

Effects of uric acid-lowering therapy on renal outcomes: a systematic review and meta-analysis

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ABSTRACT

Background. Non-randomized studies suggest an association between serum uric acid levels and progression of chronic kidney disease (CKD). The aim of this systematic review is to summarize evidence from randomized controlled trials (RCTs) concerning the benefits and risks of uric acid-lowering therapy on renal outcomes.

Methods. Medline, Excerpta Medical Database and Cochrane Central Register of Controlled Trials were searched with English language restriction for RCTs comparing the effect of uric acid-lowering therapy with placebo/no treatment on renal outcomes. Treatment effects were summarized using random-effects meta-analysis.

Results. Eight trials (476 participants) evaluating allopurinol treatment were eligible for inclusion. There was substantial heterogeneity in baseline kidney function, cause of CKD and duration of follow-up across these studies. In five trials, there was no significant difference in change in glomerular filtration rate from baseline between the allopurinol and control arms [mean difference (MD) 3.1 mL/min/1.73 m², 95% confidence intervals (CI) −0.9, 7.1; heterogeneity $\chi^2 = 1.9$, $I^2 = 0\%$, $P = 0.75$]. In three trials, allopurinol treatment abrogated increases

in serum creatinine from baseline (MD −0.4 mg/dL, 95% CI −0.8, −0.0 mg/dL; heterogeneity $\chi^2 = 3$, $I^2 = 34\%$, $P = 0.22$). Allopurinol had no effect on proteinuria and blood pressure. Data for effects of allopurinol therapy on progression to end-stage kidney disease and death were scant. Allopurinol had uncertain effects on the risks of adverse events.

Conclusions. Uric acid-lowering therapy with allopurinol may retard the progression of CKD. However, adequately powered randomized trials are required to evaluate the benefits and risks of uric acid-lowering therapy in CKD.

Keywords: chronic kidney disease, clinical trial, kidney function test, renal dialysis, uric acid

INTRODUCTION

Chronic kidney disease (CKD), defined as glomerular filtration rate (GFR) <60 mL/min/1.73 m² and/or urine albumin-creatinine ratio ≥30 mg/g for at least 3 months, affects 11–14% of adults in industrialized countries [1, 2]. People with CKD experience significantly increased risks of CKD progression, end-stage kidney disease (ESKD), cardiovascular mortality and all-cause mortality [3–5]. These risks increase markedly at

lower levels of GFR and higher levels of albuminuria [3–5]. Those patients who do progress to ESKD have a 10- to 20-fold higher age- and sex-matched mortality than the general population [6, 7]. Thus, effective prevention of CKD progression would result in substantial public health benefits.

Currently established therapies for slowing CKD progression and preventing cardiovascular events and death in CKD patients are limited to antihypertensive agents, such as angiotensin converting enzyme inhibitors and angiotensin receptor blockers [8, 9], and statins [10]. These agents each result in a modest (20%) relative risk reduction in adverse renal and/or cardiovascular outcomes in CKD. Consequently, most people with CKD continue to suffer further declines in kidney function [11], and unacceptably high rates of cardiovascular morbidity and mortality [12, 13]. The relative ineffectiveness of treatments targeting CKD progression may be due to a failure to adequately target appropriate risk factors.

Uric acid has emerged as a novel and potentially modifiable risk factor for the development and progression of CKD. Several animal studies have demonstrated that uric acid-lowering with either allopurinol or febuxostat effectively prevented the development of hypertension, elevated glomerular pressure, afferent arteriolar thickening and ischemic renal histologic changes in rats with hyperuricemia induced by oxonic acid or a high-fructose diet [14–16]. Furthermore, a number of epidemiologic studies have reported that asymptomatic hyperuricemia is strongly associated with both CKD and ESKD [17, 18]. However, hyperuricemia may be a marker of kidney function due to its reduced renal excretion. The aim of this systematic review of randomized controlled trials (RCTs) was to evaluate the benefits and risks of uric acid-lowering therapy with a particular focus on renal outcomes and serious adverse events.

MATERIALS AND METHODS

This systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [19].

Search strategy, study selection, and data extraction

Studies were eligible for inclusion if they: (i) were RCTs; (ii) compared a uric acid-lowering agent with placebo, no treatment or standard therapy; (iii) followed participants for at least 3 months post-randomization; and (iv) reported any of the following renal outcomes: changes in GFR, creatinine clearance, or serum creatinine, doubling of serum creatinine, or progression to ESKD. Studies performed in participants with normal or mildly decreased GFR or kidney transplant recipients were also eligible for inclusion. Hyperuricemia was not an eligibility criterion. Trials performed in ESKD patients were excluded. Although the angiotensin receptor blocker losartan has uric acid-lowering effects, trials evaluating the effect of this agent on renal outcomes were excluded due to the possibility of an alternative renoprotective mechanism via renin-angiotensin system blockade.

We identified relevant studies using highly sensitive electronic searches of Medline (Medical Literature Analysis and Retrieval System Online) via Ovid (from inception to December 2012), EMBASE (Excerpta Medical Database) (from inception to December 2012) and the CENTRAL (Cochrane Central Register of Controlled Trials) (December 2012) with English language restriction. Major conference proceedings were also searched from the year 2002 to 2012. In addition, reference lists of relevant review articles, systematic reviews, treatment guidelines, textbook chapters and online trial registries were searched. Missing, incomplete or unpublished data from clinical trials were requested from the respective investigators/authors by e-mail (see Supplemental Material, Appendix for complete search strategy).

The following data were extracted using a standardized form: patient demographic details, study design and conduct, outcomes (baseline and end-of-study values of GFR, serum creatinine, creatinine clearance and doubling of serum creatinine, ESKD) and adverse events. The methodological quality of each included study was assessed using the risk of bias assessment tool developed by the Cochrane Bias Methods Group [20]. The following six items were assessed: (i) random sequence generation; (ii) allocation concealment; (iii) blinding of participants, investigators and outcome assessors; (iv) incomplete outcome data; (v) selective outcome reporting; and (vi) any other bias (e.g. insufficient rationale, study design). Data extraction was carried out independently by two authors (B.B. and S.V.B.). Disagreements were resolved via consultation with two other authors (S.S.H. and D.W.J.).

Outcomes assessed

The primary outcome assessed in this meta-analysis was change in kidney function from baseline (reported as GFR or serum creatinine concentration or creatinine clearance) from baseline to end of follow-up. The secondary outcomes assessed included progression to ESKD, doubling of serum creatinine or worsening of kidney function as defined by respective investigators, change in proteinuria, change in blood pressure, change in serum uric acid concentration, all-cause mortality, major cardiovascular events, all-cause hospitalization, adverse events and withdrawal from studies.

Statistical analysis

Treatment effects were summarized using random-effects meta-analysis [21]. For dichotomous outcomes, the results were expressed as risk ratio (RR) with 95% confidence intervals (CI) and the mean difference (MD) was calculated for the continuous outcomes. The random-effects method was chosen because of its conservative summary estimate. Heterogeneity across the studies was estimated using the Cochrane's Q and I^2 statistic [22]. I^2 values of 25, 50 and 75% corresponded to low, moderate and high levels of heterogeneity [23]. If sufficient data were available, a prespecified subgroup analysis was performed to explore whether presence of CKD at baseline was a source of heterogeneity. Analyses were conducted using Comprehensive Meta-analysis software (version 2.2.046, Biostat Inc., Englewood, NJ, USA) and Stata/SE (version 11.2, Stata Corp., College Station, TX, USA).

RESULTS

Selection and description of studies

Eight trials involving 476 patients (median sample size 57, range 36–113; median follow-up 11 months, range 4–24 months) were included in the systematic review (Figure 1). Six trials were performed in 350 participants with CKD with varying degrees of renal impairment (serum creatinine >1.35 mg/dL, decreased GFR <60 mL/min/1.73 m² or diabetic nephropathy or IgA nephropathy) (see Table 1) [24–29]. The remaining two trials were performed in 126 participants with normal or mildly decreased kidney function [30, 31]. None of the studies included kidney transplant recipients. One trial excluded participants with diabetes mellitus [31], one trial included only participants with diabetic nephropathy [26] and another trial included only participants with IgA nephropathy [29]. Allopurinol was the intervention agent in all trials. The dose of allopurinol varied between 100 and 300 mg daily. Only two trials were placebo-controlled studies [25, 26]. Figure 2 summarizes the risk of bias assessment. Studies had high risk of bias for blinding of patients and investigators and unclear risks of bias for all other domains assessed.

Serum creatinine and GFR

Five trials (346 participants) reported data on end of treatment GFR [24, 25, 29–31], and the remaining three trials (130 participants) reported data on serum creatinine at end of follow-up [26–28]. There was no significant difference in the change in GFR from baseline between the allopurinol and control arms (MD 3.1 mL/min/1.73 m², 95% CI –0.9, 7.1 mL/min/1.73 m², $P = 0.1$; heterogeneity $\chi^2 = 1.9$, $I^2 = 0\%$, $P = 0.75$) (Figure 3). Subgroup analysis according to baseline CKD status showed similar results (for participants with CKD [24, 25, 29]: MD 2.6 mL/min/1.73 m², 95% CI –1.9, 7.0 mL/min/1.73 m², $P = 0.3$; heterogeneity $\chi^2 = 1.27$, $I^2 = 0\%$, $P = 0.5$; and for participants without CKD [30, 31]: MD 5.2 mL/min/1.73 m², 95% CI –3.8, 14.3 mL/min/1.73 m², $P = 0.3$; heterogeneity $\chi^2 = 0.36$, $I^2 = 0\%$, $P = 0.6$). The between group difference P -value was 0.6. The result was unchanged when the analysis was limited to the studies with at least 6 months of follow-up (MD 3.1 mL/min/1.73 m², 95% CI –1.2, 7.4 mL/min/1.73 m², $P = 0.1$; heterogeneity $\chi^2 = 1.9$, $I^2 = 0\%$, $P = 0.59$) [24, 25, 29, 30].

Meta-analysis of the three trials (all in participants with CKD) reporting creatinine data showed that the change in serum creatinine concentration from baseline was in favor of allopurinol (MD –0.4 mg/dL, 95% CI –0.8, –0.0 mg/dL, $P =$

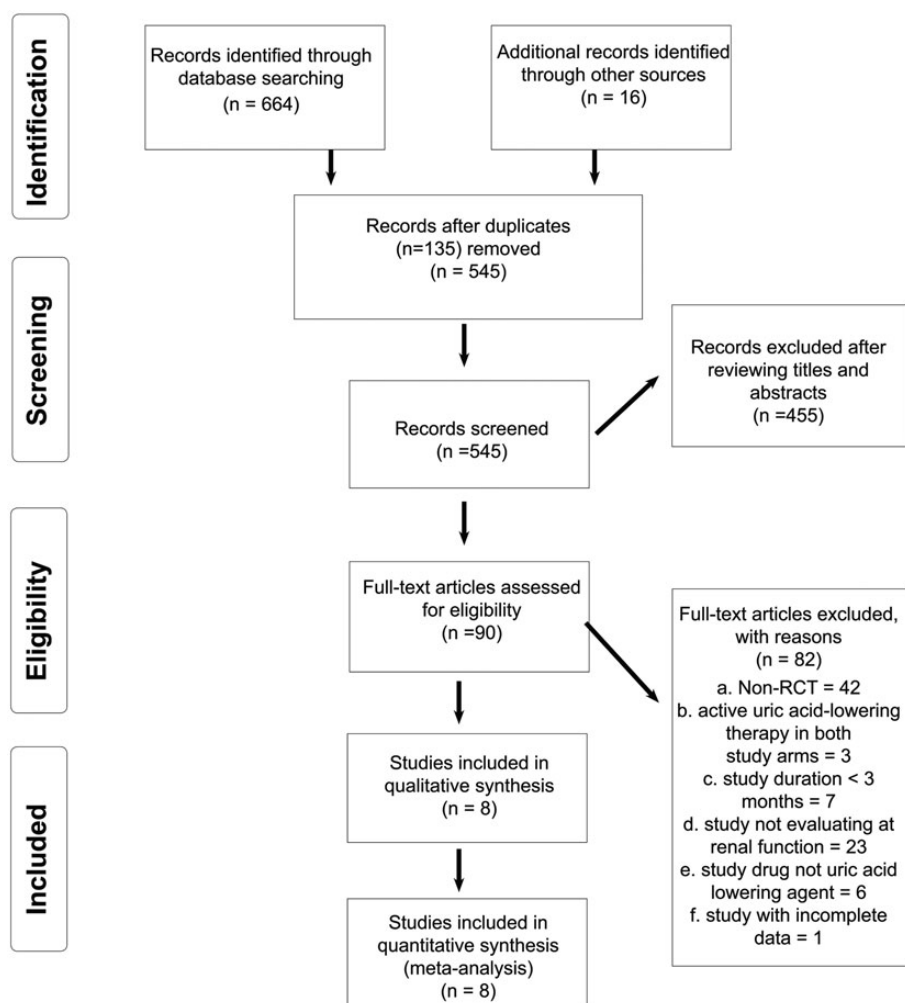


FIGURE 1: PRISMA flow diagram showing selection of studies.

Table 1. Summary of studies included in the meta-analysis

Study (location)	Inclusion criteria	n	Active treatment	Control	Baseline kidney function	Follow-up in months	Age (years)	Weight or BMI	Diabetes mellitus (%)	Uric acid (mg/dL)
Gibson [30] (UK)	Primary gout (at least one attack of acute arthritis associated with raised uric acid unrelated to drugs or other diseases)	59	Allopurinol 200 mg daily plus colchicine 0.5 mg twice a day	Colchicine 0.5 mg twice a day	GFR 94 mL/min/1.73 m ²	24	49	Weight 81 kg	Not reported	6.5
Siu [28] (Hong Kong)	Proteinuria > 500 mg/day and/or serum creatinine > 1.35 mg/dL, and serum uric acid > 7.6 mg/dL	54	Allopurinol 100 or 200 mg daily	No study medication	Serum creatinine 1.8 mg/dL	12	48	Weight 67.9 kg	25	9.8
Sarris [27] (Greece)	Serum uric acid > 7.0 mg/dL, and serum creatinine 1.5–3.0 mg/dL	36	Allopurinol 150 mg daily	No study medication	Serum creatinine 1.9 mg/dL	12	50	Not reported	Not reported	9.0
Momeni [26] (Iran)	Diabetes mellitus type 2, and diabetic nephropathy (proteinuria > 500 mg/day, and serum creatinine < 3 mg/dL)	40	Allopurinol 100 mg daily	Placebo	Serum creatinine 1.4 mg/dL	4	58	Weight 75.7 kg, BMI 27.9 kg/m ²	100	6.2
Goicoechea [24] (Spain)	eGFR < 60 mL/min/1.73 m ²	113	Allopurinol 100 mg daily	No study medication	eGFR 40 mL/min/1.73 m ²	24	72	Not reported	37	7.6
Kanbay [31] (Turkey)	Serum uric acid > 7.0 mg/dL	67	Allopurinol 300 mg daily	No study medication	eGFR 85 mL/min/1.73 m ²	4	52	BMI 29.1 kg/m ²	0	8.1
Kao [25] (UK)	CKD Stage 3, and left ventricular hypertrophy (LVMI > 115 g/m ² for men and 95 g/m ² for women)	67	Allopurinol 300 mg daily	Placebo	eGFR 45 mL/min/1.73 m ²	9	72	Not reported	11	7.5
Shi [29] (China)	IgA nephropathy on kidney biopsy, proteinuria 0.15–2.0 g/day, serum creatinine < 3 mg/dL, and serum uric acid > 7 mg/dL in men and > 6 mg/dL in women	40	Allopurinol 100–300 mg daily	No study medication	eGFR 67 mL/min/1.73 m ²	6	40	Not reported	Not reported	7.9

BMI, body mass index; GFR, estimated glomerular filtration rate; eGFR, estimated glomerular filtration rate. (To convert creatinine from mg/dL to $\mu\text{mol/L}$, multiply by 88.4. To convert uric acid from mg/dL to mmol/L, multiply by 0.05948.)

0.03; heterogeneity $\chi^2 = 3$, $I^2 = 34\%$, $P = 0.22$) (Figure 4) [26–28]. Analysis of the studies with at least 6 months follow-up showed change in serum creatinine concentration in favor of allopurinol (MD -0.6 mg/dL, 95% CI -1.1 , -0.2 mg/dL, $P = 0.003$; heterogeneity $\chi^2 = 0.02$, $I^2 = 0\%$, $P = 0.89$) [27, 28].

Progression to ESKD

For the outcome of progression to ESKD, there were no reported events of reaching ESKD in 4 of the 6 trials performed in CKD patients [25–27, 29]. In the remaining two trials (164 participants), allopurinol treatment did not significantly alter the risk of ESKD (RR 1.01, 95% CI 0.15, 6.98, heterogeneity $\chi^2 = 0$, $I^2 = 0\%$, $P = 0.9$) [24, 28]. However, there were only four reported events of ESKD with one case in each study arm from two studies. Only one trial reported data on worsening of kidney function (defined by authors as a decrease of estimated glomerular filtration rate (eGFR) > 0.2 mL/min/1.73 m²/month), hence meta-analysis was not possible [28]. Only one trial reported data on doubling of serum creatinine, hence meta-analysis was not possible [29]. Meta-analysis of five trials (250 participants) showed that change in proteinuria from baseline was similar between the allopurinol and control arms (MD -0.2 g/day, 95% CI -0.5 , 0.1 g/day, $P = 0.2$, heterogeneity $\chi^2 = 1.6$, $I^2 = 0\%$, $P = 0.8$) (Figure 5) [25, 26, 28–30]. The subgroup analysis according baseline CKD is described in Table 2.

Other outcomes

There were no significant differences between the allopurinol and control arms with respect to changes in systolic blood pressure (5 trials, 309 participants, MD -2.7 mmHg, 95% CI -7.3 , 1.9 mmHg, $P = 0.26$, heterogeneity $\chi^2 = 1.3$, $I^2 = 0\%$, $P = 0.9$) and diastolic blood pressure (5 trials, 309 participants, MD -1.9 mmHg, 95% CI -4.9 , 1.2 mmHg, $P = 0.24$, heterogeneity $\chi^2 = 0.4$, $I^2 = 0\%$, $P = 0.9$) (see Table 2 for subgroup analyses). Treatment with allopurinol significantly reduced serum uric acid concentration (8 trials, MD -2.5 mg/dL, 95% CI -3.3 , -1.7 mg/dL, $P < 0.001$). However, this summary statistic should be interpreted with caution due to the presence of a high-level of heterogeneity in treatment estimates between trials ($\chi^2 = 32$, $I^2 = 78\%$, $P < 0.001$). The heterogeneity persisted in the subgroup of studies involving CKD patients. Mortality, hospitalization and major cardiovascular events were each reported in a single trial only such that meta-analysis was not possible [24].

Adverse events

There were no significant differences between the allopurinol and control arms with respect to the risks of medication discontinuation (6 trials, 382 participants, RR 0.78, 95% CI 0.44, 1.36, $P = 0.4$; heterogeneity $\chi^2 = 2.4$, $I^2 = 0\%$, $P = 0.4$) or any adverse event (5 trials, 296 participants, RR 2.18, 95% CI 0.80, 5.96, $P = 0.1$; heterogeneity $\chi^2 = 2.4$, $I^2 = 0\%$, $P = 0.7$). In three trials (148 participants) that reported data on skin rash, there was no significant difference in the risk of skin rash between the allopurinol and control arms (RR 4.94, 95% CI 0.87, 28.09, $P = 0.07$, heterogeneity $\chi^2 = 0.1$, $I^2 = 0\%$, $P = 0.9$) [25, 27, 28]. Data for other adverse events, including Stevens–

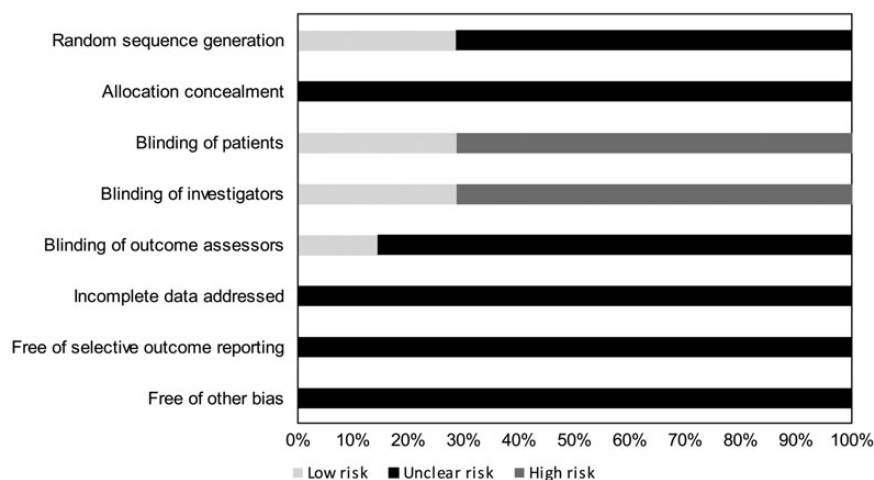


FIGURE 2: Summary of risk of bias assessment.

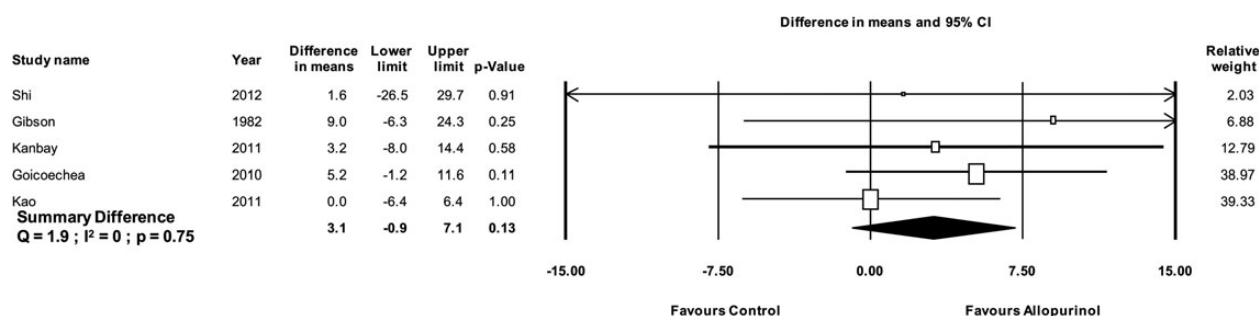


FIGURE 3: Forest plot showing the effect of uric acid-lowering therapy compared with placebo or no treatment on change in GFR (mL/min/1.73 m²) from baseline.

Johnson syndrome, toxic epidermal necrolysis, aplastic anemia and thrombocytopenia were absent.

DISCUSSION

This systematic review demonstrated that, in spite of numerous observational cohort studies showing an association between uric acid and both CKD and ESKD, data on the effects of uric acid-lowering therapy on renal outcomes are scarce. Compared with placebo or no treatment, the effects of allopurinol treatment on GFR, proteinuria, progression to ESKD and blood pressure were unclear. Data on the effects of allopurinol on total mortality, major cardiovascular events, hospitalization and adverse effects were insufficient to reliably inform medical practice. No trials of alternative urate-lowering agents to allopurinol (e.g. febuxostat) were identified.

Hyperuricemia is a ubiquitous finding in patients with CKD [32, 33] and arises as a consequence of reduced renal excretion of uric acid, inhibited tubular secretion of uric acid by co-prescribed diuretics and increased uric acid production in the setting of heightened oxidative stress [34]. However, it is not currently clear whether hyperuricemia plays a causative role in CKD progression or is merely a biomarker of reduced kidney function.

Clinical observational studies suggest an association between serum uric acid levels and renal outcomes [17, 18, 35, 36]. A post hoc analysis of the RENAAL trial (1342 participants with diabetic nephropathy, median follow-up 3.4 years) found that each 0.5 mg/dL reduction in serum uric acid concentration during the first 6 months was associated with a 6% (95% CI 3%, 10%) reduction in the risk of either doubling serum creatinine or reaching ESKD [36]. Adjustment of the overall treatment effects for serum uric acid attenuated losartan's renoprotective effect from 22% to 17%, suggesting that approximately one-fifth of losartan's renoprotective effect could potentially be attributed to its uric acid-lowering effect. Similarly, in a post hoc analysis of the FOCUS trial, participants who manifested the greatest persistent reduction in serum uric acid concentration with febuxostat therapy were significantly more likely to experience preserved GFR [35]. However, it remains unclear whether preservation of GFR was a result of reduction in serum uric acid concentration or *vice versa* or they were not causally related.

This systematic review summarizes the available evidence concerning the effect of uric acid-lowering therapy on renal outcomes. While allopurinol therapy lowered serum creatinine concentration (based on 3 trials with 130 participants), effects on GFR, proteinuria and risks of ESKD were uncertain.

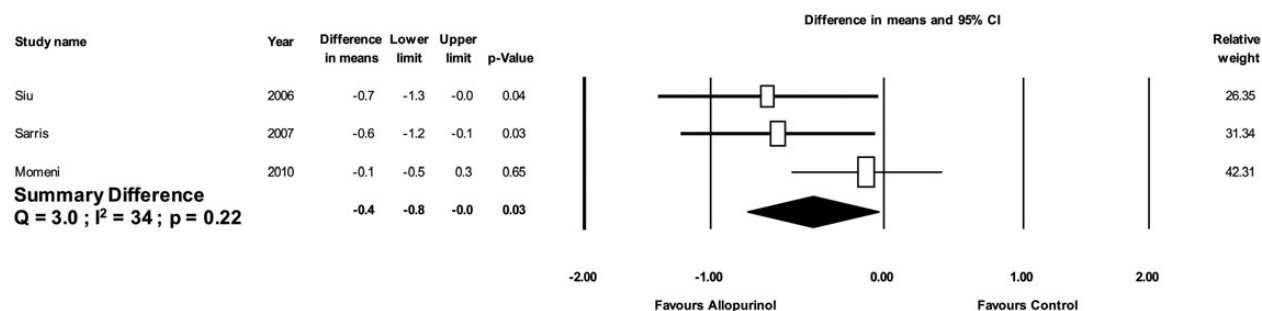


FIGURE 4: Forest plot showing the effect of uric acid-lowering therapy compared with placebo or no treatment on change in serum creatinine concentration (mg/dL) from baseline. To convert creatinine from mg/dL to $\mu\text{mol/L}$, multiply by 88.4.

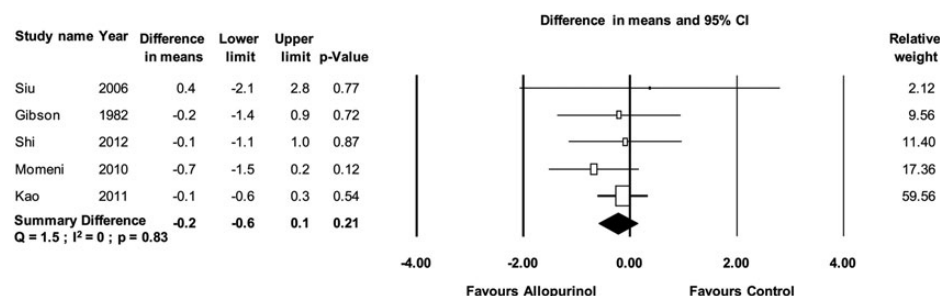


FIGURE 5: Forest plot showing the effect of uric acid-lowering therapy compared with placebo or no treatment on change in proteinuria (g/day) from baseline.

Table 2. Summary estimates of subgroup analyses

Outcome	CKD subgroup	Non-CKD subgroup
GFR (mL/min/1.73 m ²)	MD 2.6, 95% CI -1.9, 7.0, P = 0.3 $\chi^2 = 1.27$, I ² = 0%, P = 0.5 (3 studies)	MD 5.2, 95% CI -3.8, 14.3, P = 0.3 $\chi^2 = 0.36$, I ² = 0%, P = 0.6 (2 studies)
Creatinine (mg/dL)	MD -0.4, 95% CI -0.8, -0.0, P = 0.03 $\chi^2 = 3$, I ² = 34%, P = 0.22 (3 studies)	No studies
Proteinuria (g/day)	MD -0.2, 95% CI -0.5, 0.1, P = 0.22 $\chi^2 = 1.6$, I ² = 0%, P = 0.66 (4 studies)	MD -0.2, 95% CI -1.4, 0.9, P = 0.72 (once study only)
Systolic blood pressure (mmHg)	MD -1.99, 95% CI -7.5, 3.5, P = 0.48 $\chi^2 = 1.3$, I ² = 0%, P = 0.77 (4 studies)	MD -4.3, 95% CI -12.8, 4.2, P = 0.32 (once study only)
Diastolic blood pressure (mmHg)	MD -2.0, 95% CI -5.4, 1.4, P = 0.24 $\chi^2 = 0.31$, I ² = 0%, P = 0.96 (4 studies)	MD 0.9, 95% CI -8.3, 6.5, P = 0.081 (Once study only)
Uric acid (mg/dL)	MD -2.7, 95% CI -3.7, -1.7, P < 0.01 $\chi^2 = 27$, I ² = 81%, P < 0.001 (5 studies)	MD -1.9, 95% CI -2.4, -1.3, P < 0.01 $\chi^2 = 0.1$, I ² = 0%, P = 0.75 (3 studies)

Notably, the evidentiary basis for the safety and efficacy of uric acid-lowering therapy for preventing CKD progression is scant and additional large-scale trials are now needed. Based on this systematic review, we have initiated the CKD-FIX Study (Controlled trial of slowing of Kidney Disease progression From the Inhibition of Xanthine oxidase, registration number ACTRN12611000791932): a multicenter, prospective, double-blind, randomized placebo-controlled trial to assess the effect of allopurinol on slowing the decline of eGFR in 620 patients with Stages 3–4 CKD.

The strengths of this review are that it represents a comprehensive overview of the evidence, risk of bias assessment and inclusion of only RCTs. These strengths should be balanced against the review's limitations, which include a small number of single-center trials, variable duration of follow-up, and clinical heterogeneity in trials evaluating baseline kidney function and proteinuria, which could not be adequately explored. Furthermore, the methodological quality of trials was suboptimal as allocation concealment was unclear in all trials, and random sequence generation was rated as low risk in only

three trials. Only two trials were placebo-controlled. The sub-optimal quality of the included trials limited our ability to draw robust conclusions. Another limitation of this systematic review was the lack of systematic data on the adverse effects of allopurinol. Rare but potentially life-threatening complications, such as Stevens–Johnson syndrome, toxic epidermal necrolysis and aplastic anemia cannot be evaluated from an evidence synthesis of small and inferior quality RCTs alone. None of the studies evaluated febuxostat. The literature search may not have captured trials published in other languages due to restriction to English.

In conclusion, the available RCT evidence evaluating the safety and efficacy of allopurinol as a renoprotective agent in patients with CKD is limited to a small number of single-center studies with suboptimal methodology. There is therefore insufficient evidence to currently recommend widespread use of uric acid-lowering therapy to slow the progression of CKD. Nevertheless, given that there is abundant evidence of an association between uric acid and CKD progression from epidemiological and animal studies (thereby suggesting that uric acid-lowering therapy may retard the progression of CKD), adequately powered, high quality, randomized placebo-controlled trials are required to definitively evaluate the benefits and risks of uric acid-lowering therapy in patients with CKD.

SUPPLEMENTARY MATERIAL

Supplementary data are available online at <http://ndt.oxfordjournals.org>.

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CONFLICT OF INTEREST STATEMENT

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