

Comparative Effects of Febuxostat and Allopurinol on Renal Function and Serum Uric Acid Level in Chronic Kidney Disease and Hyperuricemia: A Systematic Review and MetaAnalysis

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Introduction. Hyperuricemia is a prevalent finding in chronic kidney disease (CKD), contributing to progression of kidney impairment. Febuxostat and allopurinol, both xanthine oxidase inhibitors, are widely used as urate-lowering therapies, yet their comparative efficacy and safety in patients with CKD remain uncertain.

Methods. This PRISMA-compliant systematic review and meta-analysis searched PubMed, Embase, Web of Science, and Scopus through May 2025 for randomized controlled trials (RCTs) and cohort studies comparing febuxostat with allopurinol in patients with CKD and hyperuricemia. Outcomes included estimated glomerular filtration rate (eGFR) and serum uric acid (SUA) level. Random-effects models pooled mean differences (MD), with heterogeneity assessed by I^2 and publication bias by Egger's/Begg's tests.

Results. Out of 1543 identified studies, 15 (including four RCTs and 11 cohorts) involving 19,365 patients (4,572 febuxostat, 14,793 control) were included. Febuxostat improved eGFR (weighted mean difference [WMD]: 0.81 mL/min/1.73 m², 95% CI: 0.29 to 1.33, $P < .001$) and significantly reduced SUA levels (WMD: -3.23 mg/dL, 95% CI: -5.03 to -1.43, $P < .001$) compared to allopurinol. Notable heterogeneity ($I^2 > 50\%$) was observed; however, sensitivity analyses confirmed the stability of the results. Publication bias was considerable for SUA outcomes (Egger's $P = .00$).

Conclusion. Febuxostat demonstrated superior renal protective and urate-lowering effects compared to allopurinol in CKD patients with hyperuricemia. Further long-term studies accompanied by subgroup analyses are warranted.

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INTRODUCTION

Hyperuricemia, characterized by a serum uric acid (SUA) level above 6.8 mg/dL (405 μ mol/L), represents a common metabolic abnormality associated with a spectrum of clinical sequelae, notably kidney impairment.¹ Elevated uric acid levels result from either increased production, decreased renal excretion, or a combination thereof.

Etiologies are categorized as primary (idiopathic) or secondary (acquired).² Assessment of uric acid excretion, especially during adherence to a purine-restricted diet, helps differentiate between uric acid overproduction (> 3.6 mmol/24h or 600 mg/24h) and hypouricemia, thereby informing appropriate therapeutic interventions.³ Hyperuricemia is prevalent in individuals with chronic kidney

disease (CKD), affecting approximately 43.6% of this population globally, with rates varying by region and sex. For instance, studies indicate that the prevalence can reach up to 70% in advanced stages of CKD (Stages IV-V).⁴ Moreover, hyperuricemia is increasingly recognized as an independent risk factor for CKD progression. Research shows that higher serum uric acid levels correlate with a more rapid decline in kidney function, particularly in patients without proteinuria.⁵ Elevated serum uric acid concentrations contribute to renal injury via mechanisms including endothelial dysfunction,⁶ oxidative stress,⁷ and inflammation,⁸ thereby predisposing individuals to nephrolithiasis, urate nephropathy, and acute uric acid nephropathy.

The renal sequelae of hyperuricemia are especially significant in CKD, wherein decreased glomerular filtration rate (eGFR) compromises uric acid excretion, leading to further elevations in SUA levels.⁹ Nephrolithiasis, observed in approximately 20–50% of patients with gout and elevated serum or urinary uric acid concentrations, underscores the connection between hyperuricemia and the development of renal calculi.¹⁰ Urate nephropathy is a rare condition characterized by the deposition of monosodium urate crystals in the renal interstitium, which may result in proteinuria and hypertension. In contrast, uric acid nephropathy can lead to acute kidney injury through tubular obstruction, particularly in cases of rapid urate overproduction, as observed during cytolytic therapies.^{11,12} Hyperuricemia, frequently observed as a component of metabolic syndrome, often precedes the development of conditions such as type 2 diabetes mellitus and cardiovascular disease, thereby adding complexity to the clinical management of CKD.¹³

Urate-lowering therapies (ULTs), including allopurinol and febuxostat, are crucial for managing hyperuricemia and reducing its associated renal and systemic complications. Allopurinol, a xanthine oxidase inhibitor, has historically been the primary therapeutic intervention; however, its use necessitates dosage modification in patients with CKD due to diminished renal excretion, thereby elevating the potential for adverse events, such as hypersensitivity syndromes.^{14,15} Febuxostat, a non-purine-selective xanthine oxidase inhibitor, is a viable treatment option due to its favorable pharmacokinetic profile. Its primary hepatic

metabolism may mitigate dosing limitations in patients with CKD.^{16–18} Contemporary research suggests that febuxostat may offer enhanced urate-lowering capabilities and renal protection relative to allopurinol, particularly in patients with advanced CKD.¹⁹ Nevertheless, the comparative effects of these interventions on renal function preservation and cardiovascular safety remain unclear due to inconsistent findings, underscoring the need for a thorough assessment.^{20,21}

This systematic review and meta-analysis comprehensively evaluate the existing evidence regarding the comparative effects of febuxostat and allopurinol on renal function in patients with CKD and hyperuricemia. Using objective measures, including estimated glomerular filtration rate and serum uric acid levels, this study aims to determine whether febuxostat provides superior renoprotection compared to allopurinol, thereby addressing a significant uncertainty in clinical practice. The results will inform evidence-based urate-lowering therapy strategies, considering efficacy, safety, and long-term outcomes for this high-risk patient population.

MATERIALS AND METHODS

This systematic review and meta-analysis compare the effects of febuxostat and allopurinol on kidney function in patients with CKD and hyperuricemia. This project utilized the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method.²²

Review Question

We aimed to evaluate the comparative efficacy and safety of febuxostat versus allopurinol on renal function in patients with CKD and hyperuricemia.

Eligibility Criteria

Studies were included if they: (1) enrolled patients with CKD (at any stage) and hyperuricemia (SUA > 6.8 mg/dL); (2) compared febuxostat with allopurinol or placebo; (3) reported quantitative outcomes for eGFR, SUA, or serum creatinine levels; and (4) were randomized controlled trials (RCTs) or observational cohort studies published in English. Exclusion criteria included: (1) studies involving acute kidney injury or non-hyperuricemia renal conditions; (2) case reports, reviews, or abstracts; and (3) non-English publications.

Search Strategy

A comprehensive literature search was conducted in PubMed, Embase, Web of Science, and Scopus from inception through June 2024, with guidance from a biomedical librarian. Search terms were developed using PICO (Population: CKD patients with hyperuricemia; Intervention: febuxostat; Comparison: allopurinol; Outcomes: renal function

measures) and included Medical Subject Headings (MeSH) and free-text terms (e.g., “chronic kidney disease,” “febuxostat,” “allopurinol”). Gray literature was searched via Google Scholar, and reference lists of eligible studies were hand-searched. The full search strategy is provided in Supplementary Appendix I.

Appendix I: Table 1. Search Strategies on Medline (via PubMed) in June 2024

Search number	Query	Results
1	("Renal Insufficiency, Chronic"[MESH] OR "renal insufficiencies"[tiab] OR "renal insufficiency"[tiab] OR "kidney insufficiency"[tiab] OR "kidney insufficiencies"[tiab] OR "kidney diseases"[tiab] OR "kidney disease"[tiab] OR "chronic kidney"[tiab] OR "renal diseases"[tiab] OR "renal disease"[tiab] OR "chronic renal"[tiab] OR "renal disease"[tiab] OR "renal diseases"[tiab]) AND (febuxostat[MESH] OR febuxostat[tiab] OR "TEI 6720"[tiab] OR (6720[tiab] AND TEI[tiab]) OR TEI-6720[tiab] OR TEI6720[tiab] OR uloric[tiab] OR "2-(3-cyano-4-isobutoxyphenyl)-4-methyl-5-thiazolecarboxylic acid"[tiab])	309

Appendix I: Table 2. Search Strategies on Embase in June 2024

No.	Query	Results
1	'allopurinol'/exp OR 'zyloric'/exp	27686
2	'allopurinol':ab,ti,kw OR 'zyloric':ab,ti,kw	12471
3	#1 OR #2	29000
4	'febuxostat'/exp OR 'tei 6720'/exp OR 'tei-6720'/exp OR 'tei6720'/exp OR 'uloric'/exp OR '2-(3-cyano-4-isobutoxyphenyl)-4-methyl-5-thiazolecarboxylic acid'/exp	3733
5	'febuxostat':ab,kw,ti OR 'tei 6720':ab,kw,ti OR 'tei-6720':ab,kw,ti OR 'tei6720':ab,kw,ti OR 'uloric':ab,kw,ti OR '2-(3-cyano-4-isobutoxyphenyl)-4-methyl-5-thiazolecarboxylic acid':ab,kw,ti	2300
6	#4 OR #5	3872
7	'6720':ab,ti,kw AND 'tei':ab,ti,kw	20
8	#6 OR #7	3872
9	#3 AND #8	2431
10	'renal'/exp OR 'kidney'/exp	556909
11	renal:ab,ti OR kidney:ab,ti	1523380
12	#10 OR #11	1672964
13	#9 AND #12	887
14	#13 AND ('Article'/it OR 'Article in Press'/it OR 'Conference Abstract'/it OR 'Conference Paper'/it)	609

Appendix I: Table 3. Search Strategies on Web of Science in June 2024

#	Search Query	Results
1	(TS=("renal insufficiencies") OR TS=("renal insufficiency") OR TS=(" kidney insufficiency") OR TS=("kidney insufficiencies") OR TS=("kidney diseases") OR TS=("kidney disease") OR TS=("chronic kidney") OR TS=("renal diseases") OR TS=("renal disease") OR TS=("chronic renal") OR TS=("renal disease") OR TS=("renal diseases")) AND (TS=(febuxostat) OR TS=("TEI 6720") OR (TS=(6720) AND TS=(TEI)) OR TS=(TEI-6720) OR TS=(EI6720) OR TS=(uloric) OR TS=("2-(3-cyano-4-isobutoxyphenyl)-4-methyl-5-thiazolecarboxylic acid"))	167

Appendix I: Table 4. Search Strategies on Scopus in June 2024

Search number	Query	Results
1	(TITLE-ABS("renal insufficiencies") OR TITLE-ABS("renal insufficiency") OR TITLE-ABS("kidney insufficiency") OR TITLE-ABS("kidney insufficiencies") OR TITLE-ABS("kidney diseases") OR TITLE-ABS("kidney disease") OR TITLE-ABS("chronic kidney") OR TITLE-ABS("renal diseases") OR TITLE-ABS("renal disease") OR TITLE-ABS("chronic renal") OR TITLE-ABS("renal disease") OR TS=("renal diseases")) AND (TITLE-ABS(febuxostat) OR TITLE-ABS("TEI 6720") OR (TITLE-ABS(6720) AND TITLE-ABS(TEI)) OR TITLE-ABS(TEI-6720) OR TITLE-ABS(TEI6720) OR TITLE-ABS (uloric) OR TITLE-ABS("2-(3-cyano-4-isobutoxyphenyl)-4-methyl-5-thiazolecarboxylic acid"))	962

Study Selection

Citations were imported into EndNote 21 for deduplication. Two independent reviewers screened titles and abstracts against eligibility criteria, followed by full-text assessment of potentially eligible studies. Discrepancies were resolved through consensus or consultation with a third reviewer. The selection process is detailed in a PRISMA flow diagram (Figure 1).

Risk of Bias Assessment

Study quality was evaluated by two independent reviewers using the Joanna Briggs Institute (JBI) critical appraisal tools for RCTs and cohort studies.

Studies meeting at least 50% of the JBI checklist criteria were included. Risk of bias was summarized in tabular form (Supplementary Appendix II). Disagreements were resolved through discussion.

Data Extraction

Two reviewers independently extracted data using a standardized form, capturing: (1) study characteristics (author, year, country, design); (2) patient demographics (sample size, age, sex); (3) intervention details (febuxostat/allopurinol dosage, treatment duration); and (4) outcomes (eGFR, SUA, serum creatinine, adverse events). Missing data were requested from the corresponding authors.

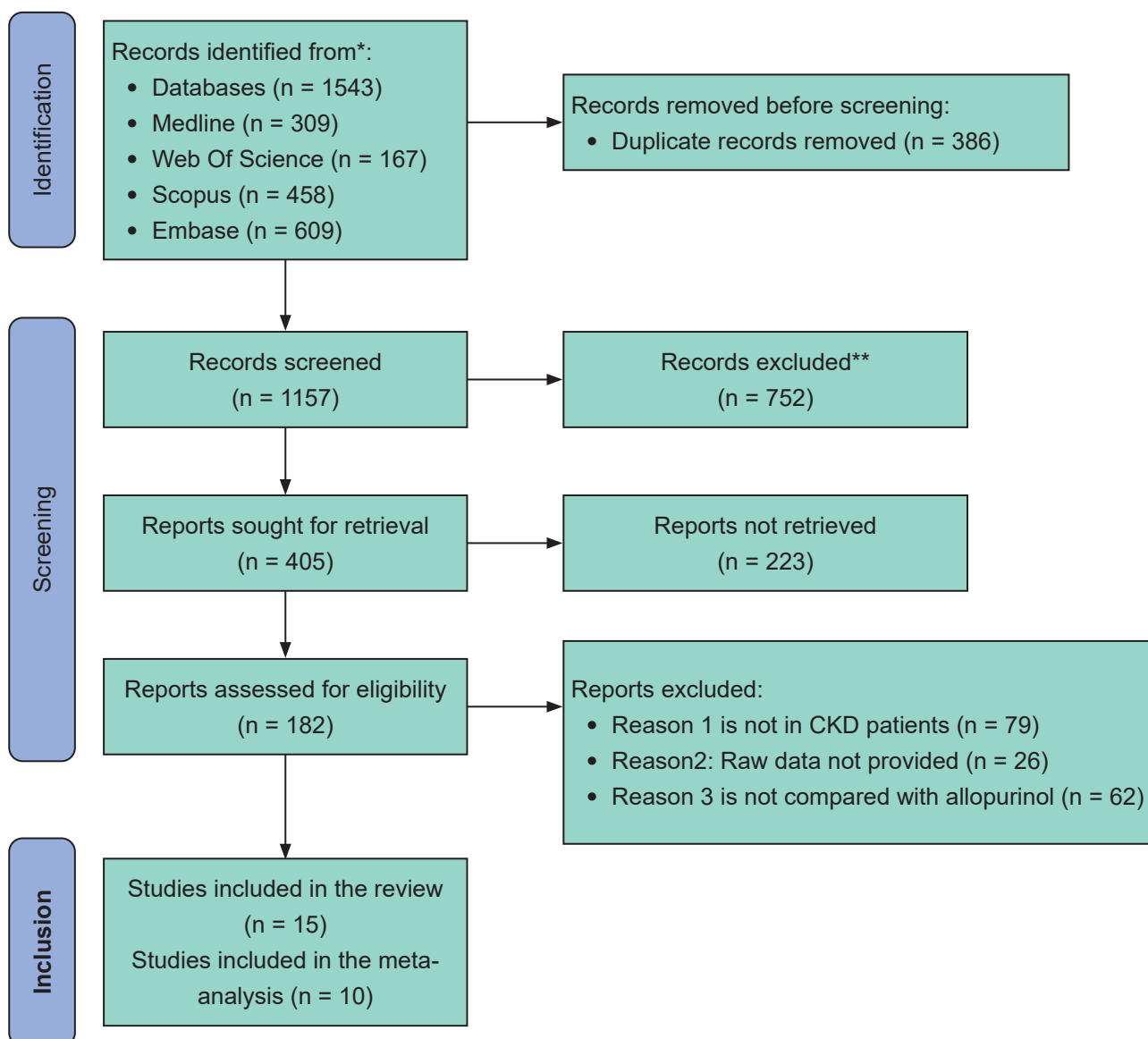


Figure 1. PRISMA study selection flow diagram.

Appendix II: Table 1. Critical Appraisal Results of Eligible RCT Studies

Studies	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Total
MATTA et al.(2023)	Y	U	Y	N	N	U	Y	Y	Y	Y	Y	Y	Y	Include
Helget et al. (2022)	Y	U	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Include
Liao et al.(2022)	Y	U	Y	U	U	U	Y	U	U	Y	Y	Y	Y	Include
Grávalos et al (2017)														Include

Q1: Was true randomization used for assignment of participants to treatment groups? Q2: Was allocation to treatment groups concealed? Q3: Were treatment groups similar at the baseline? Q4: Were participants blind to treatment assignment? Q5: Were those delivering treatment blind to treatment assignment? Q6: Were outcomes assessors blind to treatment assignment? Q7: Were treatment groups treated identically other than the intervention of interest? Q8: Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed? Q9: Were participants analyzed in the groups to which they were randomized? Q10: Were outcomes measured in the same way for treatment groups? Q11: Were outcomes measured in a reliable way? Q12: Was appropriate statistical analysis used? Q13: Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

Y: Yes, N: No, U: Unclear, NA: Not applicable

Appendix II: Table 2. Critical Appraisal Results of Eligible Cohort Studies

Studies	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Total
Lee and Lee (2019)	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Include
Zhang et al. (2019)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Include
Tsuruta et al(2014)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Include
Tsuji et al. (2018)	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Include
Chou et al. (2018)	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Include
Yang (2020)	Y	Y	Y	U	U	Y	Y	Y	U	U	Y	Include
Huang et al. (2024)	Y	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Include
Peng et al(2020)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Include
Nagaraju et al. (2023)	Y	Y	Y	Y	N	Y	Y	N	U	N	Y	Include
Lertnawapan & Jatuworapruk (2021)	Y	Y	Y	Y	Y	Y	Y	Y	U	N	Y	Include
Song et al(2017)	U	U	U	U	U	U	U	U	U	U	U	Include

Q1. Were the two groups similar and recruited from the same population?; Q2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?; Q3. Was the exposure measured in a valid and reliable way?; Q4. Were confounding factors identified?; Q5. Were strategies to deal with confounding factors stated?; Q6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?; Q7. Were the outcomes measured in a valid and reliable way?; Q8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?; Q9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?; Q10. Were strategies to address incomplete follow up utilized?; Q11. Was appropriate statistical analysis used?

Y: Yes, N: No, U: Unclear, NA: Not applicable

Inconsistencies were resolved by cross-referencing original publications or involving a third reviewer.

Statistical Analysis

Meta-analyses were performed using Stata 17. Mean differences (MD) with 95% confidence intervals (CI) were calculated for continuous outcomes (eGFR, SUA). Heterogeneity was assessed using Cochran's Q test and the I² statistic; an I² value greater than 50% indicated substantial heterogeneity, prompting the use of random-effects models. The DerSimonian and Laird random-effects model was applied for pooling continuous outcomes. Sensitivity analyses explored the impact of excluding individual studies. Publication bias was evaluated using funnel plots and Egger's and Begg's tests, with $P < .05$ indicating significant bias. Subgroup analyses by study design (RCT vs. cohort) and CKD stage were planned. However, due to

the limited number of studies in each subgroup category (fewer than three studies per subgroup), these analyses could not be performed reliably, and thus they are not presented in the results.

Ethical Considerations

As a systematic review of published data, ethical approval was not required. All included studies were assessed for compliance with ethical standards in clinical research.

Protocol Registration

This systematic review and meta-analysis were not registered in a prospective registry (e.g., PROSPERO). The authors acknowledge that protocol registration is a recommended practice for systematic reviews and meta-analyses and can help reduce the risk of reporting bias. The absence of prospective registration represents a limitation

of this study. However, the review was conducted in accordance with the PRISMA guidelines, and all methods were specified a priori to minimize the potential for bias.

RESULTS

Characteristics of the Articles Included in This Review

Following a comprehensive screening process, we excluded review articles, commentaries, editorials, case reports, correspondence, and animal studies, as illustrated in Figure 1. This review encompasses studies conducted up to the year 2023. In total, this meta-analysis includes four RCTs and eleven cohort studies, which together comprise 19,365 patients (4,572 in the febuxostat group and 14,793 in the control group). The publication dates of these trials range from 2014 to 2023, with treatment durations ranging from 4 to 24 months. The mean age of participants in the control group was 60.98 ± 8.12 years, and in the experimental group, 62.64 ± 7.44 years. Among the fifteen studies included in the systematic review, ten provided sufficient quantitative data for inclusion in the meta-analysis. It is noteworthy that Helget *et al.*, a study that focused on gout, was included exclusively in the qualitative systematic review because it failed to report extractable mean $\pm$ standard deviation values for eGFR or SUA outcomes. Conversely, Lertnawapan & Jatuworapruk, another gout-focused study, provided quantitative data; thus, it was incorporated into the meta-analysis, although its impact was assessed through sensitivity analysis. The characteristics of all studies included in this review are presented in Table 1.

Assessment of Database Overlap in Taiwanese Studies. Four studies conducted in Taiwan have been identified: Huang *et al.*, Peng *et al.*, Yong *et al.*, and Chou *et al.* (Table 2). A thorough evaluation of the potential for overlapping patient populations was undertaken by analyzing study characteristics, data sources, study periods, and inclusion criteria.

While there is some temporal overlap among these studies, they utilized different data sources, covered different study periods, and applied different inclusion criteria:

- Huang *et al.* focused specifically on patients with both diabetes mellitus and CKD, a distinct subpopulation.
- Peng *et al.* employed propensity score matching

and focused on patients newly initiating ULT.

- Yong *et al.* conducted a retrospective study with different inclusion criteria.
- Chou *et al.* had an earlier study period (2000–2012) compared to other studies.

Due to variations in study periods, data sources, and inclusion criteria, we have classified these studies as independent. Nonetheless, we recognize the likelihood of partial patient overlap, particularly among studies that use the National Health Insurance Research Database and have overlapping study periods (Peng *et al.* and Chou *et al.*). Therefore, we advise careful interpretation of the pooled estimates and encourage future research to explicitly account for potential database overlap.

Methodological Quality

Fifteen studies were critically appraised using the JBI appraisal tools for RCTs and cohort studies to assess risk of bias. All studies met more than half of the checklist criteria and were included (Appendix II).

Meta-Analysis Results

Ten reports provided data on eGFR levels in both patient groups post-treatment and showed significant heterogeneity ($P < .05$), necessitating a random-effects model for meta-analysis. The analysis results demonstrated that eGFR levels in the experimental group were not significantly higher than in the control group (WMD: 0.81; 95% CI: 0.29 to 1.33; $P < .001$) (Figure 2).

Sensitivity analysis indicated that excluding any individual study does not alter the overall combined analysis results (Figure 3).

There was evidence of publication bias based on the funnel plot (Figure 4). In contrast, Egger's test (for all studies: $P = .94$) and Begg's test ($P = .28$) revealed no evidence of publication bias.

Eleven studies reported post-treatment SUA levels in both patient groups, with significant heterogeneity ($P < .05$), necessitating a random-effects model for meta-analysis. The analysis results demonstrated that SUA levels in the experimental group were significantly lower than in the control group (WMD: -3.23; 95% CI: -5.03 to -1.43; $P < .001$) (Figure 5).

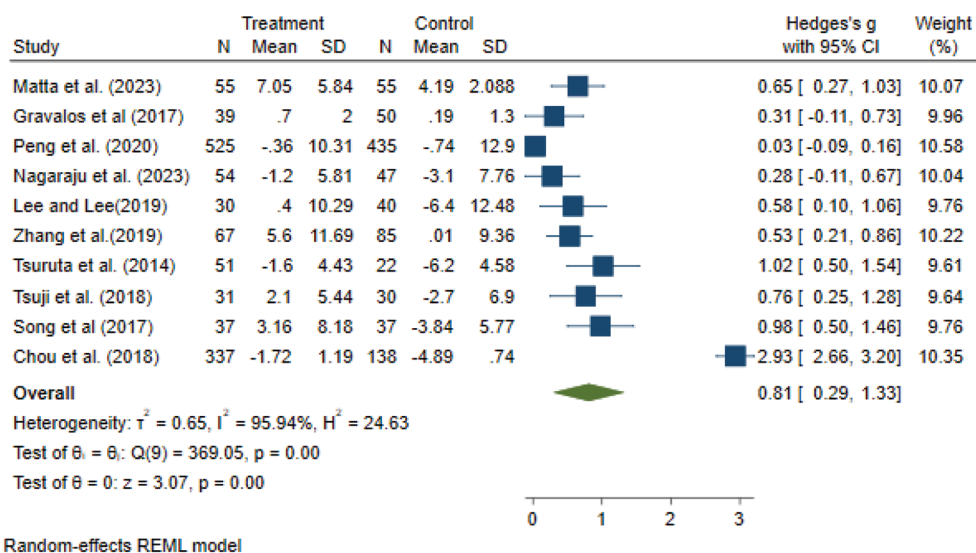
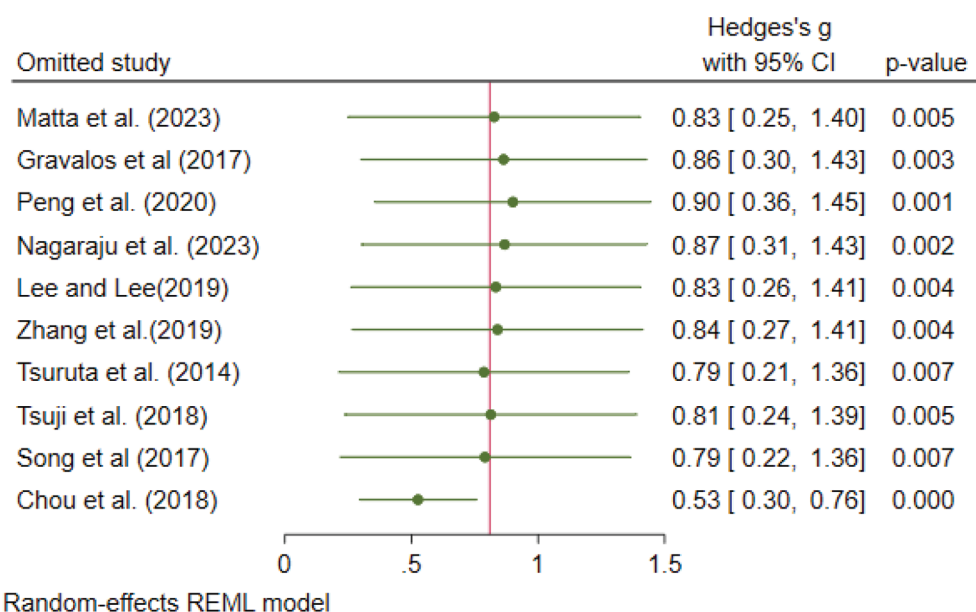
Sensitivity analysis indicated that excluding any individual study does not alter the overall results of the combined analysis. To specifically address the

Table 1. The features of studies incorporated in the systematic review and meta-analysis

No	Author	year	country	Study	Patient	Intervention		Number(F/M)		Age		Course of treatment		outcomes	Results
						Exp.g	Con.g	Exp.g	Con.g	Exp.g	Con.g	Exp.g	Con.g		
1	Matta et al.	2023	India	prospective, randomized controlled, and open-label clinical study	patients with CKD stage G3a to G5 with hyperuricemia of either	Febuxostat 40 mg OD	Allopurinol 100 mg TDS	18/37	30/25	45.25 ± 11.51 years	44.87 ± 13.08 years	4 mon		eGFR assessment, serum creatinine, SUA, total serum protein, urine creatinine, urine protein, blood urea, and number of dialysis	Febuxostat has a superior nonprotective effect than allopurinol.
2	Gravados et al.	2017	Madrid Spain	clinical Trial	CKD patients	Febuxostat 80 mg	Allopurinol 100 mg	39	50	--	--	6 mon		eGFR, SUA, blood pressure, albuminuria, and inflammatory parameters	There were no significant differences in blood pressure, albuminuria, or inflammatory parameters. Febuxostat treatment decreases UA levels in CKD patients, which is more effective than allopurinol. Uric acid lowering may indeed slow the progression of kidney disease similar to the allopurinol-treated group.
3	Helget et al.	2022	Massachusetts	multicenter, randomized, double-blind, noninferiority, comparative effectiveness trial	Gout participants with stage 3 CKD	Febuxostat	Allopurinol	6/164	4/177	68.4 ± 9.2	68.4 ± 9.9	18 mon		The primary outcome was as1 gout flare during Phase 3. Secondary outcomes included achievement of SU < 6 mg/dL at the end of Phase 2 and serious adverse events (SAEs).	Allopurinol and febuxostat are similarly efficacious and well-tolerated in the treatment of gout in people with CKD when used in a treat-to-target regimen with lower incidence of gout flares in participants randomized to allopurinol
4	Liao et al.	2022	China	RCT	Patients with chronic kidney disease at stages 3–5 with hyperuricemia	febuxostat 40 mg	allopurinol 100 mg	18/32	20/30	63.80 ± 4.21	64.13 ± 5.10	15 mon		blood urea nitrogen, serum creatinine, serum sodium, serum potassium, and serum uric acid	Compared with allopurinol, febuxostat can improve renal function, reduce UA levels, and reduce the occurrence of complications, with high safety, which is worthy of further clinical promotion
5	Huang et al.	2024	Taiwan	Retrospective observational cohort study	CKD disease and diabetes	febuxostat	allopurinol	2126/871	9849/3051	65.6 ± 12.0	63.5 ± 12.3	January 2012 to December 2017		All-cause hospitalization, heart failure, cardiovascular intervention	Use of febuxostat in patients with diabetes mellitus and chronic kidney disease is associated with higher cardiovascular risks compared to allopurinol
6	Peng et al.	2020	Taiwan	propensity score-matched cohort	Adult CKD patients newly treated with ULI	febuxostat 40 mg	allopurinol 100 mg	122/403	126/399	67.50 ± 13.73	66.10 ± 14.73	2.5 years		SUA eGFR assessment	Febuxostat and allopurinol showed no difference in renal function changes during the follow-up study.
7	Lerthawapan & Jaiworapruk	2021	Thailand	retrospective cohort	gout who approximately have CKD	Feb g40	Allo g100	16/39	31/89	66.78 ± 14.81	66.51 ± 13.74	27wks		SUA	the febuxostat groups had significantly lower mean SUA compared with the allopurinol groups
8	Song et al	2017	Korea	retrospective observational study	non-dialytic & nondiabetic CKD	allopurinol era	Febuxostat era	37	37	--	--	12 months		eGFR and SU	Febuxostat has superior potency for urate-lowering and may have a renal protective effect in non-diabetic CKD patients.
9	Yong	2020	Taiwan	retrospective study	patients with CKD and hyperuricemia	febuxostat 40 mg	allopurinol 100 mg	233	83	---	---	---		effects on cardiovascular and renal functions were assessed	in patients with CKD and hyperuricemia, febuxostat can reduce the serum uric acid level. long-term use of febuxostat may exert a protective effect on the kidneys. there were no obvious adverse reactions and the patients tolerated the drug well
10	Nagaraju et al	2023	India	single-center retrospective case-record-based study	patients with CKD and hyperuricemia	febuxostat 40 mg	allopurinol 100 mg	11/34	7/40	57.2 ± 12.7	51.7 ± 13.1	6 months		eGFR and SUA	Febuxostat was better at reducing hyperuricemia than allopurinol, but there was no significant difference in the progression of CKD
11	Lee and Lee	2019	South Korea	retrospective cohort	stage 3 CKD and hyperuricemia	febuxostat 40,80 and 20 mg	allopurinol 100, 200 and 300 mg	3/27	5/35	64.3 ± 13.1	62.3 ± 14.6	55.9 ± 31.8 months		eGFR and SUA and Renal Survival Time and Risk of Renal Disease Progression	Febuxostat seems to reduce serum uric acid level and to retard renal disease progression more effectively than allopurinol in hyperuricemic patients with CKD
12	Zhang et al.	2019	China	prospective cohort	CKD stage 2–3 patients with hyperuricemia	febuxostat 40 mg and 20 mg	allopurinol 100 mg and 200 mg	17/50	20/65	62.6 ± 7.0	61.1 ± 9.0	6 months		eGFR and SUA and serum creatinine (Scr).	febuxostat showed a superior effect in delaying renal impairment progression compared to allopurinol in CKD and hyperuricemia patients. The study found that febuxostat was more effective in increasing eGFR and reducing SUA levels than allopurinol.
13	Tsuruta et al.	2014	Japan	retrospective observational cohort	CKD patients with hyperuricemia	febuxostat 10,20 and 40 mg	allopurinol 100, 200 and 300 mg	22/29	6/16	67.4 ± 12.3	72.9 ± 10.7	12 months		eGFR and SUA	switching from allopurinol to febuxostat can be beneficial in reducing serum UA levels and slowing the progression of renal disease in hyperuricemic patients with chronic kidney disease
14	Tsuij et al.	2018	Japan	retrospective observational cohort	CKD patients with hyperuricemia	febuxostat 10,20 and 40 mg	allopurinol 100, 200 and 300 mg	10/21	11/19	65.3 ± 11.1	59.6 ± 16.1	6 month		eGFR, Blood Pressure, Urinary Protein and SUA	reducing serum uric acid levels with febuxostat may have beneficial effects on renal function and blood pressure in CKD patients with hyperuricemia
15	Chou et al.	2018	China	pharmacoepidemiology cohort study	CKD patients with hyperuricemia	febuxostat 40 mg	allopurinol 100 mg	121/116	56/82	65.1	65.8	13 month		incidence of end-stage renal disease (ESRD) requiring dialysis, SUA levels and eGFR	febuxostat and benzbromarone were found to be more effective than allopurinol in reducing the risk of progression to dialysis and in lowering SUA levels in CKD populations

Table 2. Study characteristics, data sources, study periods, and inclusion criteria in Taiwanese Studies

Study	Data Source	Study Period	Inclusion Criteria
Huang et al. (2024) ³⁰	National Health Insurance Database	January 2012 - December 2017	Diabetes mellitus + CKD with hyperuricemia
Peng et al. (2020) ³¹	National Health Insurance Research Database	2000-2016	CKD patients newly treated with ULT
Yong et al. (2020) ³⁴	Not specified	2010-2016	CKD patients with hyperuricemia
Chou et al. (2018) ³⁹	National Health Insurance Research Database	2000-2012	CKD patients with hyperuricemia

**Figure 2.** The meta-analysis of eGFR in CKD patients treated with febuxostat and allopurinol by a forest plot.**Figure 3.** The sensitivity analysis diagram of eGFR in CKD patients treated with febuxostat and allopurinol.

potential impact of including gout-focused studies, we conducted a post hoc sensitivity analysis by excluding the only gout study with quantitative

data available for meta-analysis (Lertnawapan & Jatuworapruk). The exclusion of this study resulted in minimal changes to the pooled effect

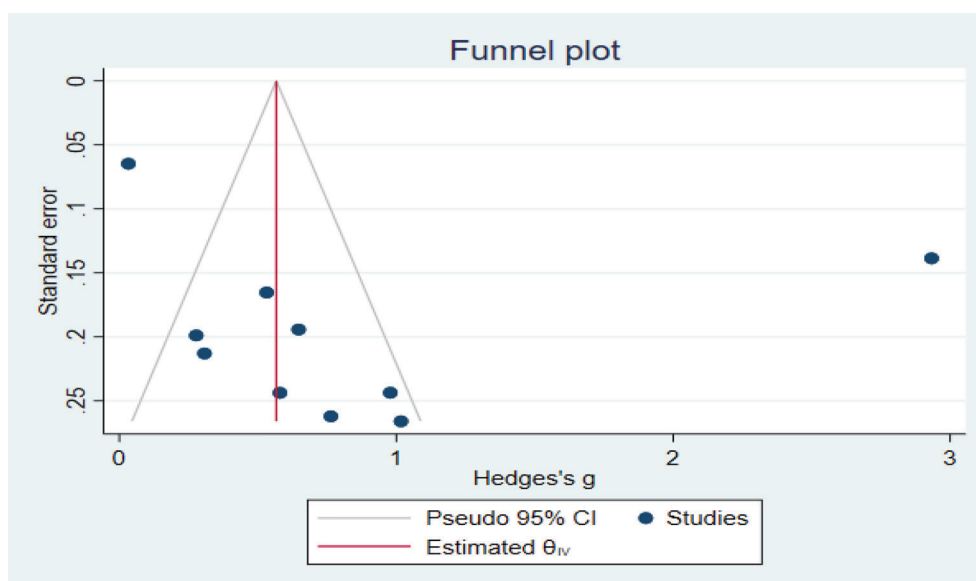


Figure 4. The funnel plot of eGFR in CKD patients treated with febuxostat and allopurinol for publication bias.

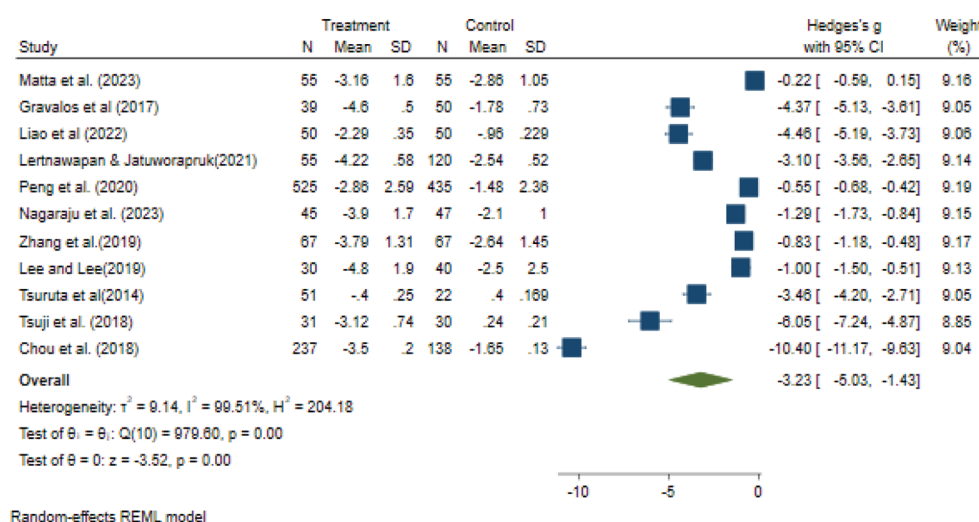


Figure 5. The meta-analysis of serum uric acid in CKD patients treated with febuxostat and allopurinol by a forest plot.

estimates. For eGFR, the WMD changed from 0.81 (95% CI: 0.29 to 1.33) to 0.79 (95% CI: 0.27 to 1.31). For SUA, the WMD changed from -3.23 (95% CI: -5.03 to -1.43) to -3.18 (95% CI: -5.01 to -1.35). These changes confirm that the inclusion of the Lertnawapan & Jatuworapruk study did not materially influence the overall findings or the direction of the conclusions. The Helget *et al.* study, which lacked extractable summary statistics, was not included in the quantitative meta-analysis and therefore could not influence the pooled effect estimates (Figure 6).

There was evidence of publication bias based

on the funnel plot (Figure 7), Egger's test (for all studies: $P = .00$), and Begg's test ($P = .01$). Additionally, we employed the trim-and-fill analysis; however, the results of the meta trim were not significantly different from those of the initial meta-analysis.

Given the potential for overlapping patient populations across Taiwanese studies, we conducted an additional sensitivity analysis excluding all four Taiwanese studies (Huang *et al.*, Peng *et al.*, Yong *et al.*, and Chou *et al.*). The pooled effect estimates remained statistically significant for both eGFR (WMD: 0.72, 95% CI: 0.24 to 1.20, $P < .001$)

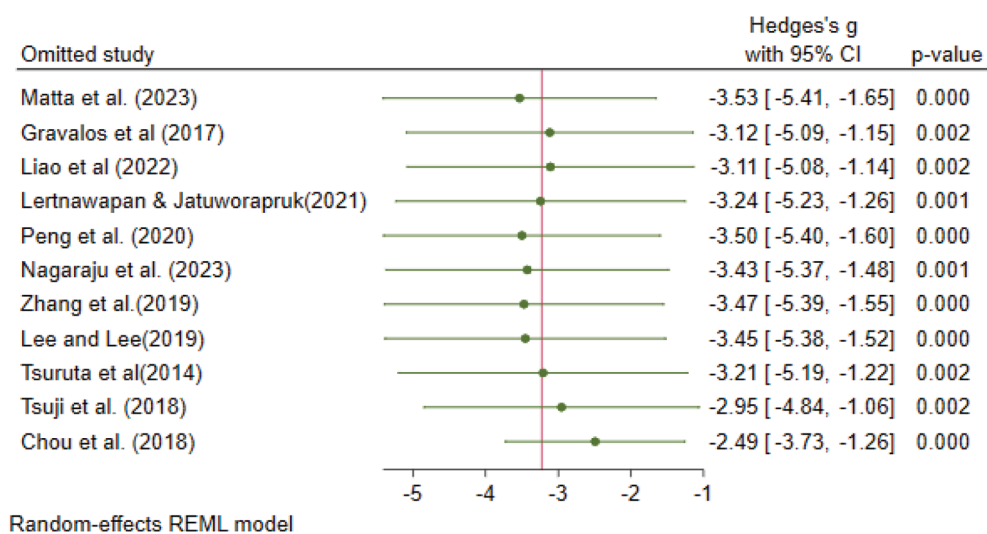


Figure 6. The sensitivity analysis diagram of serum uric acid in CKD patients treated with febuxostat and allopurinol.

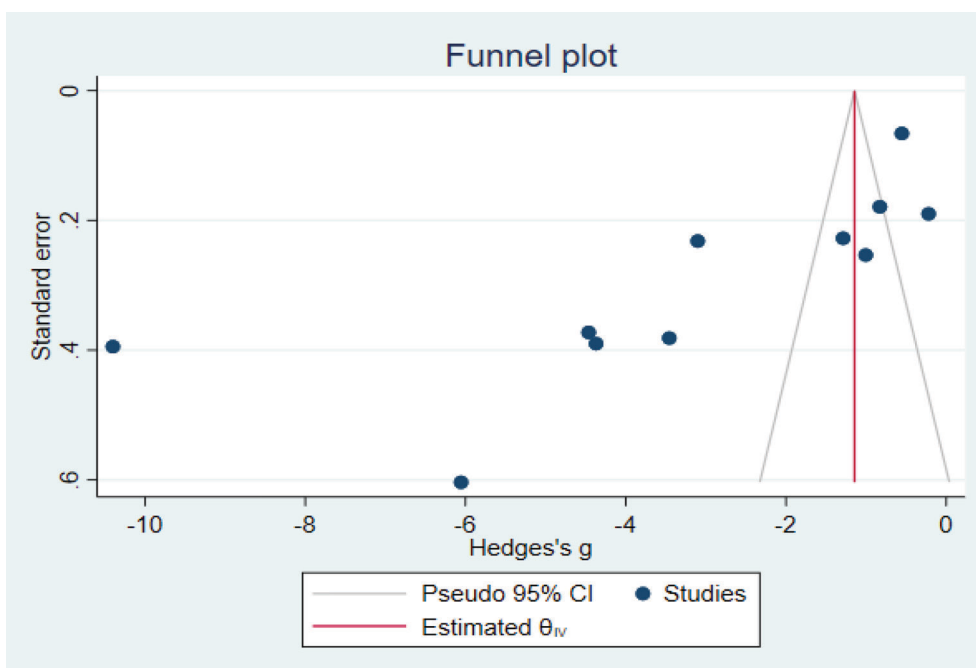


Figure 7. The funnel plot of serum uric acid in CKD patients treated with febuxostat and allopurinol for publication bias.

and SUA (WMD: -3.01, 95% CI: -4.89 to -1.13, $P < .001$), confirming the robustness of our findings, but not clinically for GFR. However, heterogeneity remained high, suggesting that other sources of variability also contributed.

Exploration of Heterogeneity Sources. To investigate potential sources of heterogeneity, a qualitative comparison of study characteristics across the included studies was conducted. The principal potential sources of heterogeneity identified are as follows:

Study Design: Randomized controlled trials (RCTs, $n = 4$) exhibited more consistent effect sizes than cohort studies ($n = 11$), which showed greater variability in outcomes and larger standard errors. The observational nature of cohort studies may have introduced confounding and selection biases, thereby contributing to the observed heterogeneity.

CKD Stage: Studies that included patients with advanced chronic kidney disease (CKD) (stages 4-5) reported different effect sizes than those focusing on early CKD (stages 2-3). Patient characteristics

and responses to urate-lowering therapy may differ in more advanced CKD, potentially affecting the observed heterogeneity.

Population Characteristics: Research focusing on patients with gout, such as that conducted by Lertnawapan and Jatuworapruk, showed different response patterns than studies that included the general CKD population with hyperuricemia. The presence of gout may alter therapeutic response and renal outcomes.

Geographic Variation: The majority of included studies were conducted in Asian populations, particularly in China, Japan, South Korea, and Taiwan, which may limit the generalizability of the findings to other populations. Variations in genetic factors, dietary habits, and healthcare systems may contribute to this heterogeneity.

Dosing Regimens: Variability in dosing for febuxostat (10-80 mg/day) and allopurinol (100-300 mg/day) across studies likely contributed to the heterogeneity. Furthermore, dose adjustments based on renal function varied across studies.

Treatment Duration: Follow-up periods across studies ranged from 4 to 86 months, with longer durations potentially allowing for more pronounced effects on renal function.

Despite the exploratory examination of these factors, formal meta-regression or subgroup analyses could not be conducted due to the limited number of studies. Consequently, the high level of heterogeneity was regarded as a significant limitation of this meta-analysis.

DISCUSSION

This systematic review and meta-analysis provide evidence that febuxostat offers superior renal-protective and urate-lowering effects compared with allopurinol in patients with CKD and hyperuricemia. The meta-analysis, encompassing 11 studies, demonstrated improvements in eGFR and significant reductions in SUA levels with febuxostat compared to allopurinol. These findings align with a growing body of literature highlighting febuxostat's efficacy in managing hyperuricemia and preserving renal function in patients with CKD.²³⁻⁴⁰ The observed mild increase in eGFR associated with febuxostat underscores its potential as a renoprotective agent, particularly in the advanced stages of CKD. This finding emphasizes the therapeutic promise of febuxostat in managing

renal function in patients with CKD. Studies such as those by Zhang *et al.* (2019) and Lee and Lee (2019) reported that febuxostat delayed the progression of renal impairment more effectively than allopurinol, particularly in patients with CKD stages 2–3 and stage 3, respectively.^{35,36} Similarly, Matta *et al.* (2023) and Nagaraju *et al.* (2023) found that febuxostat had a superior renoprotective effect, although the latter reported no significant difference in overall CKD progression.^{14,23} These findings may be attributed to febuxostat's selective inhibition of xanthine oxidase, which minimizes interference with other purine-metabolizing enzymes, and to its hepatic metabolism, which avoids the renal clearance challenges associated with allopurinol in CKD patients.¹⁶ In contrast, Peng *et al.* (2020) reported no significant differences in changes in renal function, which may be attributed to shorter follow-up periods or variations in patient demographics, underscoring the influence of study design on outcomes.³¹ The renoprotective effects of Febuxostat may be facilitated through various mechanisms. It is well established that hyperuricemia can provoke inflammatory responses, oxidative stress, and activation of the renin-angiotensin system, all of which contribute to renal damage.³²

Additionally, by reducing SUA levels, febuxostat may alleviate oxidative stress, protecting renal cells from injury, as noted by Yang *et al.* (2019).³⁴ These mechanisms collectively contribute to the preservation of glomerular filtration capabilities, as evidenced by studies like Tsuji *et al.* (2018) and Chou *et al.* (2018), which also reported benefits such as improved blood pressure control and reduced progression to end-stage renal disease (ESRD).^{38,39} Febuxostat's superior efficacy in reducing SUA levels was a consistent finding across the included studies.^{14,23-25,27,29,31,32,35-39} Schumacher *et al.* (2008) and Lertnawapan & Jatuworapruk (2021) demonstrated that febuxostat achieved lower SUA levels more effectively than allopurinol, even in patients with mild to moderate renal impairment.^{29,32} Goldfarb *et al.* (2013) further corroborated this in hyperuricosuric patients, where febuxostat significantly reduced urinary uric acid.²⁴ These findings are consistent with the research conducted by Liao *et al.* (2022) and Tsuruta *et al.* (2014), which highlight febuxostat's effectiveness in reducing serum uric acid levels. This reduction has the potential to alleviate renal stress

and inflammation.^{27,37} Grávalos *et al.* (2017) found no significant differences in secondary outcomes like blood pressure or albuminuria, indicating that febuxostat's primary benefits may be tied to eGFR preservation and SUA lowering.²⁵

While the primary focus of this meta-analysis was on renal outcomes, several individual studies included in our review reported on cardiovascular safety. Huang *et al.* (2024) reported increased cardiovascular risks, including all-cause hospitalization and heart failure, with febuxostat in CKD patients with diabetes.³⁰ This finding aligns with the CARES trial (White *et al.*, 2018), which noted higher cardiovascular and all-cause mortality with febuxostat, prompting an FDA boxed warning in 2019. However, conflicting evidence from the FAST trial (Kojima *et al.*, 2019) and other studies suggests no increased risk of major adverse cardiovascular events with febuxostat. Additionally, some studies have reported an association between febuxostat and increased atrial fibrillation risk, particularly at higher doses (80 mg/day) and in older adults. It is important to note that these cardiovascular observations are derived from individual studies and were not subjected to a pooled meta-analysis in our review. Clinicians should remain vigilant regarding potential cardiovascular risks when prescribing febuxostat, particularly in high-risk patients, until further large-scale studies with systematic cardiovascular outcome assessment become available.

The inclusion of gout studies in this systematic review and meta-analysis warrants specific consideration. Gout is a common complication of chronic hyperuricemia in patients with CKD, and understanding the comparative effectiveness of urate-lowering therapies in this population is clinically relevant. However, patients with gout may have distinct pathophysiological characteristics, including more severe hyperuricemia, chronic inflammation, and different baseline renal function trajectories, which could influence treatment response. Importantly, only one gout study (Lertnawapan & Jatuworapruk, 2021) contributed quantitative data to the meta-analysis, and sensitivity analysis confirmed that its exclusion did not materially affect the pooled effect estimates (WMD change of 0.02 for eGFR and 0.05 for SUA). The other gout study (Helget *et al.*, 2022) was included only in the qualitative synthesis

because it lacked extractable summary statistics. These findings suggest that the inclusion of gout studies did not substantially bias the overall meta-analysis results, though the potential for heterogeneity introduced by these studies should be acknowledged.

A limitation of this meta-analysis is the potential for overlapping patient populations among the four included studies from Taiwan (Huang 2024, Peng 2020, Yong 2020, Chou 2018). While these studies reported different study periods, data sources, and inclusion criteria, partial patient overlap cannot be entirely ruled out, particularly between studies that use the National Health Insurance Research Database and share overlapping time periods. Although sensitivity analyses excluding all Taiwanese studies confirmed the robustness of the overall findings, this issue may still contribute to the observed heterogeneity and may have led to an overestimation of the effect size. Future studies should explicitly address and report on database overlap to ensure the independence of included studies in meta-analyses.

The substantial heterogeneity observed in this meta-analysis reflects the inherent variability in study design, patient populations, and clinical settings across the included studies. While sensitivity analyses confirmed the stability of the overall findings, the high I^2 values suggest that the pooled effect estimates should be interpreted with caution. The heterogeneity likely arises from multiple sources, including the inclusion of both RCTs and observational studies, variations in CKD severity, differences between gout and non-gout populations, geographic variability, and differences in dosing regimens and treatment durations. The inability to perform formal subgroup analyses due to the limited number of studies in each category prevents definitive identification of the sources of heterogeneity. Future studies should aim for standardized protocols and more homogeneous populations to reduce heterogeneity and provide more reliable estimates of comparative effectiveness.

The lack of prospective protocol registration (e.g., in PROSPERO) represents a limitation of this systematic review. While the study was conducted in accordance with established guidelines and methods were clearly specified, prospective registration would have further enhanced transparency

and reduced the potential for reporting bias. Future systematic reviews in this area should consider prospective registration to strengthen methodological rigor.

CONCLUSION

Our findings indicate that treatment with febuxostat is associated with improvements in key parameters that are statistically significant but not clinically significant. These improvements include an increase in estimated glomerular filtration rate and a reduction in serum uric acid levels compared with allopurinol in patients with chronic kidney disease and hyperuricemia. Overall, these results suggest that febuxostat may represent a more effective therapeutic approach for managing CKD in this specific patient population. However, the observed heterogeneity, the potential for publication bias, and the absence of a formal cardiovascular meta-analysis underscore the necessity for cautious interpretation of the findings. Furthermore, the cardiovascular safety profile of febuxostat, as reported in individual studies, requires careful consideration and further systematic investigation. Future research, including large-scale randomized controlled trials with comprehensive safety assessments, is essential to validate these findings and elucidate the mechanisms underlying febuxostat's renal protective effects.

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CONFLICT OF INTEREST

All authors declared more competing interests for this work with subgroup analyses and long-standing studies.

AUTHOR CONTRIBUTIONS

Raei Davoud and Nasri Hamid defined the research title, keywords, and aims.¹ Raei Davoud and Mahboubeh Hojati described the search strategy, article screening, data extraction, discussion, and conclusion.^{1,3} Fariba Pashzadeh cooperated in the search strategy. Mahboubeh Hojati also performed meta-analyses and created figures under the supervision of Mansourian Marjan.

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