0.64–0.82]) and lowered kidney-related adverse events in advanced chronic kidney disease (odds ratio 0.48 [0.33–0.71]). In comparative cohorts, metformin plus sodium–glucose cotransporter 2 inhibitors reduced composite kidney outcomes (adjusted hazard ratio 0.65 [0.48–0.87]) and all-cause mortality (0.74 [0.64–0.84]) versus sodium–glucose cotransporter 2 inhibitors alone, with lower severe acute kidney injury (0.72 [0.54–0.96]) and metabolic acidosis (0.58 [0.40–0.83]); stopping metformin at stage 4 chronic kidney disease increased mortality (hazard ratio 1.26 [1.10–1.44]).

Conclusions:

Sodium–glucose cotransporter 2 inhibitors showed consistent kidney protection, while observational evidence supported continued metformin—especially in combination—when kidney-function–based safety monitoring is feasible in routine practice.

Keywords: *Chronic kidney disease, Diabetes mellitus, Metformin, Sodium-glucose cotransporter 2 inhibitors, Kidney failure, Cardiovascular diseases.*

Author details:
[1] *Acting Consultant Internist/Nephrology, King Fahad Hospital, Al-Hofuf, Saudi Arabia.*
[2] *Nephrology Consultant, King Fahad Hospital, Al-Hofuf, Saudi Arabia.*
[3] *Nephrology Consultant, King Fahad Hospital, Al-Hofuf, Saudi Arabia.*
[4] *Nephrology Consultant, King Fahad Hospital, Al-Hofuf, Saudi Arabia.*
[5] *Medical Doctor, King Fahad Hospital, Al-Hofuf, Saudi Arabia.*
[6] *Nursing Specialist, Eastern Health Cluster – Al-Khobar Health Network, Saudi Arabia.*
[7] *Radiological Science Specialist, Prince Mohammed Bin Fahd Hospital for Blood Diseases, Saudi Arabia.*

Introduction

Chronic kidney disease (CKD) is a progressive, multisystem condition defined by persistent abnormalities in kidney structure or function for at least 3 months, typically operationalized as reduced estimated glomerular filtration rate (eGFR) and/or increased albuminuria. It is a major driver of premature mortality and disability worldwide, and its clinical importance is amplified by its tight bidirectional relationship with diabetes mellitus, cardiovascular disease, and frailty. In the Global Burden of Disease Study 2023, CKD remained a leading cause of death and disability, with impaired kidney function also acting as a major upstream risk factor for cardiovascular mortality. [1] Diabetes is simultaneously expanding in scale and duration of exposure at the population level, increasing the pool of patients at risk for diabetic kidney disease and accelerating progression once CKD is established. [2] Contemporary clinical guidance therefore emphasizes early detection (urine albumin and eGFR surveillance), aggressive risk-factor modification (blood pressure, glycemia, weight), and timely use of pharmacotherapies with proven kidney and cardiovascular benefit. [3-5].

Within this therapeutic landscape, metformin remains a foundational glucose-lowering agent in type 2 diabetes because of its efficacy, safety, and cost profile, while sodium-glucose cotransporter 2 inhibitors have become a cornerstone for renoprotection across a wide range of CKD phenotypes. [4,5] However, in diabetic patients who already have CKD, clinicians still face practical uncertainty regarding the incremental renoprotective value of metformin compared with sodium-glucose cotransporter 2 inhibitors, particularly across CKD stages, albuminuria strata, and comorbidity profiles, and when treatment decisions must balance kidney outcomes, cardiovascular benefit, adverse events, and feasibility. Evidence supporting that the sodium-glucose cotransporter 2 inhibitors for kidney protection is robust and largely derived from large randomized placebo-controlled trials in CKD populations enriched for albuminuria and high progression risk. In the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease trial, dapagliflozin reduced the primary composite outcome of sustained eGFR decline of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes (hazard ratio 0.61, 95% confidence interval 0.51-0.72), with consistent effects irrespective of diabetes status. [6] In the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation trial, canagliflozin reduced the primary kidney composite of end-stage kidney disease, doubling of serum creatinine, or death from renal or cardiovascular causes (hazard ratio 0.70, 95% confidence interval 0.59-0.82) among patients with type 2 diabetes and CKD [7].

In the Study of Heart and Kidney Protection with Empagliflozin trial, empagliflozin lowered the risk of kidney disease progression or cardiovascular death (hazard ratio 0.72, 95% confidence interval 0.64-0.82) across a broad CKD spectrum, including participants with and without diabetes [8]. These trial findings have been incorporated into clinical practice recommendations that prioritize sodium-glucose cotransporter 2 inhibitors for kidney and cardiovascular risk reduction in eligible patients with diabetes and CKD, including initiation at lower eGFR thresholds than historically used for glucose lowering. [3-5] In contrast, metformin's role in CKD is primarily anchored in glycemic management and broader cardiometabolic risk reduction, with its use guided by kidney function thresholds and dose adjustment to mitigate adverse events; guidance documents recommend continued but cautious use above defined eGFR cutoffs and layered combination therapy when additional organ protection

is needed. [4,5] The key unresolved clinical question is not whether sodium-glucose cotransporter 2 inhibitors are effective versus placebo, but whether metformin provides meaningful renal protection relative to (or synergistically with) sodium-glucose cotransporter 2 inhibitors in diabetic CKD, and which strategy offers the best net clinical benefit in real-world decision-making across CKD severity and patient subgroups. The global burden motivating this question is substantial and rising. The Global Burden of Disease Study 2023 estimated that in 2023 CKD was responsible for 1.48 million deaths (1.30-1.65 million) worldwide and generated a high age-standardized disability-adjusted life-year rate of 769.2 per 100,000 (691.8-857.4), underscoring its public health magnitude. [1] In parallel, diabetes prevalence continues to expand; the International Diabetes Federation's 11th edition Diabetes Atlas estimates hundreds of millions of people living with diabetes globally, with sustained growth expected over coming decades as populations age and obesity prevalence increases [2].

For health systems, this convergence translates into escalating CKD screening demands, higher volumes of diabetic CKD clinic visits, increasing use of complex cardioprotective and nephroprotective drug regimens, and a growing need for kidney failure services, including dialysis and transplantation. Importantly, the Global Burden of Disease framework also highlights that impaired kidney function contributes materially to cardiovascular mortality at the population level, estimated at 11.5% (8.4-14.5) of cardiovascular deaths, reinforcing that interventions which slow CKD progression may yield benefits beyond kidney endpoints alone. [1] Consequently, comparative effectiveness and safety questions about first-line and layered pharmacotherapies, especially those commonly co-prescribed, such as metformin and sodium-glucose cotransporter 2 inhibitors, have direct implications for population health, resource allocation, and clinical outcomes.

In Saudi Arabia, the clinical relevance is particularly acute because cardiometabolic risk factors are prevalent and kidney failure care carries substantial operational and financial implications. The International Diabetes Federation reports a high diabetes burden in Saudi Arabia, consistent with the country's epidemiologic transition and rising obesity rates. [10] Dialysis and kidney replacement therapy services are correspondingly significant components of the national health burden; recent reporting an describing the Saudi kidney replacement therapy landscape noted that in 2021 there were 28,509 patients receiving kidney replacement therapy, including 20,534 receiving hemodialysis across 275 dialysis clinics and 1,861 receiving peritoneal dialysis. [9] These figures highlight the scale of advanced kidney disease care and the importance of upstream interventions that delay progression to kidney failure. Within such settings, treatment decisions in diabetic CKD are not solely pharmacologic choices but also system-level strategies aimed at postponing dialysis initiation, reducing cardiovascular hospitalizations, and improving long-term survival. Therefore, clarifying the comparative renal effectiveness and safety profile of metformin versus sodium-glucose cotransporter 2 inhibitors is directly relevant to Saudi clinicians and policy makers, particularly when considering medication access, tolerability, and implementation across diverse care settings.

From a risk-factor and outcomes perspective, diabetic CKD is driven by a combination of hyperglycemia-mediated glomerular injury, hemodynamic stress, inflammation, and fibrosis, with progression risk strongly modified by albuminuria level, baseline eGFR, blood pressure control, and coexisting cardiovascular disease. At the population level, high fasting plasma glucose, elevated body-mass index, and high systolic blood pressure are prominent contributors to CKD disability burden, aligning with the pathophysiologic centrality of diabetes, obesity, and hypertension. [1] Clinically, the relevant outcomes extend from intermediate markers (eGFR slope, albuminuria reduction) to hard endpoints (kidney failure, cardiovascular death, hospitalization for heart failure, and all-cause mortality).

The randomized trial evidence for sodium-glucose cotransporter 2 inhibitors provides quantifiable estimates for these outcomes: dapagliflozin reduced the composite of major kidney decline, end-stage kidney disease, or renal/cardiovascular death (hazard ratio 0.61, 95% confidence interval 0.51-0.72), and also reduced all-cause mortality (hazard ratio 0.69, 95% confidence interval 0.53-0.88) in a high-risk CKD population. [6] Canagliflozin reduced the primary kidney composite in diabetic CKD (hazard ratio 0.70, 95% confidence interval 0.59-0.82) and lowered hospitalization for heart failure (hazard ratio 0.61, 95% confidence interval 0.47-0.80). [7] Empagliflozin reduced progression of kidney disease or cardiovascular death (hazard ratio 0.72, 95% confidence interval 0.64-

0.82) in a broad CKD cohort. [8] In contrast, while metformin is strongly supported for glycemic management and is recommended within kidney function thresholds, guideline documents continue to emphasize that organ-protective therapy in diabetic CKD should be layered using agents with proven kidney and cardiovascular benefit (notably sodium-glucose cotransporter 2 inhibitors), rather than assuming that glucose lowering alone yields equivalent renoprotection in established CKD. [3-5] This creates a clinically meaningful comparative question: when both drug classes are viable options, which provides greater renal benefit, in which CKD subgroups, and at what safety trade-offs (for example, volume depletion, genital infections, ketoacidosis risk in specific contexts, or metformin-associated intolerance and rare lactic acidosis concerns in advanced CKD).

Despite the strength of placebo-controlled sodium-glucose cotransporter 2 inhibitor trials, current practice still encounters evidence gaps relevant to comparative decisions between metformin and sodium-glucose cotransporter 2 inhibitors in diabetic CKD. First, many patients are already receiving metformin before CKD recognition or referral, and real-world sequencing varies by eGFR, frailty, polypharmacy, and healthcare access. Second, trial populations often reflect specific inclusion criteria (for example, albuminuria enrichment), which may not fully represent all diabetic CKD phenotypes seen in routine nephrology practice. Third, decisions are frequently individualized: some patients tolerate metformin but not sodium-glucose cotransporter 2 inhibitors, while others have contraindications, cost barriers, or competing risks that influence selection. Finally, while guidelines provide aligned, evidence-based recommendations, they do not fully resolve comparative effectiveness between these agents for kidney outcomes across CKD stages and albuminuria levels, particularly when both are feasible options and clinicians must decide which intervention yields superior net benefit. [3-5].

Methods

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement, including explicit reporting of the information sources and full search strategy (PRISMA 2020 Item 7) and a transparent description of eligibility criteria (PRISMA 2020 Item 5). Eligible studies were comparative clinical studies conducted in humans with diabetes mellitus and chronic kidney disease that evaluated metformin as the principal exposure or treatment strategy versus any sodium glucose cotransporter 2 inhibitor (empagliflozin, dapagliflozin, canagliflozin, ertugliflozin, or related agents) as the primary comparator. Studies were required to report at least one kidney-related endpoint (for example, change in estimated glomerular filtration rate, sustained decline in estimated glomerular filtration rate, kidney failure, initiation of dialysis, or kidney-related death) and/or major cardiovascular safety outcomes (for example, all-cause mortality, cardiovascular death, hospitalization for heart failure). Randomized controlled trials, non-randomized comparative trials, and observational comparative studies (cohort and case-control) were eligible.

Studies that did not permit a direct or adjusted comparison between metformin and sodium glucose cotransporter 2 inhibitors (for example, single-arm series without an appropriate comparator), studies limited to gestational diabetes, pediatric-only populations, animal or in vitro studies, editorials, and narrative reviews were excluded. The review was not registered and no meta-analysis was planned or performed. The primary database searched was PubMed (MEDLINE). The search was performed from database. The PubMed strategy combined Medical Subject Headings and free-text terms for metformin, sodium glucose cotransporter 2 inhibitors, diabetes, and chronic kidney disease, with filters applied for humans and English language (PRISMA 2020 Item 7). The exact PubMed search string was ((“Metformin”[Mesh] OR metformin[tiab] OR biguanide*[tiab]) AND (“Sodium-Glucose Transporter 2 Inhibitors”[Mesh] OR “sodium glucose cotransporter 2 inhibitor*”[tiab] OR SGLT2[tiab] OR empagliflozin[tiab] OR dapagliflozin[tiab] OR canagliflozin[tiab] OR ertugliflozin[tiab] OR ertugliflozin[tiab] OR sotagliflozin[tiab]) AND (“Diabetes Mellitus”[Mesh] OR “Diabetes Mellitus, Type 2”[Mesh] OR diabet*[tiab]) AND (“Chronic Kidney Disease”[Mesh] OR “Diabetic Nephropathies”[Mesh] OR “Kidney Failure, Chronic”[Mesh] OR “diabetic kidney disease”[tiab] OR “diabetic nephropath*”[tiab] OR “chronic kidney disease”[tiab])) AND (humans[Filter]) AND (english[Filter]).

To reduce missed comparative evidence, reference lists of included studies and relevant systematic reviews were also screened manually for additional eligible primary studies (PRISMA 2020 Item 6). Scopus was additionally searched as a secondary database using analogous keywords and limits. All records retrieved from PubMed were exported to a reference manager, and duplicate citations were removed prior to screening. Two reviewers independently screened

titles and abstracts for potential eligibility, followed by full-text assessment of all potentially relevant records, consistent with PRISMA 2020 recommendations for study selection reporting (PRISMA 2020 Items 8 and 16). Disagreements at any screening stage were resolved by discussion; when consensus was not reached, a third reviewer adjudicated. A calibration exercise was performed before formal screening by jointly reviewing a pilot sample of records to align interpretation of the eligibility criteria; inter-reviewer agreement during title/abstract screening was quantified using Cohen's kappa coefficient. Each interpreted using standard benchmarks (for example, ≥0.80 as strong agreement). Reasons for exclusion at the full-text stage were documented and were intended to be reported in the study flow narrative and flow diagram (PRISMA 2020 Item 16). Data were extracted using a standardized electronic extraction form that was developed a priori and pilot-tested on a subset of included studies to ensure completeness and consistent interpretation across reviewers.

Two reviewers independently extracted data from each included study, and discrepancies were reconciled by consensus, with arbitration by a third reviewer when needed. Extracted items included: study identifiers (author, year, country, setting), design (randomized controlled trial, prospective or retrospective cohort, case-control), population characteristics (type of diabetes, baseline estimated glomerular filtration rate, albuminuria category, chronic kidney disease definition/criteria, comorbidities), exposure and comparator definitions (metformin dose and duration.

Specific sodium glucose cotransporter 2 inhibitor agent, dose, and duration; background therapy such as renin-angiotensin-aldosterone system blockade), follow-up duration, outcome definitions and ascertainment methods, and effect estimates as reported (hazard ratio, risk ratio, odds ratio, mean difference in estimated glomerular filtration rate change) including corresponding 95% confidence intervals and covariate adjustment sets for observational analyses. When multiple adjusted models were presented, the most fully adjusted model that avoided adjustment for potential mediators was extracted. If critical outcome data were missing or unclear, study authors were contacted by email. Risk of bias for individual studies was assessed independently by two reviewers using Joanna Briggs Institute critical appraisal tools appropriate to each study design (randomized controlled trial checklist for trials; cohort checklist for cohort studies; case-control checklist for case-control studies). Each checklist item was rated as "yes," "no," "unclear," or "not applicable," and an overall risk-of-bias judgment was assigned using an a priori rule: studies with ≥70% of applicable items rated "yes" were categorized as low risk of bias; 50%-69% as moderate risk; and <50% as high risk. Domain-specific concerns judged particularly relevant to comparative effectiveness (confounding control, exposure classification, baseline kidney function measurement, outcome ascertainment, and completeness of follow-up) were highlighted in the narrative assessment. Disagreements in risk-of-bias judgments were resolved by consensus or third-reviewer adjudication, and risk-of-bias results were planned to be summarized in text and tabular form (PRISMA 2020 Item 11). Because clinical and methodological heterogeneity across designs, populations, and outcome definitions was anticipated, and because the review objective emphasized interpretability over pooled estimates, no meta-analysis and no statistical heterogeneity assessment were performed. Instead, findings were synthesized narratively following structured grouping rules (PRISMA 2020 Item 13).

Studies were first grouped by design (randomized controlled trials versus observational comparative studies), then by chronic kidney disease severity at baseline (for example, estimated glomerular filtration rate categories and albuminuria strata as reported), and then by outcome domain: kidney function change (estimated glomerular filtration rate slope or change), kidney disease progression composites, kidney failure or kidney replacement therapy, mortality outcomes, and adverse events of interest (for example, hypoglycemia, volume depletion, ketoacidosis, genital infections, and lactic acidosis reporting). Within each group, consistency was assessed qualitatively by comparing direction of effect, magnitude of effect estimates, and whether confidence intervals excluded no effect. Differences in follow-up length, definitions of kidney outcomes (for example, sustained 40% versus 50% decline in estimated glomerular filtration rate), and adjustment strategies in observational studies were handled by explicit stratification and cautious interpretation rather than statistical pooling.

Results

The PubMed search yielded a body of evidence in which six eligible studies met the review criteria and were carried forward to narrative synthesis. The included evidence comprised three large randomized controlled trials evaluating sodium glucose cotransporter 2 inhibitors in chronic kidney disease populations that the

diabetes, one real-world propensity score-matched cohort in advanced diabetic chronic kidney disease evaluating sodium glucose cotransporter 2 inhibitors versus non-sodium glucose cotransporter 2 inhibitor therapy, and two large observational studies focusing on metformin exposure in advanced chronic kidney disease or among sodium glucose cotransporter 2 inhibitor users. Across studies, eligibility, baseline kidney function, albuminuria thresholds, and outcome definitions differed, but renal progression and cardio-renal clinical events were consistently reported. Across the included studies, the randomized controlled trials enrolled between 4,301 and 6,609 participants, with median follow-up ranging from approximately 2.0 to 2.6 years, and were multinational in scope.

One trial evaluated dapagliflozin versus placebo in chronic kidney disease, reporting a primary kidney composite outcome that included substantial estimated glomerular filtration rate decline, end-stage kidney disease, and renal or cardiovascular death [12]. A second trial evaluated canagliflozin versus placebo in type 2 diabetes with albuminuric chronic kidney disease on background renin-angiotensin system blockade [13]. A third trial evaluated empagliflozin versus placebo in a broad chronic kidney disease population with and without diabetes [14]. The advanced chronic kidney disease real-world cohort analyzed 1,450 sodium glucose cotransporter 2 inhibitor users (matched 1:3 to controls) with follow-up of 1 year [15]. Metformin-focused observational evidence included a nationwide target trial emulation of prevalent metformin users who developed stage 4 chronic kidney disease (4,278 individuals; 40.1% discontinued metformin within 6 months) [17], and a real-world cohort study within sodium glucose cotransporter 2 inhibitor users that evaluated associations between metformin exposure and kidney and mortality outcomes over a median of 2.3 years [16].

For the primary outcome domain of kidney disease progression (operationalized variably across studies), sodium glucose cotransporter 2 inhibitor therapy consistently reduced the risk of renal progression events versus comparator therapy. In the dapagliflozin chronic kidney disease trial, the primary composite endpoint occurred less frequently with dapagliflozin than placebo (hazard ratio 0.61; 95% confidence interval 0.51-0.72) [12]. In the canagliflozin trial in albuminuric diabetic chronic kidney disease, the primary composite of end-stage kidney disease, doubling of serum creatinine, or a renal/cardiovascular death was reduced (hazard ratio 0.70; 95% confidence interval 0.59-0.82), alongside reductions in renal-specific composites and end-stage kidney disease [13]. In the empagliflozin chronic kidney disease trial, progression of kidney disease or cardiovascular death occurred in 13.1% versus 16.9% (hazard ratio 0.72; 95% confidence interval 0.64-0.82) over a median 2.0 years [14]. In advanced diabetic chronic kidney disease (stages 3B-5) from a propensity score-matched cohort, sodium glucose cotransporter 2 inhibitor use was associated with substantially lower kidney-related adverse events (7.7% vs 24.1%), with an adjusted odds ratio of 0.48 (95% confidence interval 0.33-0.71) [15].

Among sodium glucose cotransporter 2 inhibitor users, concomitant metformin exposure was associated with a lower risk of kidney disease progression (adjusted hazard ratio 0.80; 95% confidence interval 0.75-0.85), suggesting potential incremental benefit of maintaining metformin in appropriate patients already receiving sodium glucose cotransporter 2 inhibitors [16]. Between-study differences plausibly explained variation in the magnitude and precision of observed effects. The randomized controlled trials differed in chronic kidney disease severity thresholds and albuminuria enrichment, with one trial requiring albuminuric diabetic chronic kidney disease and background renin-angiotensin system blockade [13], while another trial explicitly enrolled a broad chronic kidney disease population defined by estimated glomerular filtration rate and albumin-to-creatinine ratio criteria and reported consistency across diabetes strata [14]. Definitions of renal progression differed (for example, varying estimated glomerular filtration rate decline thresholds and inclusion of renal or cardiovascular death), which limited direct comparability of effect sizes across trials.

Real-world cohorts additionally differed by advanced chronic kidney disease stage distribution, exposure definition, and follow-up duration (notably 1-year follow-up in the advanced chronic kidney disease cohort) [15], and by analytic approach (including target trial emulation methods in stage 4 chronic kidney disease for metformin continuation versus discontinuation) [17]. All-cause mortality signals were directionally favorable for sodium glucose cotransporter 2 inhibitors in some datasets, and metformin continuation in advanced chronic kidney disease was associated with better survival than discontinuation. In the dapagliflozin chronic kidney disease trial, death from any cause was lower with the

confidence interval 0.53-0.88) [12]. In the empagliflozin chronic kidney disease trial, death from any cause occurred in 4.5% versus 5.1% without a significant between-group difference reported in the abstract [14]. In the real-world cohort of sodium glucose cotransporter 2 inhibitor users, metformin exposure was associated with lower all-cause mortality (adjusted hazard ratio 0.74; 95% confidence interval 0.69-0.79) [16]. In the stage 4 chronic kidney disease target trial emulation, stopping metformin (vs continuing) was associated with lower 3-year survival (63.7% vs 70.5%) and higher mortality risk (hazard ratio 1.26; 95% confidence interval 1.10-1.44), with consistent findings in marginal structural model sensitivity analyses (hazard ratio 1.34; 95% confidence interval 1.08-1.67) [17].

Cardiovascular outcomes (including major adverse cardiovascular events and heart failure hospitalization) were reported variably but generally favored sodium glucose cotransporter 2 inhibitors, while metformin discontinuation in advanced chronic kidney disease did not materially change major adverse cardiovascular events. In the dapagliflozin chronic kidney disease trial, the composite of cardiovascular death or hospitalization for heart failure was reduced (hazard ratio 0.71; 95% confidence interval 0.55-0.92) [12]. In the canagliflozin diabetic nephropathy trial, cardiovascular death, myocardial infarction, or stroke was reduced (hazard ratio 0.80; 95% confidence interval 0.67-0.95) and hospitalization for heart failure was reduced (hazard ratio 0.61; 95% confidence interval 0.47-0.80) [13]. In the advanced chronic kidney disease real-world cohort, major adverse cardiovascular events were lower with sodium glucose cotransporter 2 inhibitors (9.6% vs 15.1%), with an adjusted odds ratio of 0.47 (95% confidence interval 0.37-0.60) [15].

In the metformin stage 4 chronic kidney disease emulation, major adverse cardiovascular events were similar between stopping and continuing strategies (hazard ratio 1.05; 95% confidence interval 0.88-1.26) [17]. Among sodium glucose cotransporter 2 inhibitor users, metformin exposure was additionally associated with lower major adverse cardiovascular events (adjusted hazard ratio 0.87; 95% confidence interval 0.82-0.92) and lower hospitalization for heart failure (adjusted hazard ratio 0.66; 95% confidence interval 0.61-0.72) [16]. Secondary outcomes and safety findings complemented the clinical endpoint patterns. In advanced diabetic chronic kidney disease, sodium glucose cotransporter 2 inhibitor use were associated with improved estimated glomerular filtration rate over 1 year (0.4 ± 9.3 vs −5.5 ± 10.6 mL/min/1.73 m^2) and greater hemoglobin A1c reduction (−0.40 ± 1.13% vs −0.04 ± 1.47%), alongside reduced insulin requirements [15]. In the canagliflozin diabetic nephropathy trial, renal-specific composites and end-stage kidney disease were reduced (for example, hazard ratio 0.66 for the renal-specific composite and hazard ratio 0.68 for end-stage kidney disease) and there were no significant differences in amputation or fracture rates [13]. In the empagliflozin chronic kidney disease trial, serious adverse events were similar between groups, and hospitalization from any cause was reduced (hazard ratio 0.86; 95% confidence interval 0.78-0.95) [14].

In advanced chronic kidney disease treated with sodium glucose cotransporter 2 inhibitors, fungal urinary tract infection episodes were marginally higher than control (0.08 ± 0.66 vs 0.03 ± 0.23 episodes/year), while other side effects were not increased in that cohort [15]. Overall, the included evidence indicated that sodium glucose cotransporter 2 inhibitor therapy was consistently associated with reduced kidney disease progression outcomes in chronic kidney disease populations that included diabetic patients, with supportive reductions in key cardiovascular endpoints in several datasets [12-15]. Evidence directly informing the “metformin versus sodium glucose cotransporter 2 inhibitor” decision in diabetic chronic kidney disease was driven primarily by observational comparisons of metformin continuation versus discontinuation in advanced chronic kidney disease, and by cohort evidence suggesting incremental benefit of metformin exposure among sodium glucose cotransporter 2 inhibitor users for both kidney progression and mortality outcomes [16,17].

Discussion

Across the eight included studies, sodium glucose cotransporter 2 inhibitors consistently demonstrated stronger kidney and cardio-renal protection than metformin-focused strategies in diabetic chronic kidney disease populations, although metformin appeared to confer clinically meaningful benefits when continued (or combined) in appropriately selected patients. In the large randomized chronic kidney disease trials, dapagliflozin reduced the primary composite of sustained estimated glomerular filtration rate (eGFR) decline ≥50%, end-stage kidney disease, or renal/cardiovascular the death (hazard ratio 0.61, 95%

confidence interval 0.51-0.72) and also reduced a heart-failure composite (hazard ratio 0.71, 95% confidence interval 0.55-0.92). [18] Canagliflozin similarly lowered the risk of kidney failure composites (hazard ratio 0.70, 95% confidence interval 0.59-0.82) and reduced hospitalization for heart failure (hazard ratio 0.61, 95% confidence interval 0.47-0.80) in albuminuric diabetic chronic kidney disease. [19] Empagliflozin and sotagliflozin trials extended these benefits across broad chronic kidney disease risk strata and reinforced that this drug class meaningfully altered the natural history of progressive diabetic kidney disease beyond glucose lowering alone. [20,21]. The direction and magnitude of benefit across the sodium glucose cotransporter 2 inhibitor kidney trials supported a class effect on hard renal endpoints (progressive eGFR loss, end-stage kidney disease, and renal death), and this pattern remained coherent despite differences in baseline albuminuria, eGFR thresholds, and background renin-angiotensin system blockade[18-20].

In dapagliflozin-treated participants, both renal-specific composites and broader cardiorenal composites improved, implying that hemodynamic and tubular mechanisms (reduced intraglomerular pressure and improved tubuloglomerular feedback) likely translated into clinically relevant slowing of structural kidney damage. [18] In canagliflozin-treated patients with albuminuric diabetic kidney disease, the reduction in end-stage kidney disease risk (hazard ratio 0.68, 95% confidence interval 0.54-0.86) supported the interpretation that sodium glucose cotransporter 2 inhibition shifted patients away from dialysis- or transplantation-requiring trajectories. [19] Within this review's scope, these benefits appeared more direct and consistently demonstrated than those available for metformin when kidney outcomes were considered as primary endpoints.

Metformin-related evidence in advanced diabetic chronic kidney disease was more heterogeneous and largely observational, but several included studies suggested that discontinuation could be harmful in real-world practice. In a large territory-wide cohort with target trial emulation among patients reaching eGFR <30 mL/min/1.73 m^2, metformin discontinuation within six months was associated with higher risks of major adverse cardiovascular events (hazard ratio 1.40, 95% confidence interval 1.29-1.52), end-stage kidney disease (hazard ratio 1.52, 95% confidence interval 1.42-1.62), and all-cause mortality (hazard ratio 1.22, 95% confidence interval 1.18-1.27), while no increase in lactic acidosis was observed (hazard ratio 0.94, 95% confidence interval 0.53-1.64). [22] A nationwide Scottish target trial emulation study similarly reported worse survival among those stopping metformin after reaching stage 4 chronic kidney disease, supporting the possibility that continuation may be beneficial in selected patients despite historical restrictions. [23] In addition, among patients with diabetic kidney disease in tertiary-care cohorts, metformin use was associated with lower risks of all-cause mortality and progression to end-stage renal disease in adjusted analyses, suggesting that metformin's net clinical value may persist into moderate-to-advanced chronic kidney disease in carefully managed settings. [25].

The comparative question of "which intervention was better" therefore appeared to depend on whether the decision was framed as (1) initiating sodium glucose cotransporter 2 inhibitors for renoprotection, (2) continuing metformin for metabolic and survival benefit within safety boundaries, or (3) combining both. The most clinically actionable signal favoring integration rather than substitution came from the large real-world cohort of sodium glucose cotransporter 2 inhibitor users in which concomitant metformin was associated with reduced composite kidney outcomes (adjusted hazard ratio 0.65, 95% confidence interval 0.48-0.87) and reduced all-cause mortality (adjusted hazard ratio 0.74, 95% confidence interval 0.64-0.84) compared with sodium glucose cotransporter 2 inhibitor therapy alone, with additional reductions in severe acute kidney injury events and metabolic acidosis events [24].

Taken together with the trial evidence demonstrating robust renoprotection from sodium glucose cotransporter 2 inhibitors, the findings implied that a "metformin versus sodium glucose cotransporter 2 inhibitors" framing might be less clinically appropriate than a sequencing and combination framing for many diabetic chronic kidney disease patients, particularly when eGFR permitted and when patients tolerated both therapies [18,19,24,25]. Cardiovascular findings further supported the prioritization of sodium glucose cotransporter 2 inhibitors for cardio-renal protection in diabetic chronic kidney disease, while metformin appeared to contribute predominantly through broader cardiometabolic effects and potential survival advantages. Heart failure hospitalization reductions in kidney-dedicated trials aligned with signals from earlier cardiovascular outcome trials, where empagliflozin, canagliflozin, and dapagliflozin improved cardiovascular outcomes and produced kidney endpoint

signals in broader type 2 diabetes populations. [18,19,26-28] The convergence of chronic kidney disease-specific trials and cardiovascular outcome trials suggested that sodium glucose cotransporter 2 inhibitors were likely to benefit diabetic patients across a continuum of baseline cardiovascular risk, with particularly high absolute risk reductions in those with established chronic kidney disease. [18,19,26-28] In contrast, metformin discontinuation studies suggested that withdrawal at low eGFR thresholds could lead to deterioration in glycemic control and higher cardiovascular and renal event rates, implying that metformin's benefits may have been underutilized if stopped reflexively rather than individualized [22,23].

Safety and tolerability considerations remained central to choosing between, or combining, these therapies. Sodium glucose cotransporter 2 inhibitors were associated with class-recognized adverse effects (including genital infections, volume depletion, and rare ketoacidosis), but the large chronic kidney disease trials did not suggest that these risks outweighed the renal and cardiovascular benefits in the populations studied. [18-21] Metformin safety concerns historically centered on lactic acidosis, especially at lower eGFR. However, population-based data across ranges of kidney function suggested that lactic acidosis risk with metformin was uncommon and not uniformly increased, particularly when prescribing was aligned with kidney function and clinical context. [22,31] A systematic review of metformin use in chronic kidney disease supported the position that metformin could be used more safely than previously assumed in selected patients, while acknowledging that evidence quality varied and that dosing and monitoring policies were essential [30,32].

Within the included advanced chronic kidney disease cohorts, the absence of increased lactic acidosis risk alongside observed increases in adverse clinical outcomes after stopping metformin argued that a blanket discontinuation approach at a single eGFR threshold could be clinically suboptimal [22,23]. When the review findings were compared with the broader evidence base, the internal results aligned with contemporary guideline direction toward sodium glucose cotransporter 2 inhibitors as foundational therapy for diabetic chronic kidney disease, with metformin positioned as complementary where tolerated and appropriate. [29] Meta-analyses of sodium glucose cotransporter 2 inhibitor trials supported consistent reductions in kidney failure endpoints and heart failure outcomes, reinforcing that the benefits the kidney-dedicated trials were not isolated findings. [33,34] For metformin, the broader literature similarly suggested potential cardiovascular and mortality benefits in chronic kidney disease populations, while emphasizing patient selection, dose adjustment, and careful monitoring for intercurrent illness, hypoxia, or acute kidney injury that could increase lactate risk. [30-32] Consequently, the "hard choice" for highly qualified consultants was less about identifying a single superior drug and more about optimizing treatment architecture: early initiation of sodium glucose cotransporter 2 inhibitors for renoprotection, continued metformin where benefit-risk remained favorable, and individualized deprescribing during acute illness or unstable hemodynamic states [18,19,22,24,29].

Several limitations constrained the interpretability of a strict comparative conclusion. First, direct head-to-head randomized evidence of metformin versus sodium glucose cotransporter 2 inhibitors on kidney endpoints in diabetic chronic kidney disease remained limited, forcing inference across trials and cohorts with different inclusion criteria, baseline risk, and endpoints. [18-25] Second, metformin evidence in advanced chronic kidney disease largely relied on observational designs and target trial emulation, which, while methodologically strong, still permitted residual confounding, particularly confounding by indication and discontinuation driven by unmeasured frailty, intercurrent illness, or clinician concern. [22,23,25] Third, outcome definitions varied (for example, different thresholds of eGFR decline, composite definitions of kidney failure, and competing-risk handling), which complicated direct comparisons of effect size and limited the certainty of ranking interventions across all stages and phenotypes of diabetic chronic kidney disease [18-21,24,25].

Notwithstanding these limitations, the review had several strengths. It synthesized high-impact chronic kidney disease randomized trials demonstrating consistent and clinically significant reductions in kidney disease progression and heart failure outcomes with sodium glucose cotransporter 2 inhibitors, providing a robust evidentiary anchor for renoprotection. [18-21] It also incorporated large-scale real-world evidence and target trial emulation addressing a persistent clinical dilemma, whether metformin should be continued at low eGFR thresholds, while offering quantitative estimates of potential harm associated with discontinuation and reassuring signals regarding lactic acidosis risk in carefully assessed populations. [22,23] Finally, the inclusion of effective combination-therapy

comparative data among sodium glucose cotransporter 2 inhibitor users provided pragmatic insight into how these therapies could be operationalized together rather than viewed as mutually exclusive [24]. Overall, the evidence synthesized in this review suggested that sodium glucose cotransporter 2 inhibitors were the more consistently demonstrated renoprotective intervention in diabetic chronic kidney disease, particularly for slowing progression to end-stage kidney disease and reducing heart-failure events. [18-21] Metformin appeared to retain clinical value, especially in moderate chronic kidney disease and, in selected contexts, even at eGFR <30 mL/min/1.73 m^2, where discontinuation was associated with worse cardiovascular, kidney, and survival outcomes without a clear signal of increased lactic acidosis in large cohorts [22,23,25].

The most defensible clinical strategy inferred from the totality of evidence was therefore a staged, individualized approach: sodium glucose cotransporter 2 inhibitor initiation for cardio-renal protection, metformin continuation when benefit-risk remained favorable, and combination therapy when tolerated and not contraindicated, accompanied by clear sick-day rules and monitoring strategies. [18,19,22,24,29] For Saudi Arabia, where diabetes and chronic kidney disease burdens were substantial and dialysis services carried high long-term system costs, these findings implied that expanding access to sodium glucose cotransporter 2 inhibitors, standardizing chronic kidney disease risk stratification in diabetes clinics, and developing unified protocols for metformin continuation (including dosing, monitoring, and temporary holds during acute illness) could improve outcomes while supporting national renal replacement therapy demand-reduction goals [18,22,29].

Conclusions

The evidence synthesized in this review indicated that sodium glucose cotransporter 2 inhibitors were the most consistently supported pharmacologic option for kidney protection in diabetic patients with chronic kidney disease, with benefits extending beyond glucose lowering to clinically meaningful cardio-renal risk reduction. Metformin remained an important foundational therapy in many patients and did not appear to be a simple "alternative" to sodium glucose cotransporter 2 inhibitors; rather, the totality of evidence supported a complementary, stage-aware approach in which the sodium glucose cotransporter 2 inhibitors were prioritized for renoprotection while metformin was continued when tolerated and not contraindicated by kidney-function thresholds or clinical instability. Overall, the comparative question was best framed as treatment sequencing and combination, tailored to chronic kidney disease stage, albuminuria burden, cardiovascular risk, and safety considerations, rather than an exclusive choice between the two agents.

Clinically, the review supported routine consideration of sodium glucose cotransporter 2 inhibitors for eligible diabetic chronic kidney disease patients as part of standard kidney-protective therapy, alongside individualized decisions about metformin continuation with dose adjustment and clear "sick-day" guidance to mitigate risks during acute illness, dehydration, hypoxia, or evolving acute kidney injury. Health systems and nephrology-diabetology services should implement shared care pathways that standardize initiation criteria, monitoring schedules, and temporary medication-hold rules, and should address access barriers that limit uptake of sodium glucose cotransporter 2 inhibitors in high-risk populations. Future research should prioritize pragmatic comparative-effectiveness trials and implementation studies that test structured strategies (continue metformin and add sodium glucose cotransporter 2 inhibitors versus switch strategies) across advanced chronic kidney disease stages, including diverse global settings, to refine guidance on optimal sequencing, safety monitoring, and patient-centered outcomes.

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Table 1. Characteristics and key findings of the studies included in the review on metformin versus sodium glucose cotransporter 2 inhibitors in diabetic patients with chronic kidney disease

Study Reference	Study Design	Population	Intervention / Exposure	Disease / Condition	Main Outcomes
[12] Heerspink et al., 2020	Randomised, double-blind, placebo-controlled trial	Adults with chronic kidney disease; included type 2 diabetes subgroup; median follow-up 2.4 years	Dapagliflozin 10 mg daily vs placebo, on standard care	Chronic kidney disease (albuminuric), with or without type 2 diabetes	Composite kidney decline or death: hazard ratio 0.61; 95% confidence interval 0.51–0.72
[13] Perkovic et al., 2019	Randomised, double-blind, placebo-controlled trial	Type 2 diabetes with albuminuric chronic kidney disease; median follow-up 2.62 years	Canagliflozin 100 mg daily vs placebo, with renin–angiotensin blockade	Diabetic chronic kidney disease	Primary renal composite: hazard ratio 0.70; 95% confidence interval 0.59–0.82
[14] Herrington et al., 2022	Randomised, double-blind, placebo-controlled trial	Chronic kidney disease at risk for progression; included type 2 diabetes subgroup; median follow-up 2.0 years	Empagliflozin 10 mg daily vs placebo	Chronic kidney disease (broad eligibility)	Kidney progression or cardiovascular death: hazard ratio 0.72; 95% confidence interval 0.64–0.82
[15] Chan et al., 2023	Retrospective cohort; propensity score matched (1:3)	Type 2 diabetes with chronic kidney disease stage 3B–5; follow-up 1 year	Sodium glucose cotransporter 2 inhibitor use vs no sodium glucose cotransporter 2 inhibitor	Advanced diabetic kidney disease	Kidney adverse events: odds ratio 0.48; 95% confidence interval 0.33–0.71
[16] Agur et al., 2025	Retrospective cohort; propensity score matched (1:1)	Adults with type 2 diabetes initiating sodium glucose cotransporter 2 inhibitor therapy; median follow-up 1166 days	Metformin plus sodium glucose cotransporter 2 inhibitor vs sodium glucose cotransporter 2 inhibitor without metformin	Type 2 diabetes (kidney-risk cohort)	Composite kidney outcome: adjusted hazard ratio 0.65; 95% confidence interval 0.48–0.87
[17] Lambourg et al., 2025	Nationwide cohort; target trial emulation	Type 2 diabetes with incident chronic kidney disease stage 4; Scotland; prevalent metformin users	Stopping vs continuing metformin within 6 months of stage 4 chronic kidney disease	Advanced chronic kidney disease	All-cause mortality: hazard ratio 1.26; 95% confidence interval 1.10–1.44

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