Review

Impact of Dapagliflozin on Kidney Function Decline in Chronic Kidney Disease Patients: A Systematic Review

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Introduction. This systematic review aimed to evaluate the impact of dapagliflozin therapy on the progression of chronic kidney disease (CKD) in individuals with CKD.

Methods. A comprehensive search for randomized controlled trials (RCTs) concerning dapagliflozin was conducted across multiple databases, including PubMed, Scopus, Web of Science, Cochrane Library, ClinicalTrials.gov, and Google Scholar, from their inception until January 10, 2025. Of 2,806 identified studies, 15 trials met the inclusion criteria. Upon careful assessment to avoid overlapping populations, 11 publications derived from the Dapagliflozin and Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) parent trial were excluded, leaving four unique independent trials for narrative synthesis. Due to substantial heterogeneity ($I^2 > 90\%$) and the limited number of studies, meta-analysis was not performed and findings are presented narratively.

Results. A total of 15 articles were identified, 11 were secondary analyses of the DAPA-CKD trial (NCT03036150) reporting on the same 4,304 participants. Following exclusion of overlapping publications, four unique trials remained. The findings for eGFR decline were highly variable across studies, ranging from a mean difference of -6.60 mL/min/1.73m² (Cherney *et al.*, 2020) to +0.93 mL/min/1.73m² (Heerspink *et al.*, 2020). Substantial heterogeneity ($I^2 = 93.7\%$) precluded meaningful meta-analysis. For composite renal outcomes, only one unique trial reported this outcome, preventing quantitative synthesis.

Conclusion. While the effect of Dapagliflozin on eGFR decline was inconclusive due to substantial heterogeneity, the available evidence from the DAPA-CKD trial suggests a reduction in the risk of adverse clinical renal outcomes. However, the limited number of independent trials and considerable heterogeneity underscore the need for more standardized RCTs. Overall, dapagliflozin appears to confer renal protective benefits and is considered safe for patients with CKD.

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INTRODUCTION

Chronic Kidney Disease (CKD) presents a significant global public health challenge, characterized by a progressive and irreversible decline in kidney function.[1,2] This condition is typically associated with a gradual reduction in

glomerular filtration rate (GFR) and, if inadequately managed, may lead to end-stage kidney disease (ESKD), necessitating dialysis or kidney transplantation.[3] Beyond its renal implications, CKD is linked to an increased risk of cardiovascular disease,[4] hypertension,[5] and various metabolic complications, hereby imposing a substantial burden on healthcare systems and communities. It is estimated that more than 850 million individuals worldwide are affected by varying degrees of CKD.[6] A critical challenge in managing CKD is the scarcity of effective therapies capable of halting its progression.[7] Current treatment modalities, such as blood pressure management and the use of renin-angiotensin-aldosterone system (RAAS) inhibitors, can only slow the progression of the disease but do not prevent it entirely.[8] In this context, sodium-glucose cotransporter type 2 (SGLT2) inhibitors, including dapagliflozin, have emerged as a novel therapeutic strategy for CKD. These agents, in addition to their glucose-lowering effects, offer protective benefits for renal function.[9,10]

Dapagliflozin, initially developed for the treatment of type 2 diabetes, has garnered attention due to its significant renal protective effects.[9,11,12] One of the key mechanisms by which dapagliflozin exerts its protective effects on the kidneys involves the modulation of glomerular filtration rate (GFR). This effect is primarily mediated through the reduction of glomerular pressure, inhibition of sodium reabsorption in the renal tubules, and enhancement of glomerular autoregulation.[13,14] Studies indicate that SGLT2 inhibition leads to decreased glomerular hyperfiltration and mitigates pressure-induced damage to glomerular structures. Moreover, dapagliflozin plays a vital role in slowing the progression of kidney disease by reducing oxidative stress, inflammation, and renal fibrosis. Clinical trials have demonstrated that dapagliflozin significantly slows the rate of GFR decline and prevents progression to end-stage kidney disease in both diabetic and non-diabetic patients with CKD.[15,16] Additional studies have indicated that dapagliflozin can lower the risk of severe declines in kidney function, kidney failure, and mortality related to kidney or cardiovascular issues.[17,18]

Numerous randomized controlled trials (RCTs) have investigated the impact of dapagliflozin on mean changes in estimated GFR (eGFR) from baseline,[19-21] alongside systematic reviews examining the effects of SGLT2 inhibitors in CKD populations,[22,23] or specifically evaluating the role of dapagliflozin in chronic kidney disease progression among selected cohorts.[24] This study aims to assess the effect of dapagliflozin on CKD progression in CKD patients. Specifically, this systematic review aims to evaluate the impact of treatment with dapagliflozin on CKD progression by measuring mean changes in eGFR from baseline in individuals with CKD.

MATHERIALS AND METHODS

Protocol Registration

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[25] The review protocol was registered with PROSPERO under the registration number CRD420251003753.

Searching Strategy

Two researchers independently conducted searches of electronic databases, including PubMed, Scopus, Web of Science, Cochrane Library, ClinicalTrials.gov, and Google Scholar, covering the period from January 2000 to January 2025. Only randomized controlled trials (RCTs) evaluating the efficacy of dapagliflozin in patients with CKD were included. To ensure comprehensive coverage, we reviewed the bibliographies of articles identified in our initial search. Subsequently, these studies were assessed against our PICO (Population, Intervention, Comparison, Outcome) criteria. EndNote software was utilized to screen and remove duplicate citations, ensuring consistency in our search strategy across all databases. Unpublished studies were excluded from the analysis. Our search strategy was thorough and rigorous, allowing for the identification of all pertinent studies globally (see Supplementary Table 1).

Inclusion/Exclusion Criteria

We included RCTs that compared the effects of dapagliflozin with placebo in patients diagnosed with chronic kidney disease (CKD) with an estimated GFR (eGFR) of < 60 mL/min/1.73 m². To avoid double-counting of participants from overlapping populations, we applied a conservative inclusion strategy. Where multiple publications from a single parent trial were identified, only the primary outcome publication reporting the most

Supplementary Table 1. Characteristics of All Identified RCTs, Including Unique Trials and Overlapping Publications Excluded from the Primary Analysis

Study (First Author, Year)	Parent Trial	Relationship to Parent Trial	Action
Heerspink, 2020	DAPA-CKD (NCT03036150)	Primary publication of DAPA-CKD trial; largest sample; most comprehensive data	
Fioretto, 2018	DERIVE (NCT02413398)	Independent DERIVE trial; different patient population	
Cherney, 2020	DIAMOND (NCT03190694)	Independent DIAMOND trial; non-diabetic CKD patients; different design (crossover)	
Kohan, 2014	NCT00660907	Independent trial; different patient population; different dapagliflozin doses tested	
Chertow, 2021	DAPA-CKD (NCT03036150)	Secondary (DAPA-CKD)	
McMurray, 2021	DAPA-CKD (NCT03036150)	Secondary (heart failure subgroup)	
Jongs, 2021	DAPA-CKD (NCT03036150)	Secondary (UACR analysis)	
Wheeler, 2021	DAPA-CKD (NCT03036150)	Secondary (diabetes status)	
Hiddo J.L, 2021	DAPA-CKD (NCT03036150)	Secondary (duplicate)	
Chertow, 2021	DAPA-CKD (NCT03036150)	Secondary (stage 4 CKD)	
Provenzano, 2021	DAPA-CKD (NCT03036150)	Secondary (MRA use)	
Vart, 2022	DAPA-CKD (NCT03036150)	Secondary (geographic)	
Chertow, 2023	DAPA-CKD (NCT03036150)	Secondary (CV medications)	
Chertow, 2022	DAPA-CKD (NCT03036150)	Secondary (BMI analysis)	
McEwan, 2024	DAPA-CKD (NCT03036150)	Secondary (time-to-event)	

comprehensive dataset was retained. Secondary analyses, post-hoc subgroup analyses, and derivative publications were excluded from the primary analysis to prevent overlapping patient populations. A comprehensive list of excluded duplicate publications with justification is provided in Supplementary Table 1. Eligible studies involved adult patients (age > 18) and assessed either GFR or composite renal outcomes. Studies with a mean eGFR > 60 mL/min/1.73 m² were included only if data on the subgroup with eGFR < 60 mL/min/1.73 m² were available. We excluded studies involving patients taking dapagliflozin in combination with other medications, comparisons of dapagliflozin with drugs other than placebo, as well as review articles, single-arm studies, case reports, case series, conference proceedings, animal studies, observational studies, and letters to the editor.

Risk of Bias

Two authors evaluated the quality of each included study using the revised Cochrane Risk of Bias tool (RoB 2.0),[26] which assesses bias across five domains: randomization process (D1), deviations from intended interventions (D2), missing outcome data (D3), outcome measurement (D4), and selection of reported results (D5). Each domain was classified as having a low risk of bias, high risk of bias, or some concerns, according to the Cochrane Handbook for Systematic Reviews of Interventions, version 6.3.[27] Disagreements between reviewers were resolved through consensus with the third author (NH).

Summary Measures and Outcomes

The primary outcome was the difference in eGFR decline rates between the dapagliflozin and placebo groups. Secondary outcomes included composite renal events, defined as: 1) eGFR decline of at least 50%, 2) end-stage kidney disease (ESKD), defined as eGFR < 15 mL/min/1.73m² (kidney failure, Stage 5 CKD) requiring dialysis (for a minimum of four weeks) or kidney transplantation, and 3) renal death, defined as death attributed to kidney failure or its complications, including death from uremia, complications of dialysis or kidney transplantation, or death in patients with kidney failure not receiving renal replacement therapy. Adjudication of renal death followed standard clinical event committee procedures as per the original trial protocols.

Data Extraction

From the eligible studies, we extracted the following information: first author or study name, publication year, study duration, median follow-up, interventional and comparator drugs, sample size, and outcome-related data. Data extraction

Table 1. Baseline characteristics of included studies

First author, year	Study design	Patient population	Location	Number of participants	Mean age (years), mean (SD)	Males (%)	eGFR inclusion criteria (ml/min/1.73 m^2)	UACR inclusion criteria (mg/g)	Baseline eGFR (ml/min/1.73 m^2)	Baseline UACR (mg/g) median (IQR)	Drug dosages	Follow-up median (weeks)
Heerspink,2020	Randomized, double-blind with placebo	Patients with chronic kidney disease	386 centers in 21 countries	4304	61.8 (12.1)	69.9	Adults with eGFR of 25–75 ml/min per 1.73 m^2	200 to < 5000	43.1 ± 12.4	900 (539.6–1515.0) (IQR)	Dapagliflozin 10 mg	124
Fioretto,2018	Randomized, double-blind with placebo	Type 2 diabetes with moderate renal impairment	88 centers in 8 countries	321	65.3 (unclear SD)	56.9	45 to 59	-	53.3 ± 8.7	23.5 (2.7–5852.0) (IQR)	Dapagliflozin 10 mg	24
Chertow, 2021	Randomized, double-blind with placebo	Patients with chronic kidney disease	386 centers in 21 countries	624	Placebo:62.6 (12.4), Dapagliflozin:61.9 (11.8)	Placebo:64.8, Dapagliflozin:63.1	Adults with eGFR of 25–75 ml/min per 1.73 m^2	200 to < 5000	eGFR,30 ml/min per 1.73 m^2	UACR > 1000 mg/g, Placebo:57.3%, Dapagliflozin: 53%	Dapagliflozin 10 mg	51
Cherney,2020	Randomized, double-blind, placebo-controlled crossover trial	Adult patients (aged 18–75 years) with chronic kidney disease, without a diagnosis of diabetes	6 centers in 3 countries	58	51 years (SD 13)	67.8	eGFR of at least 25 mL/min per 1·73 m^2	A 24-h urinary protein excretion greater than 500 mg and less than or equal to 3500 mg	mGFR was 58·3 mL/min per 1·73 m^2 (SD 23)	Placebo: 884 (538·0–1142·0) Dapagliflozin:891 (599·0–1338·0) (range)	Dapagliflozin 10 mg	6
Kohan,2014	Randomized, double-blind, multicentric, placebo-controlled trial	Type 2 diabetes and moderate renal impairment	111 sites in 13 countries	252	68 ± 7.7 years		eGFR: 30–60 mL/min/1.73 m^2 (MDRD)		Dapagliflozin: 43.9 ± 10.6 Placebo: 45.6 ± 10.0	Placebo: 67 (20–367) Dapagliflozin: 73 (9–352) median (range)	Dapagliflozin 10 mg once daily and 5 mg once daily	104
McMurray, 2021	Randomized, double-blind with placebo	Patients with chronic kidney disease	386 centers in 21 countries	4304	No Heart Failure:61.4 (12.3), Heart Failure:65.3 (12.1)	No Heart Failure: (67.3), Heart Failure: (63.9)	Adults with eGFR of 25–75 ml/min per 1.73 m^2	200 to < 5000	No Heart Failure:43.1 ± 12.3,Heart Failure:43.2 ± 12.4	No Heart Failure:949.8 (480.4-1,890),Heart Failure:940 (455.6-1,846.9)	Dapagliflozin 10 mg	124
Jongs, 2021	Randomized, double-blind with placebo	Patients with chronic kidney disease	386 centers in 21 countries	4304	62 ± 12.1 years	69.9	Adults with eGFR of 25–75 ml/min per 1.73 m3	200 to < 5000	Both groups with diabetes: 43.8 ± 12.6	Both groups with diabetes: 1,016.5	Dapagliflozin 10 mg	124
Wheeler, 2021	Randomized, double-blind with placebo	Patients with chronic kidney disease	386 centers in 21 countries	4304	Type 2 diabetes & dapagliflozin: 64.1 (9.8), Type 2 diabetes &placebo: 64.7 (9.5), without diabetes & dapagliflozin: 56.9 (14.6), without diabetes & placebo: 56 (14.6)	Type 2 diabetes & dapagliflozin: 34, Type 2 diabetes &placebo:32.5, without diabetes & dapagliflozin:30.8, without diabetes & placebo: 35	Adults with eGFR of 25–75 ml/min per 1.73 m4	200 to < 5000	Type 2 diabetes & dapagliflozin: 44 (12.6), Type 2 diabetes &placebo: 43.6 (12.6), without diabetes & dapagliflozin:41.7 (11.5), without diabetes & placebo: 41.8 (11.9)	Type 2 diabetes & dapagliflozin: 1024.5, Type 2 diabetes &placebo: 1004.5, without diabetes & dapagliflozin:870.5, without diabetes & placebo: 841.5	Dapagliflozin 10 mg	124
Hiddo J. L, 2021	Randomized, double-blind with placebo	Patients with chronic kidney disease	386 centers in 21 countries	4304	61.8 ± 12.1 years	69.9	Adults with eGFR of 25–75 ml/min per 1.73 m3	200 to < 5000	Both groups with diabetes: 43.8 ± 12.6	Both groups with diabetes: 1,016.5	Dapagliflozin 10 mg	124

Table 1. Continued

First author, year	Study design	Patient population	Location	Number of participants	Mean age (years), mean (SD)	Males (%)	eGFR inclusion criteria (ml/min/1.73 m^2)	UACR inclusion criteria (mg/g)	Baseline eGFR (ml/min/1.73 m^2)	Baseline UACR (mg/g) median (IQR)	Drug dosages	Follow-up median (weeks)
McMurray, 2021	Randomized, double-blind with placebo	Patients with chronic kidney disease	386 centers in 21 countries	4304	Baseline cardiovascular disease& dapagliflozin: 66.5, baseline cardiovascular disease &placebo: 66.2, no baseline cardiovascular disease& dapagliflozin: 59, no baseline cardiovascular disease &placebo: 59.4,	Baseline cardiovascular disease dapagliflozin: 72.2, baseline cardiovascular disease placebo: 68.8, no baseline cardiovascular disease dapagliflozin: 63.9, no baseline cardiovascular disease placebo: 65.5	Adults with eGFR of 25–75 ml/min per 1.73 m4	200 to < 5000	Baseline cardiovascular disease dapagliflozin: 43.3 (12), baseline cardiovascular disease placebo:43 (12.6), no baseline cardiovascular disease dapagliflozin: 43.2 (12.5), no baseline cardiovascular disease placebo: 42.9 (12.3)	Baseline cardiovascular disease dapagliflozin: 1012 (446-1956), baseline cardiovascular disease placebo:944 (473-1825), no baseline cardiovascular disease dapagliflozin: 937 (487-1856), no baseline cardiovascular disease placebo: 933 (488-1911)	Dapagliflozin 10 mg	124
Provenzano, 2021	Randomized, double-blind with placebo	Patients with chronic kidney disease with or without type 2 diabetes	386 centers in 21 countries	A total of 229 of 4304 DAPA-CKD participants (5.3%) were receiving conventional MRAs at baseline (dapagliflozin n = 109, placebo n = 120).	Dapagliflozin & MRA use:61.8 (10.9), dapagliflozin & no MRA use:61.8 (12.1), placebo & MRA use: 62.6 (10.7), placebo & no MRA use:31.8 (12.2)	Dapagliflozin & MRA use: 62.5, dapagliflozin & no MRA use: 67.8, placebo & MRA use: 73.3, placebo & no MRA use: 66.3	Adults with eGFR of 25–75 ml/min per 1.73 m^2	200 to < 5000	Dapagliflozin & MRA use:44.3 (12.4), dapagliflozin & no MRA use:43.2 (12.3), placebo & MRA use:43.1 (11.4), placebo & no MRA use: 43 (12.5)	Dapagliflozin & MRA use:1165 (541-1977), dapagliflozin & no MRA use: 951 (469-1894), placebo & MRA use:1005 (477-2010), placebo & no MRA use: 931 (484-1861)	Dapagliflozin 10 mg	124
Vart, 2022	Randomized, double-blind with placebo	Patients with chronic kidney disease with or without type 2 diabetes	386 centers in 21 countries	Asia (N = 1346), Europe (N = 1233), Latin America (N = 912), North America (N = 813)	Dapagliflozin & Asia: 59 (12.5), placebo & Asia:59.1 (12.8), dapagliflozin &Europe: 61.8 (12.3), placebo & Europe: 62.1 (11.7), dapagliflozin & Latin America: 62.6 (10.8), placebo & Latin America: 63.1 (11.5), dapagliflozin & North America:65.8 (11), placebo & North America:64.6 (11.6)	Dapagliflozin & Asia: (65.3), placebo & Asia: (66.1), dapagliflozin &Europe: (69.5), placebo & Europe: (68.2), dapagliflozin & Latin America: (64.8), placebo & Latin America: (63.5), dapagliflozin & North America: (68.8), placebo & North America: (69.2)	Adults with eGFR of 25–75 ml/min per 1.73 m^2	200 to < 5000	Dapagliflozin & Asia: 42.4 (11.1), placebo & Asia: 41.9 (11.3), dapagliflozin &Europe: 43.7 (12.4), placebo & Europe: 44.1 (12.5), dapagliflozin & Latin America:44.3 (13.8), placebo & Latin America:43.7 (13.4), dapagliflozin & North America: 42.7 (12.2), placebo & North America: 42.2 (12.5)	Dapagliflozin & Asia: 984 (493-1854), placebo & Asia: 930 (492-1895), dapagliflozin &Europe: 1043 (467-1821), placebo & Europe: 914 (488-1608), dapagliflozin & Latin America: 1089 (499-2273), placebo & Latin America: 1061 (496-2099), dapagliflozin & North America: 770 (412-1554), placebo & North America: 869 (449-1915)	Dapagliflozin 10 mg	124

Table 1. Continued

First author, year	Study design	Patient population	Location	Number of participants	Mean age (years), mean (SD)	Males (%)	eGFR inclusion criteria (ml/min/1.73 m^2)	UACR inclusion criteria (mg/g)	Baseline eGFR (ml/min/1.73 m^2)	Baseline UACR (mg/g) median (IQR)	Drug dosages	Follow-up median (weeks)
Chertow, 2023	Randomized, double-blind with placebo	Patients with chronic kidney disease with and without other cardiovascular medications	386 centers in 21 countries	Dapagliflozin & with type 2 diabetes: (n = 1455), placebo & with type 2 diabetes: (n = 1451), dapagliflozin &without type 2 diabetes: (n = 697), placebo & without type 2 diabetes: (n = 701)	Dapagliflozin & with type 2 diabetes: 64.1 (9.8), placebo & with type 2 diabetes: 64.7 (9.5), dapagliflozin &without type 2 diabetes: 56.9 (14.6), placebo & without type 2 diabetes: 56 (14.6)	Dapagliflozin & with type 2 diabetes: (66), placebo & with type 2 diabetes: (67.5), dapagliflozin &without type 2 diabetes: (69.2), placebo & without type 2 diabetes: (65)	Adults with eGFR of 25–75 ml/min per 1.73 m^2	200 to < 5000	Dapagliflozin & with type 2 diabetes: 44 (12.6), placebo & with type 2 diabetes: 43.6 (12.6), dapagliflozin &without type 2 diabetes: 41.7 (11.5), placebo & without type 2 diabetes: 41.8 (11.9)	Dapagliflozin & with type 2 diabetes:1024.5 (472.5-2111), placebo & with type 2 diabetes: 1004.5 (493.2-2017), dapagliflozin &without type 2 diabetes: 870.5 (472-1533.5), placebo & without type 2 diabetes: 841.5 (458.5-1554.5)	Dapagliflozin 10 mg	124
Chertow,2022	Randomized, double-blind with placebo	Adults with or without type 2 diabetes	386 centers in 21 countries	Lean or ideal (n = 888), Overweight (n = 1491), Grade 1 obesity (n = 1136), Grade 2/3 obesity (n = 781)	Lean or ideal & dapagliflozin: 58.6 (14.4), Lean or ideal & Placebo: 59.3 (14.6), Overweight & dapagliflozin: 62.4 (11.8), Overweight & Placebo: 62.6 (12.1), Grade 1 obesity & dapagliflozin: 62.9 (11), Grade 1 obesity & Placebo: 63.2 (10.6), Grade 2/3 obesity & dapagliflozin: 62.7 (10.4), Grade 2/3 obesity & Placebo: 61.7 (11)	Lean or ideal & dapagliflozin: (61.6), Lean or ideal & Placebo: (62.5), Overweight & dapagliflozin: (72.3), Overweight & Placebo: (70.3), Grade 1 obesity & dapagliflozin: (67.2), Grade 1 obesity & Placebo: (68.8), Grade 2/3 obesity & dapagliflozin: (62.4), Grade 2/3 obesity & Placebo: (62.3)	Adults with eGFR of 25–75 ml/min per 1.73 m8	200 to < 5000	Lean or ideal & dapagliflozin: 42.6 (12.3), Lean or ideal & Placebo: 41.7 (11.8), Overweight & dapagliflozin: 43.2 (12), Overweight & Placebo: 43 (12.4), Grade 1 obesity & dapagliflozin: 44.2 (12.6), Grade 1 obesity & Placebo: 43.2 (12.7), Grade 2/3 obesity & dapagliflozin: 42.5 (12.4), Grade 2/3 obesity & Placebo: 44 (12.5).	Lean or ideal & dapagliflozin: (975), Lean or ideal & Placebo: (949), Overweight & dapagliflozin: (949), Overweight & Placebo: (875), Grade 1 obesity & dapagliflozin: (987), Grade 1 obesity & Placebo: (994), Grade 2/3 obesity & dapagliflozin: (901), Grade 2/3 obesity & Placebo: (950)	Dapagliflozin 10 mg	124
McEwan, 2024	Randomized, double-blind with placebo	Patients with chronic kidney disease	386 centers in 21 countries	4304	61.8 (12.1)	69.9	Adults with eGFR of 25–75 ml/min per 1.73 m^2	200 to < 5000	43.1 ± 12.4	900 (539.6–1515.0) (IQR)	Dapagliflozin 10 mg	124

was conducted independently by two authors, with cross-verification by a third author (see Supplementary Table 1).

Heterogeneity Assessment

Quantitative data from each study were analyzed using STATA 17 software, employing the I^2 statistic to assess heterogeneity, with a cutoff of 75% indicating high heterogeneity.[28] However, due to the identification of overlapping populations from the Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Diseas(DAPA-CKD) parent trial and substantial statistical heterogeneity (I^2 = 93.7%) persisting after exclusion of duplicate publications, meta-analysis was not performed.

RESULTS

Study Selection

A total of 2,806 records were retrieved from various electronic databases: PubMed (419), Scopus (1,002), Web of Science (728), Cochrane Library (290), ClinicalTrials.gov (83), and Google Scholar (254). After eliminating approximately 1,656 duplicate entries using a citation manager (EndNote), an additional 1,639 irrelevant studies were discarded based on their titles and abstracts. Two authors independently reviewed the remaining 17 records against the eligibility criteria. This thorough review, which involved reading the full texts, resulted in the exclusion of 2 records. Ultimately, 15 studies, encompassing a total of 44,524 participants, were included in the systematic review. However, upon careful assessment to avoid overlapping patient populations, we identified that 11 of these publications were secondary analyses derived from the DAPA-CKD parent trial (NCT03036150), all reporting on the same patient cohort (n = 4,304). These publications (Chertow 2021, McMurray 2021, Jongs 2021, Wheeler 2021, Hiddo J.L 2021, Chertow 2023, Chertow 2022, Provenzano 2021, Vart 2022, and McEwan 2024) were excluded from the primary analysis to prevent double-counting of participants (Supplementary Table 1 provides detailed justification for each exclusion). Following this consolidation, four unique trials remained for narrative synthesis: Heerspink *et al.*, 2020 (DAPA-CKD parent trial);[19] Fioretto *et al.*, 2018 (DERIVE trial); Cherney *et al.*, 2020 (DIAMOND trial);[21] and Kohan *et al.*, 2014 (long-term T2DM+CKD trial) (Figure 1). The excluded articles can be found in Supplementary Table 3.

Study Characteristics

The studies included in this systematic review were published until January 10, 2025. A total of 15 studies met the inclusion criteria; however, following the exclusion of 11 overlapping publications derived from the DAPA-CKD parent trial (NCT03036150), 4 unique independent trials remained for narrative synthesis. Among the 4 unique trials, sample sizes ranged from 58 to 4,304. Only one study utilized dapagliflozin 5 mg once daily, while the remaining studies employed dapagliflozin 10 mg once daily as their primary intervention. The durations of these studies ranged from 6 weeks to 2.4 years, with a mean baseline eGFR of 30 to 58.3 mL/min/1.73 m^2. Key study characteristics are summarized in Table 1, with the 4 unique trials clearly distinguished from the excluded overlapping publications.

Risk of Bias in Studies

Domain 1: Randomization Process (D1)

All 15 studies described adequate random sequence generation and allocation concealment. Most studies provided detailed descriptions of computer-generated randomization sequences and central allocation systems, ensuring low risk of bias for this domain.

Domain 2: Deviations from Intended Interventions (D2)

All studies were double-blinded with participants and investigators masked to treatment allocation.

Domain 3: Missing Outcome Data (D3)

All 15 studies reported complete outcome data with low attrition rates (< 5%). The studies provided detailed descriptions of participant flow, reasons for discontinuation, and used intention-to-treat or modified intention-to-treat analyses. Therefore, all studies were rated as low risk for this domain.

Domain 4: Measurement of the Outcome (D4)

All studies utilized standardized methods for measuring eGFR and composite renal outcomes, including validated laboratory assessments with external quality control. Outcome assessors were blinded to treatment allocation in all double-blind trials. The crossover trial maintained consistent outcome measurement protocols across treatment periods. All studies were rated as low risk for this domain.

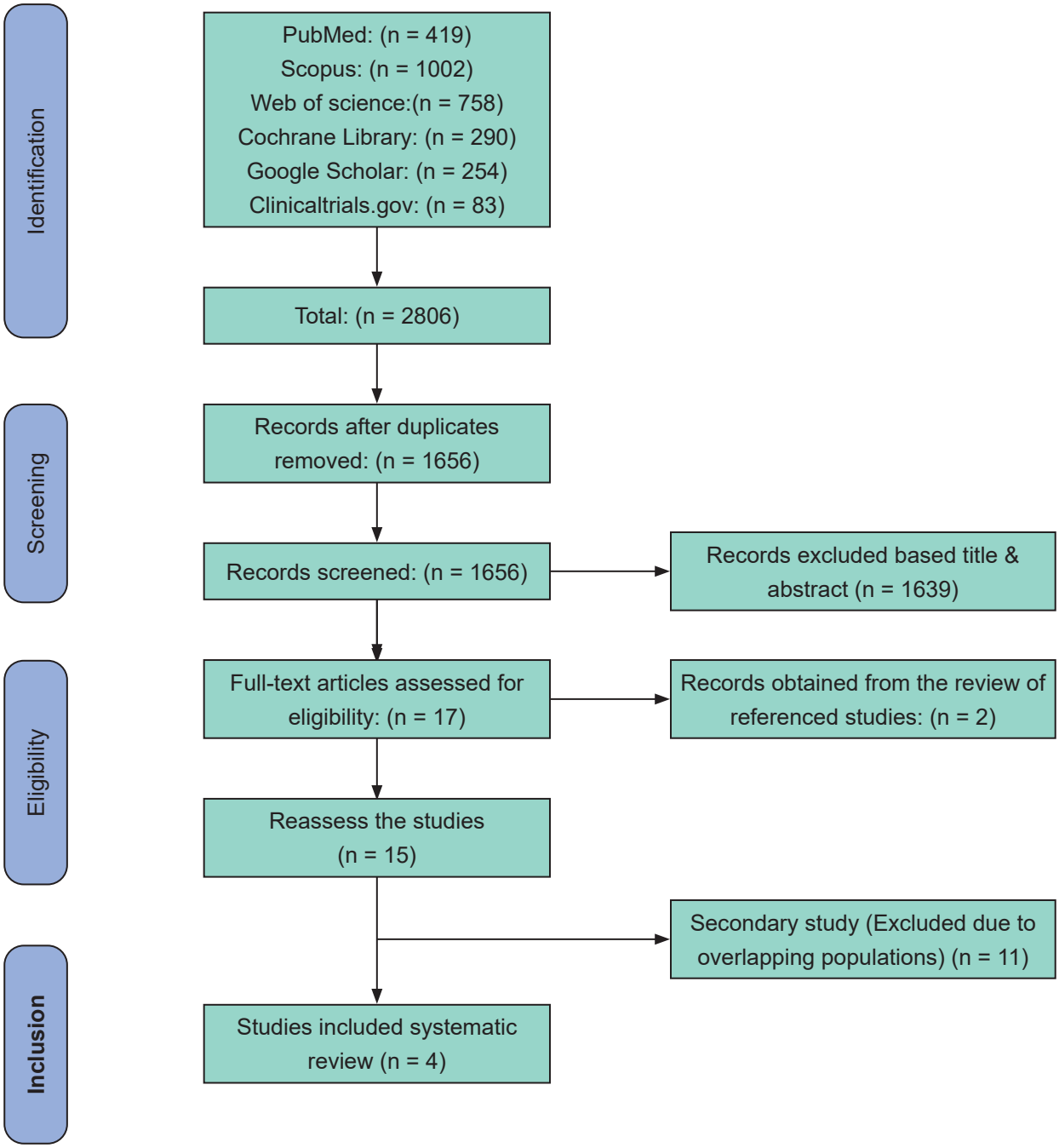

Figure 1. PRISMA flowchart of selection of studies

Domain 5: Selection of Reported Results (D5)

All studies reported outcomes according to pre-specified protocols or statistical analysis plans. Outcome definitions were clearly stated, and all planned analyses were presented. No evidence of selective reporting was identified. Therefore, all studies were rated as low risk for this domain.

Overall Risk of Bias

All 15 studies were rated as having low risk of bias. No studies were rated as high risk (see Table 2).

Primary Outcome

Mean Change in eGFR from Baseline

Following the exclusion of 11 overlapping

Table 2. Quality Assessment Results Using the Cochrane Risk of Bias Tool (RoB 2.0)

Study	D1	D2	D3	D4	D5	Overall
Heerspink, 2020	Low	Low	Low	Low	Low	Low
Fioretto, 2018	Low	Low	Low	Low	Low	Low
Chertow, 2021	Low	Low	Low	Low	Low	Low
Cherney, 2020	Low	Low	Low	Low	Low	Low
Kohan, 2014	Low	Low	Low	Low	Low	Low
McMurray, 2021	Low	Low	Low	Low	Low	Low
Jongs, 2021	Low	Low	Low	Low	Low	Low
Wheeler, 2021	Low	Low	Low	Low	Low	Low
Hiddo J.L, 2021	Low	Low	Low	Low	Low	Low
McMurray, 2021	Low	Low	Low	Low	Low	Low
Provenzano, 2021	Low	Low	Low	Low	Low	Low
Vart, 2022	Low	Low	Low	Low	Low	Low
Chertow, 2023	Low	Low	Low	Low	Low	Low
Chertow, 2022	Low	Low	Low	Low	Low	Low
McEwan, 2024	Low	Low	Low	Low	Low	Low

Abbreviations: D1, Randomization process; D2, Deviations from intended interventions; D3, Missing outcome data; D4, Measurement of the outcome; D5, Selection of reported results.

DAPA-CKD-derived publications, only four unique trials remained eligible for the analysis of eGFR decline. However, the assessment of statistical heterogeneity using the I^2 statistic revealed extreme heterogeneity ($I^2 = 93.7\%$, $P < .001$), indicating that the studies were not estimating a common effect size. This level of heterogeneity substantially exceeded the conventional threshold of 75% for considerable heterogeneity, as defined by the Cochrane Handbook (Higgins *et al.*, 2003).[29]

In accordance with Cochrane Handbook recommendations (Section 9.5.4),[27] which explicitly advise against pooling data when heterogeneity exceeds 75%, we refrained from performing a meta-analysis for this outcome. Instead, we provide a narrative synthesis of individual study findings, summarized in Table 3 and described below.

Narrative Synthesis and Clinical Interpretation

The direction and magnitude of the effect of dapagliflozin on eGFR decline varied considerably across the four unique trials, ranging from a significant decline of -6.60 mL/min/1.73m² (Cherney *et al.*, 2020),[21] to a non-significant increase

Table 3. Summary of Individual Trial Findings for Mean Change in eGFR from Baseline

Study (Year)	Trial Name	Population	Follow-up (weeks)	Sample Size (n)	Dose	Mean Difference (MD) in eGFR (mL/min/1.73m²)	95% Confidence Interval	Interpretation
Heerspink et al. (2020)	DAPA-CKD	Mixed CKD (with/without T2DM)	124	4,304	10 mg	+0.93	0.41 to 1.45	Non-significant (neutral effect)
Fioretto et al. (2018)	DERIVE	T2DM + CKD Stage 3A	24	58	10 mg	-0.34	-0.68 to 0.002	Non-significant (marginally negative; CI crosses null)
Cherney et al. (2020)	DIAMOND	Non-diabetic CKD + proteinuria	6	53	10 mg	-6.60	-8.17 to -5.03	Significant decline (acute hemodynamic effect likely)
Kohan et al. (2014)	—	T2DM + moderate renal impairment	104	~300	5 mg	+0.67	0.001 to 1.34	Non-significant (borderline positive)
Kohan et al. (2014)	—	T2DM + moderate renal impairment	104	~300	10 mg	-1.12	-1.73 to -0.51	Significant decline (dose-dependent effect observed)

Abbreviations: CKD, chronic kidney disease; T2DM, type 2 diabetes mellitus; CI, confidence interval; eGFR, estimated glomerular filtration rate; MD, mean difference.

of +0.93 mL/min/1.73m^2.[19] No consistent pattern emerged across studies.

The substantial heterogeneity (I^2 = 93.7%) is attributable to several key factors:

1. *Differences in study populations:* Mixed CKD (with/without T2DM) vs. T2DM+CKD vs. non-diabetic CKD.
2. *Variation in baseline eGFR:* Ranging from 43.1 to 58.3 mL/min/1.73m^2.
3. *Disparate follow-up durations:* Ranging from 6 to 124 weeks.
4. *Sample size discrepancies:* Ranging from 58 to 4,304 participants.
5. *Dose variations:* 5 mg vs. 10 mg of dapagliflozin.

Clinical Insight:

- The significant eGFR decline observed in the DIAMOND trial (Cherney *et al.*, 2020),[21] is likely attributable to acute hemodynamic effects (afferent arteriolar vasoconstriction) rather than progressive kidney function loss, given the short 6-week follow-up.
- In contrast, the DAPA-CKD trial (Heerspink *et al.*, 2020), with the largest sample size and longest follow-up (124 weeks), demonstrated a neutral effect on eGFR slope, consistent with the known renoprotective benefits of SGLT2 inhibitors that emerge over the long term.[19]
- The dose-dependent response observed in the Kohan *et al.* (2014) study (non-significant benefit at 5 mg vs. significant decline at 10 mg) suggests that higher doses may transiently reduce eGFR, though this effect is not necessarily clinically harmful.

The limited number of unique trials (n = 4) precluded meaningful subgroup analyses or meta-regression to explore these sources of heterogeneity, as such methods require a minimum of 10 studies per covariate to provide reliable estimates (Cochrane Handbook, Section 10.11.4.1).

Secondary Outcome: Composite Renal Outcomes

Following the systematic exclusion of overlapping DAPA-CKD-derived publications, only one unique trial—Heerspink *et al.* (2020), the DAPA-CKD parent trial—reported composite renal outcomes.[19] The composite renal outcome was defined as: (1) sustained eGFR decline of ≥50%, (2) end-stage kidney disease (ESKD) defined as eGFR < 15 mL/min/1.73m^2 (kidney failure, Stage 5 CKD) requiring chronic dialysis (for a minimum of four weeks) or kidney transplantation, and 3) renal death, defined as death attributed to kidney failure or its complications, including death from uremia, complications of dialysis or kidney transplantation, or death in patients with kidney failure not receiving renal replacement therapy.

Given that only a single unique trial reported this outcome, a meta-analysis was not feasible. The DAPA-CKD trial (Heerspink *et al.*, 2020) demonstrated a statistically significant reduction in the risk of composite renal outcomes with dapagliflozin compared to placebo (Hazard Ratio: 0.56, 95% CI: 0.45 to 0.68; $P < .001$).[19] This finding suggests a robust renal protective effect of dapagliflozin on hard clinical endpoints. However, this evidence is derived from a single trial and therefore requires confirmation in additional independent, well-powered randomized controlled trials. The absence of independent replication limits the generalizability of this finding, and the results should be interpreted with appropriate caution.

Sensitivity and Subgroup Analyses

Due to the limited number of unique trials (n = 4) remaining after the exclusion of overlapping DAPA-CKD publications, sensitivity analyses and subgroup analyses were not feasible. According to established methodological guidelines,[27,30,31] subgroup analyses require a minimum of 4 studies per subgroup to provide meaningful results, and meta-regression requires at least 10 studies per covariate. With only 4 unique trials available, any attempt to perform such analyses would be statistically underpowered and could yield spurious findings. Therefore, sensitivity analyses (e.g., leave-one-out, exclusion of short-duration studies) and subgroup analyses (e.g., by T2DM status, by CKD stage) were not performed. This limitation is explicitly acknowledged in the Discussion section.

Heterogeneity and Publication Bias

The assessment of statistical heterogeneity for the eGFR outcome, based on the 4 unique trials, revealed substantial heterogeneity (I^2 = 93.7%, $P < .001$). This indicates that approximately 93.7% of the total variation in effect estimates across studies is attributable to between-study heterogeneity rather than random sampling error. This level of heterogeneity is classified as "considerable"

according to the Cochrane Handbook,[27] and precludes meaningful meta-analysis.

Several factors likely contributed to this substantial heterogeneity:

1. Clinical heterogeneity: Differences in patient populations (CKD with/without T2DM, diabetic vs. non-diabetic CKD, varying CKD stages), baseline eGFR levels (43.1 to 58.3 mL/min/1.73m²), and baseline proteinuria levels.
2. Methodological heterogeneity: Disparate follow-up durations (6 to 124 weeks), varying sample sizes (58 to 4,304), and differences in study designs (parallel-group vs. crossover).
3. Statistical heterogeneity: The considerable variation in effect estimates (MD ranging from -6.60 to +0.93 mL/min/1.73m²) further confirms the lack of a common underlying effect size.

Given that meta-analysis was not performed, assessment of publication bias using funnel plots or Egger's test was not applicable. The primary limitation in interpreting these findings remains the small number of unique trials and the substantial heterogeneity, which limits the generalizability of the conclusions.

DISCUSSION

This systematic review reveals a critical dissociation between the effect of dapagliflozin on the surrogate endpoint of eGFR decline and its impact on hard clinical renal outcomes. Due to the extreme statistical heterogeneity (I^2 = 93.7%) observed across the four unique trials, meta-analysis was precluded, and no pooled estimate for eGFR decline was presented. This level of heterogeneity, far exceeding the conventional threshold of 75% for considerable heterogeneity as defined by the Cochrane Handbook,[27,29] indicates that the studies are not estimating a common effect size and any pooled estimate would be methodologically unsound and clinically misleading. The magnitude of heterogeneity further supports interpretation through narrative synthesis rather than quantitative aggregation.[28]

Our findings should be interpreted in the context of previously published systematic reviews. Lin *et al.* found that treatment with 10 mg of dapagliflozin showed the greatest efficacy in reducing composite renal outcomes (OR 0.55, 95% CI: 0.42 to 0.72),[32] while Katkam *et al.*,[33] reported that dapagliflozin significantly reduced the risk of kidney failure (RR 0.68, 95% CI: 0.53 to 0.86). Zou *et al.*,[34] and Su *et al.*,[35] similarly demonstrated improved renal outcomes with SGLT2 inhibitors in CKD populations. However, none of these reviews systematically addressed the issue of overlapping populations from the same parent trials, and most evaluated SGLT2 inhibitors as a class rather than focusing on individual agents. Our review advances the field through three distinctive contributions: (1) focusing specifically on dapagliflozin, (2) systematically excluding 11 overlapping DAPA-CKD-derived publications to prevent double-counting of the 4,304 participants, and (3) converting from meta-analysis to narrative synthesis when extreme heterogeneity (I^2 = 93.7%) precluded meaningful pooling, thereby providing a more methodologically sound and clinically meaningful interpretation of the available evidence.

The heterogeneity in eGFR response likely reflects true biological and methodological variation across studies. The significant eGFR decline observed in the DIAMOND trial (Cherney *et al.*,: MD −6.60 mL/min/1.73m^2),[21] is consistent with the well-established acute hemodynamic effects of SGLT2 inhibition, whereby restoration of tubuloglomerular feedback reduces intraglomerular pressure and transiently lowers measured GFR without indicating progressive nephron loss.[21,36,37] This acute dip is generally regarded as a physiological response and has been repeatedly documented across SGLT2 inhibitor trials.[36,37] Conversely, the neutral long-term effect on eGFR slope observed in DAPA-CKD over extended follow-up aligns with the sustained renoprotective effects demonstrated in large outcome trials.[19,38]

Several prior systematic reviews have examined the renal effects of dapagliflozin and SGLT2 inhibitors. Kanimozhi *et al.* reported that dapagliflozin did not significantly affect pooled eGFR estimates among patients with T2DM and CKD stages 2–5, although long-term treatment attenuated chronic eGFR decline in selected studies.[24,39] Similarly, broader meta-analyses of SGLT2 inhibitors have shown limited effects on eGFR despite significant reductions in clinically relevant renal outcomes.[22,23,34,40] These studies are consistent with our finding that pooled eGFR data remain highly heterogeneous and fail to provide a coherent estimate of treatment effect.

The contrasting findings for composite renal

outcomes, while derived primarily from the DAPA-CKD parent trial, demonstrate a robust and clinically meaningful reduction in renal risk (HR 0.56, 95% CI 0.45–0.68; $P < .001$).[19] This benefit is supported by prespecified analyses from DAPA-CKD demonstrating reductions in major adverse kidney events irrespective of diabetes status,[17] reduced albuminuria,[15] lower mortality risk,[13] and favorable outcomes even among patients with advanced CKD.[38] Collectively, these findings provide strong evidence that dapagliflozin confers clinically meaningful renoprotection beyond its effects on surrogate renal biomarkers.

Dapagliflozin exerts renoprotective effects through multiple complementary pathways, including restoration of glomerular hemodynamic balance, attenuation of inflammatory and profibrotic signaling, reduction of oxidative stress, and improvement of albuminuria.[7,15,36,37] These mechanisms provide biological plausibility for the observed reduction in hard renal outcomes despite heterogeneous effects on eGFR trajectories.

Strengths and Limitations

This systematic review analyzed 15 publications encompassing over 44,000 participants, with rigorous exclusion of 11 overlapping DAPA-CKD-derived publications to avoid double-counting participants from the same parent trial. This conservative approach enhances the validity of our findings by preventing duplication of patient data and ensuring that each participant is represented only once in the narrative synthesis. The comprehensive search strategy across six major databases (PubMed, Scopus, Web of Science, Cochrane Library, ClinicalTrials.gov, and Google Scholar) from inception to January 2025 ensured broad coverage of the available evidence. Furthermore, the application of the revised Cochrane Risk of Bias tool (RoB 2.0) provided a standardized and rigorous assessment of methodological quality across all included trials.

However, this study faces several important limitations that warrant consideration. Firstly, the extreme statistical heterogeneity ($I^2 = 93.7\%$) observed across the four unique trials precluded meaningful meta-analysis for eGFR decline, preventing the generation of a precise pooled estimate. This level of heterogeneity, far exceeding the conventional threshold of 75% for considerable heterogeneity as defined by the Cochrane Handbook, indicates that the studies are not estimating a common effect size and any pooled estimate would be methodologically unsound.

Secondly, clinical heterogeneity arose from substantial differences across studies, including variable renal conditions (diabetic and non-diabetic CKD), comorbidities, baseline eGFR levels (ranging from 43.1 to 58.3 mL/min/1.73m²), treatment duration (ranging from 6 to 124 weeks), and study design (parallel-group vs. crossover). Several included studies were primarily designed for cardiovascular outcomes rather than renal outcomes, potentially resulting in inadequate statistical power for the renal outcomes we aimed to assess.

Thirdly, the small number of unique trials (n = 4) remaining after excluding overlapping DAPA-CKD publications precluded meaningful subgroup analyses or meta-regression to explore heterogeneity sources. According to established methodological guidelines, subgroup analyses require a minimum of four studies per subgroup to provide meaningful results, and meta-regression requires at least 10 studies per covariate to provide reliable estimates. This limitation is particularly significant as it prevented us from investigating the impact of key factors such as diabetes status, baseline CKD stage, or dose variation on eGFR response.

Fourthly, the composite renal outcome finding is derived from a single unique trial (DAPA-CKD parent trial), and while robust within that trial (Hazard Ratio: 0.56, 95% CI: 0.45 to 0.68; $P < .001$), it requires confirmation in additional independent, well-powered randomized controlled trials. The absence of independent replication limits the generalizability of this finding, and the results should be interpreted with appropriate caution.

Fifthly, publication bias could not be formally assessed using funnel plots or Egger's test due to the limited number of studies, as such methods require a minimum of 10 studies to provide reliable estimates . While small-study effects were observed in preliminary assessments, the inability to conduct formal publication bias testing represents a limitation of the current analysis.

Future research should prioritize head-to-head comparisons with uniform populations and standardized follow-up durations to enable robust pooled analyses.[27]

CONCLUSION

Dapagliflozin significantly reduces major renal outcomes, but its effect on eGFR decline is inconclusive due to high heterogeneity across trials, limiting eGFR as a reliable surrogate. The discrepancy between surrogates and hard endpoints highlights the need to prioritize patient-centered outcomes; acute eGFR dips are hemodynamic, not nephrotoxic, and long-term renal protection is consistent across diabetes status. Future work should adopt uniform designs, explore dosing/combinations, identify responders (e.g., rapid progressors), and clarify mechanisms of heterogeneous eGFR responses to optimize therapy.

AUTHORS' CONTRIBUTIONS

- Drafted study protocol: SSH
- Conducted electronic database search: MZV, MMO
- Screened citations from searches: MZV, MMO
- Consulted on screening and data extraction discrepancies: RKH
- Performed data extraction: RKH, MZV, MMO
- Conducted data synthesis and analysis: SSH, NK, RKH
- Interpreted data: SSH, NK
- Written and drafted manuscript: SSH, NK
- Reviewed and edited manuscript: SSH, NK, RKH
- All authors approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY

The datasets generated and analyzed in this study are available upon reasonable request from the corresponding author.

ETHICAL APPROVAL

Not applicable.

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