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ORIGINAL ARTICLE

Prevention of kidney function decline using uric acid-lowering therapy in chronic kidney disease patients: a systematic review and network meta-analysis

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Abstract

Introduction Several previous studies have suggested that uric acid-lowering therapy (ULT) can slow the progression of chronic kidney disease (CKD). Although crucial for CKD patients, few studies have evaluated the effects of different ULT medications on kidney function. This systematic review summarizes evidence from randomized controlled trials (RCTs) regarding the effects of ULT on kidney function.

Method We performed a systematic search of PubMed, MEDLINE, Embase, Scopus, and the Cochrane Library up to September 2021 to identify RCTs in CKD patients comparing the effects of ULT on kidney function with other ULT medications or placebo. A network meta-analysis was performed to compare each ULT indirectly. The primary outcome was a change in estimated glomerular filtration rate (eGFR) from baseline.

Results Ten studies were selected with a total of 1480 patients. Topiroxostat significantly improved eGFR and reduced the urinary albumin/creatinine ratio compared to placebo (mean difference (MD) and 95% confidence interval [95% CI]: 1.49 [0.08; 2.90], $P=0.038$ and 25.65% [13.25; 38.04], $P<0.001$, respectively). Although febuxostat did not show a positive effect overall, it significantly improved renal function (i.e., eGFR) in a subgroup of CKD patients with hyperuricemia (MD [95% CI]: 0.85 [0.02; 1.67], $P=0.045$). Allopurinol and pegloticase did not show beneficial effects.

Conclusions Topiroxostat and febuxostat may have better renoprotective effects in CKD patients than other ULT medications. Further large-scale, long-term studies are required to determine whether these effects will lead, ultimately, to reductions in dialysis induction and major adverse cardiovascular events.

Key Points
- *This study is the first network meta-analysis comparing the nephroprotective effects of ULT in CKD patients.*
- *Topiroxostat and febuxostat showed better renoprotective effects in CKD patients than other ULT medications.*
- *Heterogeneity was low in this study, suggesting consistency of results.*

Keywords Chronic kidney disease · Febuxostat · Renoprotective effects · Topiroxostat · Uric acid-lowering therapy · Xanthine oxidase inhibitors

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Introduction

Chronic kidney disease (CKD) is a major public health problem affecting an estimated 697.5 million people worldwide, and the prevalence is still increasing [1]. A large proportion of CKD patients have comorbid lifestyle-related diseases, such as diabetes and hypertension [2]. In addition, the risks of cardiovascular disease (CVD) and cerebrovascular disease also increase as CKD progresses [3]. Therefore, preventing the progression of CKD and protecting renal function are important issues that must be addressed worldwide.

Hyperuricemia is one of the most common complications of CKD. The major symptom of hyperuricemia is gout. Moreover, emerging data show that hyperuricemia is involved in the development and progression of CKD [4–6]. Recent evidence suggested that hyperuricemia is associated with a variety of diseases closely related to CKD, including hypertension, type 2 diabetes, obesity, heart failure, and cardiovascular disease [4, 5, 7–9]. In general, the prevalence of hyperuricemia increases as renal function declines [10]. Therefore, hyperuricemia and CKD form a vicious cycle, adversely affecting each other. Conversely, uric acid-lowering therapy (ULT) may help to preserve renal function in CKD patients. However, there is controversy regarding the effects of ULT on kidney function. Several studies showed that ULT was beneficial in preserving renal function [11–13]. On the other hand, contrary to expectations, ULT did not alleviate kidney function decline in other studies [14, 15]. There are several possible explanations for these discrepancies. First, there may be differences in efficacy among drugs. Although xanthine oxidase inhibitors were the most commonly used drugs in these studies, different results have been reported for different drugs, such as allopurinol, febuxostat, and topiroxostat [16–18]. Few studies have evaluated the effects of each ULT medication on kidney function, although this is a crucial issue for CKD patients. Therefore, we investigated the effects of ULT with different drugs in CKD patients by network meta-analysis. This study will have some impact on the future management of CKD patients.

Method

Literature search and study selection

The search strategy was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for network meta-analysis [19, 20]. The protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO) with identification number CRD42021253825.

We performed a systematic search of PubMed, MEDLINE, Embase, Scopus, and the Cochrane Library from inception to September 16, 2021. Research strategies and keywords are outlined in the Supplementary Data (Table S1). Studies were eligible for inclusion if the following criteria were met: they were randomized controlled trials (RCTs); included adults (age ≥ 18) with CKD (defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 and/or proteinuria and/or albuminuria); compared uric acid-lowering agent(s) with other uric acid-lowering agent(s) or placebo; followed participants for at least 3 months post-randomization; and reported changes in eGFR, serum creatinine, albuminuria, or proteinuria from baseline to the end of the study. The reference lists of studies included in the meta-analysis were reviewed to minimize missing relevant studies. Two independent authors (S.T. and N.O.) reviewed the search results separately and in a blinded manner to select studies based on inclusion and exclusion criteria. When a consensus was not reached between the two authors, a third author (T.Y.) was consulted to reach a decision. There was no restriction on publication language. Studies were excluded if they included non-human subjects, and there were insufficient data for analysis even after contacting the authors.

Outcome

The primary outcome was a change in kidney function as measured by eGFR from baseline to last measurement or the end of follow-up. The secondary outcomes included changes in albuminuria, proteinuria, and the incidence of adverse events (AEs).

Data extraction and quality assessment

All data from eligible studies were abstracted independently by two investigators (S.T. and N.O.). Any conflicts in data extraction or quality assessment were resolved by a third reviewer (T.Y.). In each study, data regarding the mean difference (MD) (and standard error) of eGFR, serum uric acid (SUA), and urinary albumin/protein to creatinine ratio (ACR) from baseline and the incidence of AEs in each group were extracted. If the standard error of the MD was not directly stated, it was calculated. We used the Cochrane risk of bias assessment to explore sources of bias in the RCTs included in the analysis [21]. Applying this tool, we evaluated the risk of bias in random sequence generation, allocation concealment, the blinding of participants and researchers, the blinding of outcome assessments, selective

reporting, incomplete outcome data, and other metrics. A funnel plot was used to assess for potential evidence of publication bias. The certainty of evidence for each trial was rated as high, moderate, low, or very low using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach [22].

Statistical analysis

For each study, the MD in treatment effect on continuous outcomes from baseline to last measurement between treatment and control groups was calculated with the 95% confidence interval (95% CI) and standard error. For dichotomous outcomes, the results are expressed as the risk ratio (RR) with 95% CI. We performed a network meta-analysis using the netmeta package (version 1.1–0) and R programming language (R Foundation for Statistical Computing, Vienna, Austria). A random-effects model was used for the analysis. Heterogeneity was assessed by the *P*-value of the I^2 variable [23, 24]. Heterogeneity was considered to be low, moderate, or high if I^2 was 25%, 50%, or 75%, respectively. Subgroup analyses were conducted according to CKD stage (stage ≥ G3) and the presence of hyperuricemia (male, SUA ≥ 7 mg/dL; female, SUA ≥ 6 mg/dL).

Results

Literature search and included studies

A diagram of the study selection is shown in Fig. 1. First, a total of 1926 studies were identified in the primary database search, and five additional studies were identified through examination of references. We removed 850 duplicate studies; 1076 studies were screened. By screening titles and abstracts, 1011 papers were excluded because

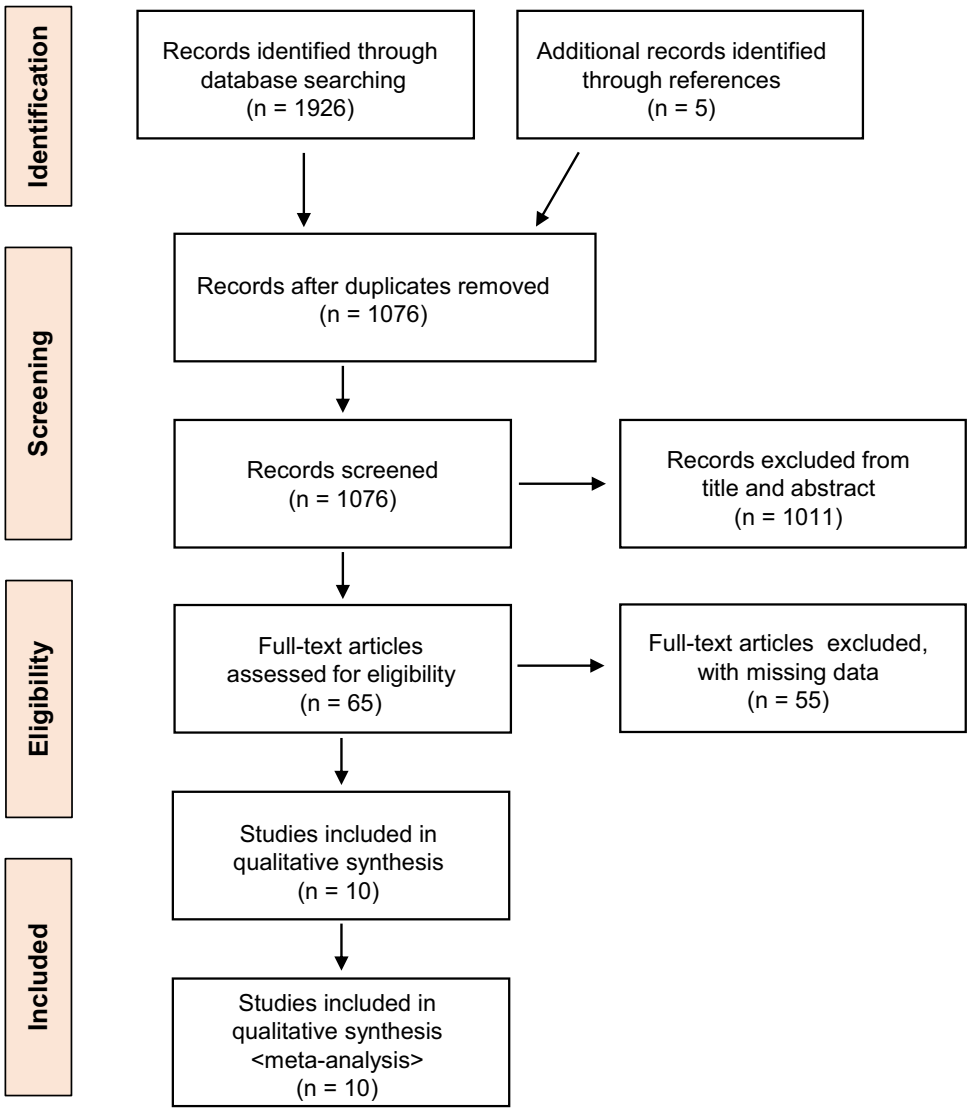

Fig. 1 PRISMA flow diagram showing study selection

they did not meet the inclusion criteria. By assessing full-text articles, 55 additional studies were excluded due to missing data. Finally, ten studies published up to September 16, 2021, were selected for our meta-analysis according to the inclusion criteria [14, 15, 17, 25–31].

Of the ten RCTs, three compared allopurinol and placebo [15, 25, 30], three compared febuxostat and placebo [14, 27, 31], two compared topiroxostat and placebo [26, 28], one compared febuxostat and topiroxostat [17], and one compared pegloticase and placebo [29].

The pooled population consisted of 1480 patients (242 treated with allopurinol, 151 treated with topiroxostat, 368 treated with febuxostat, 83 treated with pegloticase, and 636 treated with placebo). One study was excluded from analysis of eGFR because the MD in eGFR from baseline was not available.

Study characteristics and quality assessment

Table 1 shows the inclusion criteria of the individual studies used in the analysis. Table 2 highlights the baseline characteristics and laboratory data after the intervention in the included studies. The quality evaluation of the included studies is shown in Fig. S1. The conflicts of interest statements and funding information for each trial are summarized in Table S2.

Network meta-analysis of treatment groups

Kidney function (eGFR)

Network plots are shown in Supplementary Data (Fig. S2). Only topiroxostat significantly improved eGFR compared to placebo (MD [95% CI]: 1.49 [0.08; 2.90], $P = 0.038$;

Table 1 Summary of studies included in the analysis

Study		Design	Drug dose	Follow-up (months)	Inclusion criteria with regard to age, SUA, and kidney function	Reference
Label	Author (year)					
1	Perrenoud et al. (2020)	RCT	Allopurinol 100–300 mg/day vs. placebo	3	Age, 18–74; eGFR, 30–59 mL/min/1.73 m^2; SUA,: ≥ 7 (male) or ≥ 6 (female) mg/dL	[25]
2	Badve et al. (2020)	RCT	Allopurinol 100–300 mg/day vs. placebo	24	Adult, eGFR: 15–59 mL/min/1.73 m^2; urine albumin/creatinine ≥ 265 mg/g or a decrease in eGFR of at least 3.0 mL/min/1.73 m^2 in the preceding 12 months	[15]
3	Matsuo et al. (2020)	RCT	Topiroxostat 40–160 mg/day vs. febuxostat 10–60 mg/day	6	Age, 20–80; SUA, ≥ 7 mg/dL; eGFR, 15–60 mL/min/1.73 m^2; urine protein/creatinine, 0.15–3.5 g/gCr	[17]
4	Kimura et al. (2018)	RCT	Febuxostat 10–40 mg/day vs. placebo	24	Age, ≥ 20; SUA, > 7–10 mg/dL; eGFR, 30–59 mL/min/1.73 m^2	[14]
5	Wada et al. (2018)	RCT	Topiroxostat 40–160 mg/day vs. placebo	7	Age, 20–75; urine albumin/creatinine, 45–300 mg/g; eGFR, ≥ 30 mL/min/1.73 m^2	[26]
6	Saag et al. (2016)	RCT	Febuxostat 40–80 mg/day vs. placebo	12	Age,: ≥ 18 (male) or ≥ 45 (female); eGFR, 15–50 mL/min/1.73 m^2; SUA, > 7 mg/dL; serum creatinine ≥ 1.5 mg/dL	[27]
7	Hosoya et al. (2014)	RCT	Topiroxostat 160 mg/day vs. placebo	6	Age, 20–75; SUA, > 475.84 µmol/L or 416.36 µmol/L + gout; eGFR, 30–60 mL/min/1.73 m^2	[28]
8	Yood et al. (2014)	RCT	pegloticase 8 mg/2 or 4 week vs. placebo	6	Age, ≥ 18; SUA, ≥ 8 mg/dL; eGFR, 15–59 mL/min/1.73 m^2	[29]
9	Kao et al. (2011)	RCT	Allopurinol 100–300 mg/day vs. placebo	9	Adult, eGFR: 30–60 mL/min/1.73 m^2	[30]
10	Beddhu et al. (2016)	RCT	Febuxostat 80 mg/day vs. placebo	6	Age, ≥ 18; SUA, ≥ 327 µmol/L (male) or ≥ 274 µmol/L (female); eGFR, 30–60 mL/min/1.73 m^2 or ≥ 60 mL/min/1.73 m^2 + urine dipstick ≥ 1 + proteinuria or urine albumin/creatinine ≥ 3.4 mg/mmol	[31]

eGFR estimated glomerular filtration rate, *RCT* randomized controlled trials, *SUA* serum uric acid

Table2 Baseline characteristics and laboratory data in the included studies

Study		No. of patients (% male)	Age	Baseline SUA (mg/dL)	After SUA (mg/dL)	Baseline eGFR (mL/min/1.73 m^2)	After eGFR (mL/min/1.73 m^2)	Baseline UACR (mg/g)	After UACR
Label	Author (year)								
1	Perrenoud et al. (2020) [25]	Allopurinol: 33 (82) Placebo: 36 (80)	Allopurinol: 59 Placebo: 58	Allopurinol: NA Placebo: NA	Allopurinol: NA Placebo: NA	Allopurinol: 41.4 Placebo: 41.7	Allopurinol: 43.2 Placebo: 40.9	Allopurinol: NA Placebo: NA	Allopurinol: NA Placebo: NA
2	Badve et al. (2020) [15]	Allopurinol: 182 (62) Placebo: 181 (64)	Allopurinol: 62.3 Placebo: 62.6	Allopurinol: 8.2 Placebo: 8.2	Allopurinol: 5.3 Placebo: 8.2	Allopurinol: 31.6 Placebo: 31.9	Allopurinol: 28.3 Placebo: 28.4	Allopurinol: 716.9 Placebo: 716.9	Allopurinol: NA Placebo: NA
3	Matsuo et al. (2020) [17]	Topiroxostat: 46 (74) Febuxostat: 48 (69)	Topiroxostat: 61.8 Febuxostat: 61.9	Topiroxostat: 8.4 Febuxostat: 8.5	Topiroxostat: 6.0 Febuxostat: 5.9	Topiroxostat: 35.9 Febuxostat: 35.9	Topiroxostat: 36.0 Febuxostat: 36.7	Topiroxostat: NA Febuxostat: NA	Topiroxostat: NA Febuxostat: NA
4	Kimura et al. (2018) [14]	Febuxostat: 219 (78) Placebo: 222 (77)	Febuxostat: 65.3 Placebo: 65.4	Febuxostat: 7.8 Placebo: 7.8	Febuxostat: 4.1 Placebo: 7.9	Febuxostat: 45.2 Placebo: 44.9	Febuxostat: 45.3 Placebo: 44.2	Febuxostat: 124 Placebo: 120.5	Febuxostat: NA Placebo: NA
5	Wada et al. (2018) [26]	Topiroxostat: 43 (86) Placebo: 22 (91)	Topiroxostat: 60.5 Placebo: 63	Topiroxostat: 7.3 Placebo: 7.0	Topiroxostat: 4.3 Placebo: 6.8	Topiroxostat: 66.3 Placebo: 68.3	Topiroxostat: 66.1 Placebo: 64.3	Topiroxostat: 114.5 Placebo: 141.5	Topiroxostat: Δ0% Placebo: Δ + 17%
6	Saag et al. (2016) [27]	Febuxostat: 64 (80) Placebo: 32 (81)	Febuxostat: 65.5 Placebo: 66.3	Febuxostat: 10.4 Placebo: 10.8	Febuxostat: 5.8 Placebo: 10.7	Febuxostat: 34.1 Placebo: 29.3	Febuxostat: 33.3 Placebo: 27.6	Febuxostat: NA Placebo: NA	Febuxostat: NA Placebo: NA
7	Hosoya et al. (2014) [28]	Topiroxostat: 62 (85) Placebo: 60 (93)	Topiroxostat: 62.5 Placebo: 64.6	Topiroxostat: 8.5 Placebo: 8.5	Topiroxostat: 7.7 Placebo: 8.5	Topiroxostat: 49.4 Placebo: 48.9	Topiroxostat: 48.8 Placebo: 48.4	Topiroxostat: 41.7 Placebo: 29.9	Topiroxostat: Δ − 33% Placebo: Δ − 6%
8	Yood et al. (2014) [29]	pegloticase: 83 (NA) Placebo: 20 (NA)	Pegloticase: NA Placebo: NA	Pegloticase: NA Placebo: NA	Pegloticase: NA Placebo: NA	Pegloticase: 40.3 Placebo: 43.3	Pegloticase: 38.3 Placebo: 40.6	pegloticase: NA Placebo: NA	pegloticase: NA Placebo: NA
9	Kao et al. (2011) [30]	Allopurinol: 27 (59) Placebo: 26 (46)	Allopurinol: 70.6 Placebo: 73.7	Allopurinol: 7.4 Placebo: 7.1	Allopurinol: 4.4 Placebo: 6.8	Allopurinol: 44.0 Placebo: 46.0	Allopurinol: 44.2 Placebo: 46.2	Allopurinol: NA Placebo: NA	Allopurinol: NA Placebo: NA
10	Beddhu et al. (2016) [31]	Febuxostat: 37 (60) Placebo: 37 (70)	Febuxostat: 67 Placebo: 68	Febuxostat: 7.2 Placebo: 7.2	Febuxostat: 3.9 Placebo: 7.2	Febuxostat: 52.2 Placebo: 54.8	Febuxostat: 49.1 Placebo: 51.2	Febuxostat: 20.8 Placebo: 18.0	Febuxostat: Δ − 24% Placebo: Δ − 28%

eGFR estimated glomerular filtration rate, *NA* not available, *SUA* serum uric acid, *UACR* urine albumin/creatinine

low certainty evidence) (Fig. 2, Table S3). Febuxostat showed a trend toward a positive effect compared to placebo, but the effect was not significant (MD [95% CI]: 1.10 [−0.07; 2.27], $P = 0.067$). Allopurinol and pegloticase had no significant effect on eGFR (MD [95% CI]: 0.32 [−0.99; 1.63] and 0.70 [−4.07; 5.47], respectively). There were no significant differences between topiroxostat and other drugs (MD [95% CI] vs. allopurinol, 1.17 [−0.76; 3.09]; vs. febuxostat, 0.39 [−1.13; 1.92]; vs. pegloticase, 0.79 [−4.19; 5.77]). Heterogeneity in this analysis was low ($I^2 = 21.1\%$).

Albuminuria

Albuminuria was evaluated based on the percentage decrease in urinary albumin/creatinine ratio (UACR) after the intervention. We analyzed four studies with this approach [15, 26, 28, 31]. Topiroxostat significantly reduced the UACR compared to placebo (MD [95% CI]: 25.65% [13.25; 38.04], $P < 0.001$; low certainty evidence) (Fig. 3, Table S3). Allopurinol and febuxostat showed no improvement in UACR compared to placebo. There were no significant differences between topiroxostat and other drugs (MD [95%

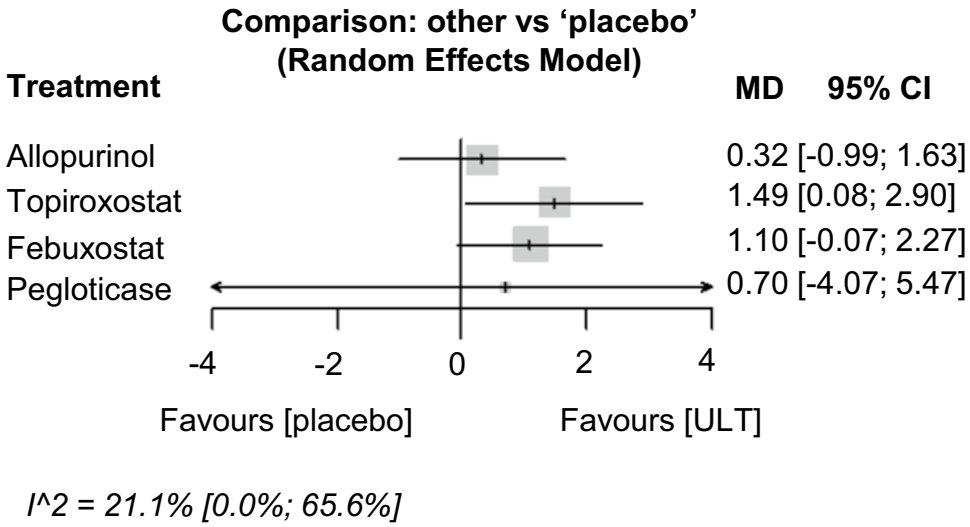

Fig. 2 Network meta-analysis reporting the effects of ULT on kidney function (estimated glomerular filtration rate) from baseline to last measurement in CKD patients. CI, confidence interval; MD, mean difference

CI] vs. allopurinol, 16.65 [−4.38; 37.68]; vs. febuxostat, 0.39 [−16.94; 75.43]). There was no heterogeneity ($I^2=0\%$).

Subgroup analysis

We performed subgroup analysis limited to patients with stage G3 CKD (eGFR 30–59 mL/min/1.73 m^2). There were seven applicable studies [14, 15, 25–28, 30]. The results showed a significant improvement in eGFR with topiroxostat compared to placebo (MD [95% CI]: 1.97 [0.16; 3.78], $P=0.033$; low certainty evidence) (Fig. 4a, Table S3). There were no significant improvements with allopurinol or febuxostat (MD [95% CI]: 0.43 [−1.25; 2.12] and 0.88 [−0.59; 2.34], respectively). These results were consistent with the analysis for the overall population. Heterogeneity in this analysis was low ($I^2=24.6\%$). Next, we performed subgroup analysis only in patients with hyperuricemia (male, SUA ≥ 7 mg/dL; female, SUA ≥ 6 mg/dL). There were six applicable studies [14, 17, 25, 27–29]. In this analysis, febuxostat showed a significant improvement in eGFR (MD [95% CI]: 0.85 [0.02; 1.67], $P=0.045$; moderate certainty evidence) (Fig. 4b, Table S3). On the other hand, allopurinol and topiroxostat did not show any improvement (MD [95% CI]: 2.62 [−0.57; 5.81] and 0.84 [−0.47; 2.16], respectively). There was no heterogeneity ($I^2=0\%$).

Adverse events

Six trials assessed safety [14, 15, 26–28, 30]. As it is difficult to evaluate the detailed AE breakdown, the evaluation was based on the number of all reported events. The results showed that there were no differences in the occurrence of AEs with allopurinol, febuxostat, or topiroxostat compared to placebo (RR [95% CI]: 1.01 [0.90; 1.14], 0.98 [0.84; 1.14], and 1.10 [0.87; 1.38], respectively; very low

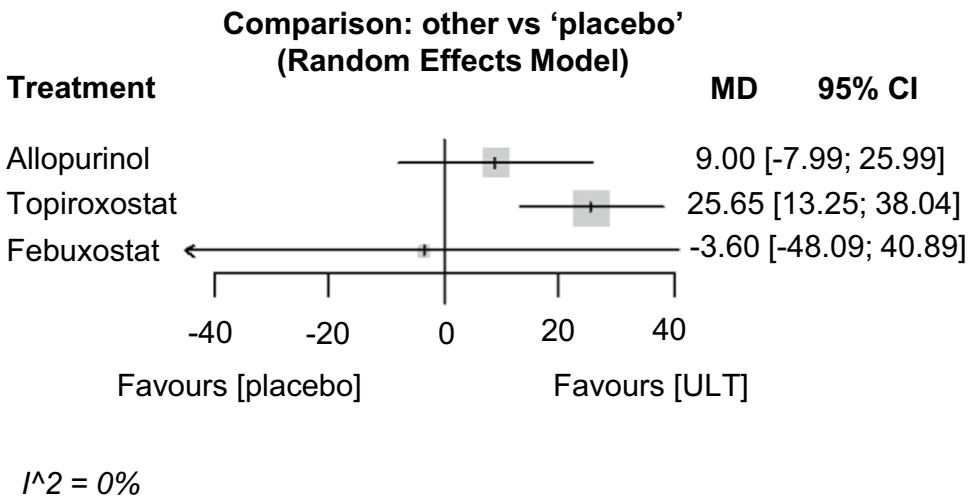

Fig. 3 Network meta-analysis reporting the changes in albuminuria evaluated by the percentage decrease in urinary albumin/creatinine ratio after the intervention in CKD patients. CI, confidence interval; MD, mean difference

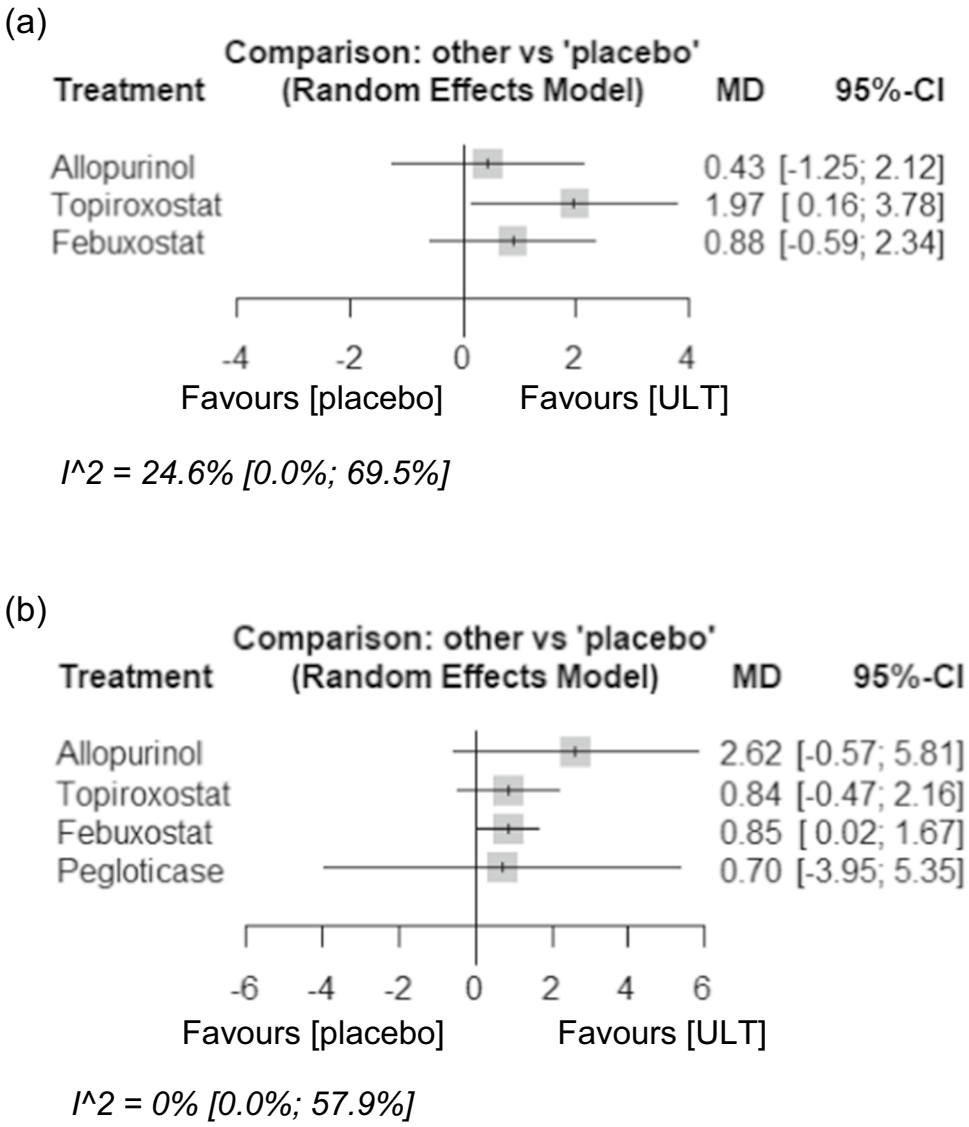

Fig. 4 Network meta-analysis regarding subgroup analysis. Forest plot showing the effects of ULT on kidney function (estimated glomerular filtration rate, eGFR) from baseline to last measurement **a** in patients with stage 3 CKD (eGFR: 30–59 mL/min/1.73 m^2) and **b** in CKD patients with hyperuricemia (male, SUA ≥ 7 mg/dL; female, SUA ≥ 6 mg/dL). CI, confidence interval; MD, mean difference

certainty evidence) (Fig. S3, Table S3). The funnel plots for each analysis group are shown in Fig. S4.

Discussion

We conducted a network meta-analysis using four uric acid-lowering drugs and placebo. This study demonstrated that ULT with topiroxostat can slow the progression of CKD. Topiroxostat improved kidney function, as assessed by eGFR, and significantly suppressed albuminuria compared to placebo. Febuxostat did not show significant improvement in renal function, although it showed numerically better results. Interestingly, in subgroup analysis performed in patients with hyperuricemia, febuxostat significantly improved eGFR compared with placebo. On the other hand, neither allopurinol nor pegloticase showed any positive effects in this meta-analysis.

Several mechanisms have been proposed for the positive impact of topiroxostat on kidney function. First, topiroxostat has a stronger inhibitory effect on xanthine oxidoreductase (XOR) activity and reduces oxidative stress to a greater extent than allopurinol and febuxostat. In basic research in a rat model of intestinal ischemia–reperfusion (I/R) [32] and in mouse and rat models of myocardial I/R injury [33, 34], non-purine analog XOR inhibitors, such as topiroxostat and febuxostat, showed better organ protection than allopurinol. These reports suggested that the superior efficacy of non-purine analog inhibitors was due to their greater inhibition of XOR activity, which reduced oxidative stress. In addition, another study showed that topiroxostat inhibited XOR more strongly and had a better nephroprotective effect compared to febuxostat in a mouse model of adenine-induced CKD

[35]. Second, topiroxostat can suppress albuminuria. Clinical trials have shown that topiroxostat attenuates albuminuria [36]. Animal studies with diabetic model mice have shown that topiroxostat suppresses urinary albumin excretion by preventing podocyte damage [37], and this suppressive effect on albuminuria may be stronger than that of febuxostat [38]. The outcome of the present study was consistent with the results of these basic studies. On the other hand, allopurinol was not as effective as topiroxostat or febuxostat, possibly due to the dosage of the drug. CKD patients are at increased risk of allopurinol toxicity (e.g., rash, gastrointestinal problems, and severe hypersensitivity reactions) because oxipurinol, a metabolite of allopurinol, is cleared by the kidney [6, 39]. Due to these serious side effects, the dose of allopurinol may not have been sufficient for CKD patients. In contrast, topiroxostat and febuxostat do not require dose reduction, which may have resulted in stronger XOR inhibition.

In a subgroup analysis, febuxostat showed superior nephroprotective effects in hyperuricemia patients. Sezai et al. reported that febuxostat was more nephroprotective than topiroxostat in a clinical trial in CKD patients with hyperuricemia, and they suggested that the mechanism involved rapid and stable lowering of SUA by febuxostat [40]. This was consistent with the results of the present study, in which febuxostat showed better nephroprotective effects in CKD patients with hyperuricemia. Febuxostat has also been suggested to inhibit inflammation and apoptosis through MAPK signaling [41], and these other pathways may also be involved although the detailed mechanism remains unclear. This analysis included only a small number of studies of pegloticase, and the analysis was therefore not sufficient. Further studies are needed to determine its efficacy, including its nephroprotective effects.

A major strength of the present study is that this was the first network meta-analysis comparing the nephroprotective effects of ULT in CKD patients. In addition, the heterogeneity was low, suggesting consistency of the results. Although individual RCTs have yielded inconsistent results, based on the results of this study, we recommend ULT with non-purine analog inhibitors for patients with CKD.

This study had several limitations. First, our study was mostly about XOR inhibitors and did not examine other urate-lowering drugs with different mechanisms of action in detail. Second, we were unable to compare the effects of allopurinol, febuxostat, and topiroxostat when they were matched at the same potency. Third, we did not examine the effects of each drug on serum uric acid level, and variation of uric acid among studies may have resulted in bias. Fourth, we were unable to evaluate long-term events, such as major adverse cardiovascular events (MACE) and dialysis induction. Fifth, we were not able to analyze safety in detail and only had data for the overall number of events.

In conclusion, this meta-analysis suggested that topiroxostat and febuxostat may have good renoprotective effects in CKD patients. However, whether these effects will lead, ultimately, to a reduction in events, such as dialysis induction and MACE, is still unclear, and further large-scale and long-term studies are needed.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10067-021-05956-5.

Author contribution Research idea and study design, S.T., N.O., and T.Y.; data acquisition, S.T. and N.O.; data analysis/interpretation, S.T., N.O., T.Y., K.A., T.Y., S.K., K.U., T.K., H.W., and K.T.; statistical analysis, S.T. and N.O.; writing manuscript, S.T., N.O., T.Y., K.A., T.Y., S.K., K.U., T.K., H.W., and K.T.; supervision or mentorship, T.Y., H.W., and K.T. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

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Data availability The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Ethics approval The manuscript does not contain clinical studies or patient data.

Disclosures None.

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