ORIGINAL RESEARCH

To Treat or Not to Treat? Effect of Urate-Lowering Therapy on Renal Function, Blood Pressure and Safety in Patients with Asymptomatic Hyperuricemia: A Systematic Review and Network Meta-Analysis

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Purpose: **Hyperuricemia is associated with increased cardiovascular risk. Because patients with asymptomatic hyperuricemia (AH) experience no immediate discomfort and there are possible side effects of urate-lowering drugs, treatment for AH is controversial. We aimed to perform a network meta-analysis (NMA) to investigate the effects of different urate-lowering therapies (ULTs) on serum uric acid level, renal function, blood pressure (BP), and safety in AH patients.**

Methods: **This NMA focused on AH patients. The intervention group (patients receiving urate-lowering drugs) was compared with others using other types of drugs, placebo, or usual care. We undertook a NMA under the frequentist framework by R.**

Results: **Thirteen eligible trials were identified. The interventions included allopurinol, febuxostat, and benzbromarone, which are not approved in the United States. Benzbromarone and allopurinol had the best efficacy on lowering serum uric acid level in short-term and long-term follow-up (mean difference [MD] = −3.05; 95% CI, −5.19 to −0.91 vs MD = −3.17; 95% CI, −5.19 to −1.15). Patients using allopurinol had significantly higher eGFR than using placebo in both short-term and long-term follow-up (MD = 3.07; 95% CI, 0.18 to 5.95 vs MD = 4.10; 95% CI, 2.66 to 5.54). No difference in BP was found between groups, except for febuxostat to diastolic BP after long-term treatment (MD = −1.47; 95% CI, −2.91 to −0.04). No statistically increased odds of safety events were found with the use of ULT.**

Conclusions: **Our result showed that in AH patients, allopurinol has a renoprotective effect. Febuxostat has a significant impact in lowering diastolic BP. ULT does not result in a higher risk of safety events. (J Am Board Fam Med 2022;35:140–151.)**

Keywords: **Asymptomatic Hyperuricemia, Blood Pressure, Disease Management, Family Medicine, Network Meta-Analysis, Serum Uric Acid, Systematic Review, Renal Function**

Introduction

Vascular endothelium, a monolayer of endothelial cells, controls vascular tone and maintains vascular homeostasis, allowing it to maintain normal physiologic mechanisms.[1] Endothelial dysfunction means endothelial cells lose their normal function and is found to be associated with hypertension and chronic kidney disease (CKD).[2,3] Hyperuricemia is 1 of its causes, and urate-lowering therapy (ULT) is proved to improve endothelial function.[4–7] Therefore, many trials investigated whether patients under ULT attained better blood pressure (BP) control and renal function.[8–10] ULT is commonly prescribed for patients if any symptom or sign of hyperuricemia develops.

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However, more than half of hyperuricemic individuals remain asymptomatic.[11] Asymptomatic hyperuricemia (AH) is defined as hyperuricemic patients without either symptoms or signs of gout, tophi, hyperuricemic nephropathy, or uric acid nephrolithiasis.[12] Because there are possible side effects of urate-lowering drugs, treatment for AH is controversial.[13,14] Urate-lowering drugs include xanthine oxidase inhibitors, such as allopurinol and febuxostat, and uricosuric agents, such as benzbromarone and probenecid. Severe skin reaction, higher cardiovascular (CV) risk or impaired liver function related to those drugs have been reported.[15–19] Benzbromarone was, therefore, withdrawn from the market in 2003 and has never been approved in the United States due to its reports of hepatotoxicity. [20,21] Japanese guidelines for managing hyperuricemia and gout recommend initiating ULT for AH when serum urate levels increase to >8.0 mg/dL.[22] However, this approach is not recommended in the United States and Europe owing to the side effects of these drugs.[14]

Xanthine oxidase inhibitors are thought to have the potency to decrease oxidative stress causing endothelial dysfunction.[10,23] The metabolite of allopurinol is excreted predominantly by the kidney, and febuxostat is believed to be safe for patients with CKD owing to its hepatic elimination.[24] The comparative effects of these drugs have not been investigated.

Network meta-analysis (NMA) is, therefore, a useful tool because it can use both direct and indirect evidence to compare the effects of all ULT. In contrast, previous meta-analyses either considered ULT as a single group or compared each drug to the control separately. Therefore, we conducted a systematic review and NMA to investigate the effects of different urate-lowering drugs on serum uric acid level, renal function, and BP in patients with AH. We would also investigate the safety of those treatments to attain a balanced consideration for AH patients.

Methods

We conducted a systematic review and NMA of randomized controlled trials on patients with AH. The intervention group (patients receiving urate-lowering drugs) was compared with groups of other types of urate-lowering drugs, placebo, or usual care. The outcomes were serum uric acid level, renal function, BP, and adverse events. We registered our systematic review on PROSPERO website. This NMA followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) extension guideline, which incorporated NMA for health care interventions and was registered in PROSPERO (registration number: CRD42021256528).

Literature Search

Two investigators (YYT and CPT) independently searched PubMed and Embase from their inception through October 8, 2020. We had also searched at ClinicalTrials. gov and hand-searched reference lists of relevant publications. The population of included trials was AH patients. Given that there are some controversies over the definition of hyperuricemia, we respected authors' definition of hyperuricemia in each study.[12] If "asymptomatic" was not used to describe its population, a trial was still considered eligible if it enrolled patients without a history of gout or other related symptoms. Chronic hyperuricemic nephropathy is usually asymptomatic and is not easy to diagnose. If a trial described its patients as AH and with CKD, this was interpreted as that CKD in those patients was not caused by their hyperuricemia. Therefore, those studies would still be included. We used the keywords "hyperuricemia," "asymptomatic," "urate-lowering therapy," and classification or name of the drugs for searching. The search details are shown in Appendix 1. The bibliographies of recent review articles and previous meta-analyses were also manually searched for relevant studies.

Study Outcome

The primary outcomes were serum uric acid level, measured in units of mg/dL, renal function, assessed by estimated glomerular filtration rate (eGFR), and BP, measured in units of mmH,g and divided to systolic and diastolic BP. The eGFR was calculated with 1 of the following methods: Cockcroft-Gault formula, the 4-variable modification of diet in renal disease study equation, or CKD epidemiology collaboration equation. The secondary outcome was adverse events, including the occurrence of impaired liver function, gastrointestinal event, CV event, skin reaction, and musculoskeletal event in patients within the trials identified by our search strategy.

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Study Selection

All titles and abstracts retrieved from the literature search were screened by 2 reviewers to determine the eligibility of a study. We included clinical trials where patients were randomly allocated to receive different treatments or placebo/usual care groups. We excluded conference proceedings without full text, nonrandomized controlled trials, the intervention group not receiving approved medicine, and studies not specific to asymptomatic adults.

Data Extraction

The outcomes were extracted independently from the included studies by 2 investigators mentioned above. For the primary outcomes, we evaluated the treatment effect by dividing the duration of treatment into short-term (≤ 6 months) and long-term follow-up (> 6 months). We assumed that it takes at least 6 months for a drug to show a robust effect, so we used 6-month to separate the short and long-term effects.

For the secondary outcomes, we analyzed events of impaired liver function, gastrointestinal events, CV events, skin reaction, and musculoskeletal events. Details are shown in Appendix 2.

Quality Assessment of Methods

We used Cochrane Risk of Bias Tool to assess the quality and risk of bias for the included studies (Appendix 3). We defined the risk of bias as adequate, unclear, or inadequate for assessing 6 aspects of the trials: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. The assessment was conducted by 2 independent reviewers, with a third consulted for resolution of any disagreements.

Statistical Analysis

We used "meta," "netmeta" and "dmetar" packages for the free statistical software R (version 4.0.3, Vienna, Austria) to undertake a frequentist pairwise meta-analysis and NMA.

NMA uses both direct and indirect evidence to compare multiple interventions within a statistical model. If 2 interventions have never been compared head-to-head, but both have been compared with a common comparator (such as placebo), an indirect comparison can be evaluated via the common comparator. [25] An estimate of mean difference (MD) in treatment effect between 2 interventions is a weighted average of direct and indirect comparisons, with confidence intervals (CI).

For each primary outcome, we created network plot which shows the overall structure of comparisons in the NMA. The size of the circles is proportional to the number of patients randomized to each intervention, and the width of the edges is proportional to the number of studies making each comparison.

We had also performed pairwise meta-analyses of all head-to-head comparisons to evaluate the heterogeneity within each comparison.[25]

For continuous outcomes, such as serum uric acid level, eGFR, and BP, we estimated the difference in mean changes between the treatment and control groups. If a trial did not report such a result, we would calculate the difference in the follow-up measurements between 2 groups at a specific time point. We used the recommended methods by the Cochrane Handbook to impute missing values.[26] League tables were created to summarize the results of pairwise comparisons from NMA. If a trial reported 2 or more results within the period, we used data of the shortest follow-up for short-term analysis and the longest follow-up for long-term analysis to distinguish the short-term and long-term effects better. For dichotomous outcomes, such as safety outcomes, we used the Peto odds ratio model because the event numbers were small or even zero in some studies.[26] The study effect sizes were then synthesized using a random-effects NMA model.

To rank the treatments for each outcome, we used P-score, which measures how likely a treatment is better than the other competing treatments. P-scores are derived from the *P* values of pairwise comparisons for a treatment is compared with the other treatments in the network. P-scores reflect the differences between the point estimates of treatment effects but also take the precision into account. The range of P-scores is from 0 to 1, and a large P-score (eg, >0.90) suggests a high certainty of a treatment being more effective or safer than others. [27] However, P-scores are descriptive, and a large difference between 2 P-scores does not necessarily mean the difference between the 2 treatments is statistically significant. There is no formal method to test the difference in P-scores either.

If both direct and indirect evidence is available for a comparison between 2 treatments, we use the

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design-by-treatment interaction model and node-splitting model to evaluate the consistency between direct and indirect evidence. We evaluated the assumption of transitivity for indirect comparisons by examining the distribution of confounding variables, such as baseline kidney function, or undertook subgroup analyses if the number of included studies is sufficient to conduct such analyses.

Results

Our literature search identified 777 potentially eligible studies. Thirteen randomized controlled trials were finally included in our systematic review, totaling 2842 people.[28–40] Figure 1 shows the study selection process in detail. Table 1 outlines the basic characteristics of the included studies. The intervention included allopurinol, benzbromarone, and febuxostat. The results of a pairwise meta-analysis on direct comparisons are shown in Appendix 6. Most comparisons show no substantial heterogeneity between studies.

Primary Outcome

Short-Term Urate-Lowering Effect

Eight studies were included in the analysis of the urate-lowering effect for short-term (≤ 6 months) follow-up.[29,30,32,33,35,37,39,40] The network plot and results of our NMA are summarized in Appendix 4 and Table 2. Patients used allopurinol, benzbromarone and febuxostat showed significantly lower serum uric acid level compared with placebo (MD = −2.16 mg/dL; 95% CI, 3.2 to −1.13 vs MD = −3.05 mg/dL; 95% CI, −5.19 to −0.91 vs MD = −2.71 mg/dL; 95% CI, −3.9 to −1.52), but there were no significant differences between drugs. Benzbromarone had the highest P-score of being ranked first for urate-lowering efficacy (Table 3).

Long-Term Urate-Lowering Effect

Three studies reported a long-term (> 6 months) urate-lowering effect.[28,31,40] The network plot and results of our NMA are summarized in Appendix 4 and Table 2. Patients using allopurinol had significantly lower serum uric acid level compared with placebo (MD = −3.17 mg/dL; 95% CI, −5.19 to −1.15). Patients using febuxostat had lower blood uric acid levels (but not significantly different) compared with placebo. The serum uric acid level showed no significant difference between drugs. Allopurinol had the highest P-score of being ranked first for better urate-lowering efficacy (Table 3).

Renal Function: Short-Term Follow-up

Five studies were included in this analysis.[30,32,34,37,39] The intervention included allopurinol group and febuxostat group, and the network plot and results of our NMA are summarized in Appendix 4 and Table 2. Patients used allopurinol had significantly higher eGFR compared with placebo (MD = 3.07 mL/min/1.73m^2; 95% CI, 0.18 to 5.95). Patients who used febuxostat had a higher eGFR (but not significantly different) compared with placebo. Besides, allopurinol group also had higher eGFR compared with febuxostat group, but no statistical significance was found. Allopurinol had the highest P-score of being ranked first for better renal function (Table 3).

Renal Function: Long-Term Follow-up

Three studies were included in this analysis.[31,36,40] The intervention included allopurinol group and febuxostat group. Appendix 4 and Table 2 showed the network plot and results of our NMA. Patients used allopurinol had significantly higher eGFR than using febuxostat or placebo (MD = 3.70 mL/min/1.73m^2; 95% CI, 1.94 to 5.46 vs MD = 4.10 mL/min/1.73m^2; 95% CI, 2.66 to 5.54). Patients used febuxostat had higher eGFR than using placebo but without statistical significance. Allopurinol had the highest P-score (Table 3).

Blood Pressure: Short-Term Follow-up

Three eligible studies were included, and the network plot and results of our NMA for systolic/diastolic BP are summarized in Appendix 4 and Table 2.[30,34,35] No significant difference in systolic/diastolic BP between groups was found. P-score was summarized in Table 3.

Blood Pressure: Long-Term Follow-up

Four studies were included, and Appendix 4 and Table 2 showed the network plot and results of our NMA.[28,31,36,40] No significant difference of systolic/diastolic BP was found between groups, except patients in febuxostat group had 1.47 mmHg statistically lower diastolic BP than patients in placebo group (MD = −1.47 mmHg; 95% CI, −2.91 to −0.04). P-score was summarized in Table 3.

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Figure 1. Flowchart of the process to identify eligible studies with reasons for inclusion or exclusion.

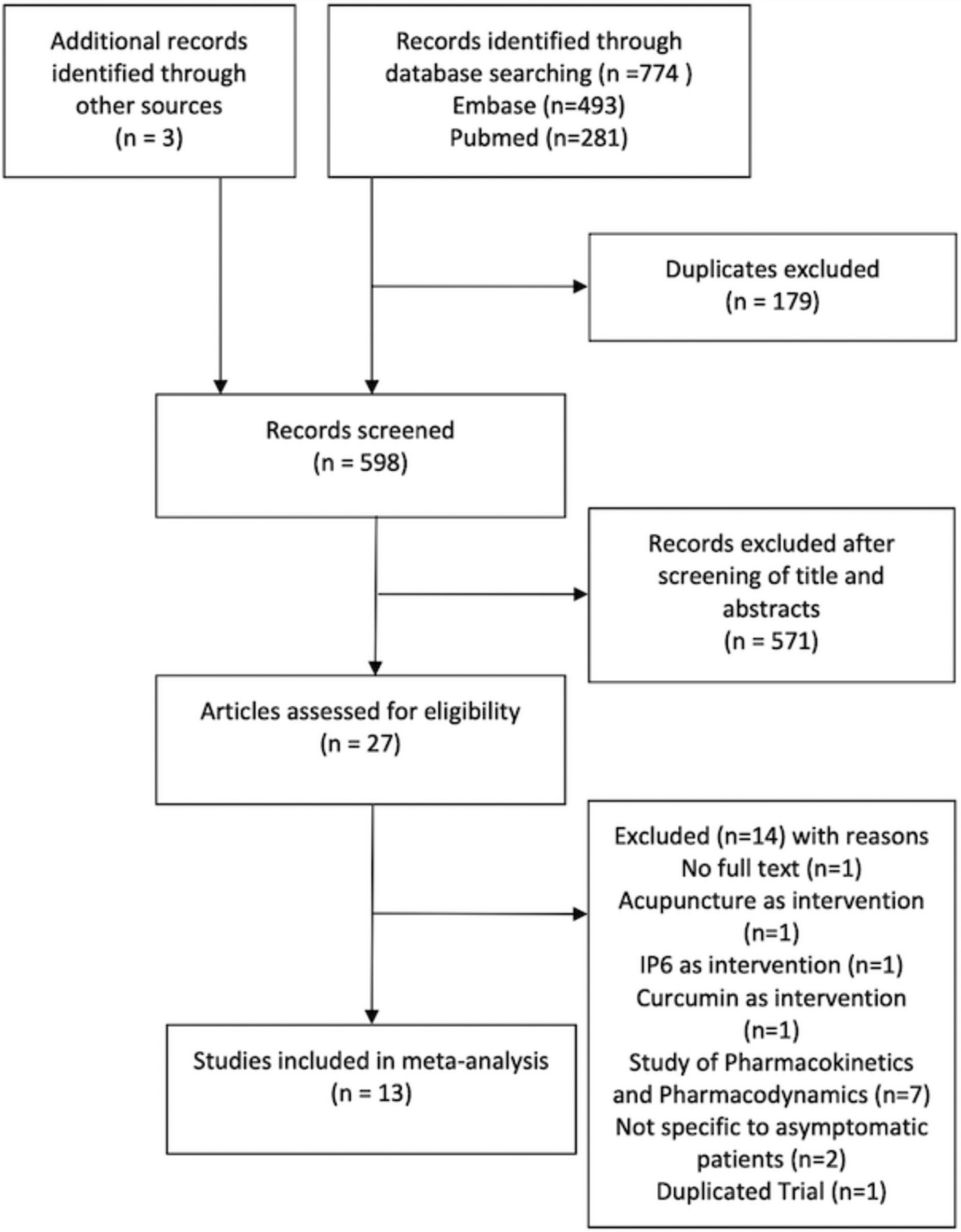

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Table 1. Overview of Included Studies

Author/Country	Population	Study Design	No. of Patients (Treatment/ Control)	Baseline Characteristic* (Treatment/Control)	Treatment	Comparison	Period (weeks)	Primary Outcome
Siu, 2005 China[28]	patients with chronic kidney disease	randomized controlled trial	25/26	uric acid (mg/dL): 9.75/5.88 Cr (mg/dL): 1.62/1.86 SBP (mm Hg): 138/135 DBP (mm Hg): 79/71	allopurinol, 100 to 300 mg/day	no urate-lowering medical therapy	48	– stable kidney function with less than 40% increase in serum creatinine level – impaired renal function with creatinine level increase greater than 40% of baseline value
Ogino, 2010 Japan[29]	patients with stable compensated CHF	double-blind, placebo-controlled, randomized crossover study	14/14	uric acid (mg/dL): 10.2/10.2	Benzbromarone 50 mg/day	placebo	8	– the change of BNP levels – change in echocardiographic parameters of left ventricle dimensions and LVEF
Kanbay, 2011 Turkey[30]	patients with normal renal function	randomized, controlled trial	30/37	uric acid (mg/dL): 8.3/ 7.9†,‡ eGFR: 86.3/84.3 SBP (mm Hg):127.6/123.2 DBP (mm Hg): 75.1/75.6	allopurinol 300 mg/day	no urate-lowering medical therapy	16	– endothelial dysfunction – BP – eGFR
Liu, 2015 China[31]	patients with type 2 diabetes	randomized open parallel-controlled study	88/88	uric acid (μmol/L) : 433/432 eGFR: 90.1/90.1SBP (mm Hg): 121/121 DBP (mm Hg): 74/74	allopurinol starting from 100 mg/day	no urate-lowering medical therapy	144	changes in the carotid IMT
Sircar, 2015 India[32]	eastern India aged 18 to 65 years with CKD stages 3 and 4	double-blind, randomized, parallel-group, placebo-controlled study	45/48	uric acid (mg/dL): 9.0/8.2 eGFR: 31.5/32.6	febuxostat 40 mg/ day	placebo	24	≥10% decline in eGFR from baseline
Takir, 2015 Turkey[33]	patients without a history of diabetes mellitus, kidney and liver disease	randomized, controlled trial	40/33	uric acid (mg/dL): 7.86/7.45 Cr (mg/dL): 0.9/1.07	allopurinol 300 mg/day	no urate-lowering medical therapy	12	improvement in insulin resistance defined by homeostatic model assessment of insulin resistance
Beddhu, 2016 USA[34]	overweight or obese adults with type 2 diabetic nephropathy	double-blinded randomized controlled trial	37/39	uric acid (μmol/L): 426/422 eGFR: 52.2/54.8SBP (mm Hg): 125.2/128.3DBP (mm Hg): 68.1/72.0	febuxostat 80 mg/ day	placebo	24	– adipose tissue TBARS and adiponectin concentrations – urinary transforming growth factor–β
Jalal, 2017 USA[35]	≥ 18 years of age with stage 3 CKD	double-blind, randomized, controlled trial	39/41	uric acid (mg/dL): 8.3/8.7 eGFR: 41.3/42.4 SBP (mm Hg): 127/ 130 DBP (mm Hg): 77.4/77.7	allopurinol 300 mg/day (200 mg, 100 mg)	placebo	12	change in brachial artery flow-mediated Dilation
Kimura, 2018 Japan[36]	patients with CKD stage 3	randomizeddouble-blind, parallel-	219/222	uric acid (mg/dL): 7.8/7.8eGFR: 45.2/44.9 SBP (mm Hg):	febuxostat (10 mg, 20 mg, 40 mg)	placebo	108	eGFR slope

Continued

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Table 1. Continued

Author/Country	Population	Study Design	No. of Patients (Treatment/ Control)	Baseline Characteristic* (Treatment/Control)	Treatment	Comparison	Period (weeks)	Primary Outcome
		group, placebo-controlled trial		132.5/129.6 DBP (mm Hg): 77.9/77.3				
Mukri, 2018 Malaysia[37]	CKD stage 3 and 4 patients with diabetic nephropathy	open-label, randomized study	47/46	uric acid (μmol/L): 539.5/537.3 eGFR: 26.2/28.2 SBP (mm Hg): 141/146 DBP (mm Hg): 73.7/71.7	febuxostat 40 mg/ day	no urate-lowering medical therapy	24	slowing the eGFR decline
Kojima, 2019 Japan[38]	elderly patients who had one or more risks for cerebral, cardiovascular, or renal disease	randomized open-label, blinded endpoint study	537/533	uric acid (mg/dL): 7.54/7.50 eGFR: 54.62/55.35 SBP (mm Hg): 132.9/132.3 DBP (mm Hg): 73.5/73.6	febuxostat (10-40 mg/day)	non-febuxostat groupno treatment or allopurinol 100 mg (27.2% patients)	144	– fatal and non-fatal cerebral, cardiovascular and renal – death other than cerebral or cardiorenal vascular disease
Perrenoud, 2020 USA[39]	patients with CKD stage 3	double-blind randomized placebo-controlled study	39/41	eGFR: 41.4/41.7 SBP (mm Hg): 127/129 DBP (mm Hg): 77/77	allopurinol 300 mg/day	placebo	12	– change of albumin-creatinine ratio – neutrophil gelatinase-associated lipocalin – kidney injury molecule 1 transforming growth factor β1
Tanaka, 2020 Japan[40]	adults with maximum IMT of the CCA $\geq$ 1.1 mm at screening	randomized, open-label, blinded-endpoint clinical trial	257/257	uric acid (mg/dL): 7.76/7.73 eGFR: 56.26/57.12 SBP (mm Hg): 128.9/127.3 DBP (mm Hg): 73.3/74.18	febuxostat (10-60 mg/day)	no urate-lowering medical therapy	96	– percentage change from baseline to 24 months in mean IMT of the CCA

Abbreviations: BNP, brain natriuretic peptide; BP, blood pressure; CCA, common carotid artery; CHF, chronic heart failure; CKD, chronic kidney disease; CRP, C-reactive protein; CV, cardiovascular; DBP, diastolic blood pressure; DN, diabetic nephropathy; eGFR, estimated Glomerular filtration rate; FMD, Flow-mediated dilation; IMT, intima-media thickness; IL-6, interleukin-6; LVEF, left ventricular ejection fraction; MCP-1, monocyte chemotactic protein-1; Ox-LDL, oxidized low-density lipoprotein; NF-kB, nuclear factor-kappa B; SBP, systemic blood pressure; TBARS, thiobarbituric acid-reducing substances; UAER, urinary albumin excretion rate.

* Values are expressed as mean.

† The unit of eGFR is mL/min/1.73 m^2.

‡ Values are expressed as median.

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Table 2. League Table of Random-Effects Network Meta-Analysis for Effect of Urate-Lowering Therapy*

Serum Uric Acid Level (Short-Term Follow-Up, mg/dL)			
Allopurinol	.	.	−2.16 (−3.20 to −1.13)
0.89 (−1.49 to 3.26)	**Benzbromarone**	.	−3.05 (−5.19 to −0.91)
0.55 (−1.03 to 2.13)	−0.34 (−2.79 to 2.11)	**Febuxostat**	−2.71 (−3.90 to −1.52)
−2.16† (−3.20 to −1.13)	−3.05* (−5.19 to −0.91)	−2.71† (−3.90 to −1.52)	**Placebo**
Serum Uric Acid Level (Long-Term Follow-Up, mg/dL)			
Allopurinol	.		−3.17 (−5.19 to −1.15)
−0.55 (−3.97 to 2.88)	**Febuxostat**		−2.62 (−5.39 to 0.15)
−3.17† (−5.19 to −1.15)	−2.62 (−5.39 to 0.15)		**Placebo**
Renal Function (Short-Term Follow-Up, mL/min/1.73 m^2)			
Allopurinol	.		3.07 (0.18 to 5.95)
2.00 (−2.54 to 6.53)	**Febuxostat**		1.07 (−2.43 to 4.57)
3.07† (0.18 to 5.95)	1.07 (−2.43 to 4.57)		**Placebo**
Renal Function (Long-Term Follow-Up, mL/min/1.73 m^2)			
Allopurinol	.		4.10 (2.66 to 5.54)
3.70† (1.94 to 5.46)	**Febuxostat**		0.40 (−0.60 to 1.40)
4.10† (2.66 to 5.54)	0.40 (−0.60 to 1.40)		**Placebo**
Systolic Blood Pressure (Short-Term Follow-Up, mm Hg)			
Allopurinol	.		0.04 (−4.22 to 4.30)
4.54 (−4.29 to 13.37)	**Febuxostat**		−4.50 (−12.23 to 3.23)
0.04 (−4.22 to 4.30)	−4.50 (−12.23 to 3.23)		**Placebo**
Systolic Blood Pressure (Long-Term Follow-Up, mm Hg)			
Allopurinol	.		−4.74 (−11.12 to 1.63)
−3.96 (−10.58 to 2.66)	**Febuxostat**		−0.78 (−2.57 to 1.01)
−4.74 (−11.12 to 1.63)	−0.78 (−2.57 to 1.01)		**Placebo**
Diastolic Blood Pressure (Short-Term Follow-Up, mm Hg)			
Allopurinol	.		1.58 (−2.31 to 5.48)
1.48 (−4.06 to 7.03)	**Febuxostat**		0.10 (−3.85 to 4.05)
1.58 (−2.31 to 5.48)	0.10 (−3.85 to 4.05)		**Placebo**
Diastolic Blood Pressure (Long-Term Follow-Up, mm Hg)			
Allopurinol	.		0.86 (−3.88 to 5.61)
2.34 (−2.62 to 7.29)	**Febuxostat**		−1.47 (−2.90 to −0.04)
0.86 (−3.88 to 5.61)	−1.47† (−2.91 to −0.04)		**Placebo**

*Data are shown as mean difference (95% confidence interval).
†Difference in treatment effect is statistically significant.

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Table 3. P-Score of Different Rankings of Each Treatment Strategy

SHORT-TERM		LONG-TERM	
Serum Uric Acid		Serum Uric Acid	
Benzbromarone	0.7908	Allopurinol	0.8108
Febuxostat	0.7146	Febuxostat	0.6728
Allopurinol	0.4937	Placebo	0.0164
Placebo	0.0009	Renal Function	
Renal Function		Allopurinol	1.0000*
Allopurinol	0.8937	Febuxostat	0.3912
Febuxostat	0.4598	Placebo	0.1088
Placebo	0.1465	Systolic Blood Pressure	
Systolic Blood Pressure		Allopurinol	0.9035*
Febuxostat	0.8581	Febuxostat	0.4626
Allopurinol	0.3246	Placebo	0.1340
Placebo	0.3173	Diastolic Blood Pressure	
Diastolic Blood Pressure		Febuxostat	0.9000
Placebo	0.6534	Placebo	0.3307
Febuxostat	0.5900	Allopurinol	0.2693
Allopurinol	0.2567		

*Large value of P-score (eg, >0.90) may reflect that treatment is quite certain to be the most efficacious or safest.

Secondary Outcome: Adverse Events

Six trials, 1269 patients, were included in the analysis of impaired liver function.[29,31,34–36,40] Six trials, 986 patients, were included in the analysis of gastrointestinal events.[31,32,34,35,37,40] Five trials, 1195 patients, were included in the analysis of cardiovascular event.[32,34,36,37,40] Four trials, 1102 patients, were included in the analysis of musculoskeletal events.[34,36,37,40] Three trials, 1009 patients, were included in the analysis of skin reaction [35,36,40] Compared with placebo via NMA, ULT did not significantly increase the odds of any secondary outcome (Appendix 5).

As no treatment groups formed a loop in any outcomes, we could not evaluate inconsistency between direct and indirect evidence. No subgroup analysis was undertaken because the number of the low number of included studies. Baseline eGFR of patients showed quite a wide variation across the included trials, but the assumption of transitivity was not considered seriously violated due to the hepatic metabolism of febuxostat, and both similar and typical dose was used in most trials of allopurinol. [28,30,31,33,35,39]

Discussion

Our NMA showed that benzbromarone and allopurinol have the best efficacy on lowering serum uric acid levels in short-term and long-term follow-up within AH patients. Patients using allopurinol have better eGFR than using placebo. ULT seems to have no significant effect on BP, except for febuxostat on diastolic BP after long-term treatment. ULT does not significantly increase the risk of safety outcomes. Asymptomatic patients are often neglected for treatment, and our results provide much-needed evidence for treating those patients to attain better renal function.

Uric Acid

Previous meta-analysis or NMA included patients who were mostly symptomatic, so the doses of their drugs were relatively larger than those we recruited. Li et al reported a NMA for comparing efficacy of ULT in patients with or without gout.[41] Their results showed benzbromarone (100 to 200 mg/day) had better urate-lowering effect than allopurinol (100 to 600 mg/day), and allopurinol (100 to 600 mg/day) had better urate-lowering effect than febuxostat (20 mg/day). In our NMA, only 1 trial reported the result of benzbromarone with a dose of 50 mg/day, but we still found a similarly strong effect of benzbromarone in the short-term follow-up. However, no trial on benzbromarone reported results with more than 6 months of follow-up, so its long-term efficacy is uncertain. Our result showed that allopurinol (starting from 100 mg/day) had better effect on lowering serum uric acid levels than febuxostat (10 to 60 mg/day) in the long term. This result partly agrees with what Li et al found that allopurinol had a better effect than a low dose of febuxostat.[41]

Nevertheless, the effect on uric acid is related to the dose of drugs. The selection of drugs and their doses also depends on patients' kidney function, responses to the treatment, and other factors.

Renal Function

Meta-analysis by Kanji et al showed patients with CKD using ULT had significantly better eGFR with a mean difference of 3.2 mL/min/1.73 m^2 than using placebo.[42] Slower eGFR decline rate by 4.1 mL/min/1.73m^2 per year compared with control group was found in the study of Su et al[43] Those meta-analyses focused on patients with CKD and were not limited to asymptomatic patients. Our NMA included more diverse population, not only patients with CKD, but the result still showed that patients using allopurinol had 3.07/

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4.1 mL/min/1.73m^2 significantly higher eGFR than using placebo in short-term/long-term follow-up. Although the differences are small, they may be of great significance for patients who already have kidney disease. In addition, the results were similar to previous research.[42,43]

Our result showed that febuxostat yielded a nonsignificant increase in eGFR compared with placebo. This was similar to a meta-analysis by Li et al which included symptomatic and asymptomatic CKD patients.[44] As only 3 trials were included in their meta-analysis and 5 trials included in ours; these nonsignificant benefits may become significant if the number of subjects increases.

We did not find any trial of uricosuric agents reporting renal function of asymptomatic patients, so we cannot distinguish the possibly different effect between xanthin oxidase inhibitors and uricosuric agents.

Blood Pressure

The meta-analysis by Qu et al found allopurinol found a greater reduction in systolic BP and diastolic BP.[45] They included patients with hyperuricemia with or without symptoms, so the dose of allopurinol (100 mg/day to 900 mg/day) was relatively larger than our studies. This may explain why allopurinol showed smaller effects on BP in our analysis. We found a decreasing trend of systolic BP under treatment of allopurinol and febuxostat in the long-term follow-up, but the effect of ULT on BP needs more research.

Safety

White et al found that in patients with gout and major CV coexisting conditions, using febuxostat showed higher all-cause mortality and CV mortality than using allopurinol in a median of 32 months in 6190 patients.[17] Five trials, totaling 1195 patients, were recruited in our NMA reporting CV events.[32,34,36,37,40] The result showed patients using febuxostat did not have a higher risk than those using placebo. However, no allopurinol-related trial was included in our analysis, so we could not compare the effects of these 2 drugs on CV events. The longest follow-up period in these trials was 27 months, but CV events may require more time and more patients to observe.

Allopurinol is frequently associated with Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).[15] Three trials in our NMA, totaling 1009 patients, reported skin reaction and did not show a higher risk of skin reaction in patients using allopurinal.[35,36,40] Previous reports showed that the incidence rates of SJS/TEN range from 1.4 to 12.7 cases per million person-years.[46,47] Therefore, such serious skin reaction is rare if the patient number is not large enough.

Strengths and Limitations

The strength of our NMA was that we focused on patients with AH and compared the efficacy of individual drugs. We also divided the treatment duration into short-term and long-term. However, this study has some limitations. First, only 3 drugs, allopurinol, febuxostat, and benzbromarone, were included in our analyses, while probenecid, lesinurad, and other urate-lowering drugs were not because these drugs had not been studied among AH patients. Second, no head-to-head trials that compared allopurinol and febuxostat were included in our analysis. Although it is the advantage of NMA that an indirect comparison can still be undertaken for these 2 treatments as both have been compared with placebo, we cannot verify the results because we do not have data from a direct comparison.[48] Thirdly, the number of the included studies was too few to undertake subgroup analysis. For instance, only 1 trial focusing on CKD population was included in the analysis of long-term renal function, so we could not compare the efficacy of those drugs on renal function among CKD patients. In our NMA, the included trials recruited patients of different comorbidities. However, considering the kidney plays a major role in uric acid homeostasis, we felt that renal function was the most important factor, and we noted that the average eGFR of each trial in our analysis was different. Febuxostat undergoes hepatic metabolism, and its dose adjustment and effects are less affected by patients' renal function.49 Trials on allopurinol used similar doses, 200 to 300 mg/day, [50] and this range of dose is considered suitable for CKD patients included in our NMA.[51] Although the heterogeneous populations should be considered in the interpretation of our results, we felt that the assumption of transitivity was not seriously violated. Fourthly, our results showed Allopurinol has a renoprotective effect, and this finding seems quite robust in Asian population as our results were mainly derived from Asian studies. More randomized controlled trials from non-Asian countries are required to verify the protective effect.

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Conclusions

Our result showed that in AH patients, benzbromarone and allopurinol have the best urate-lowering effect in the short-term and long-term follow-up. Allopurinol has a significant renoprotective effect. Febuxostat has a significant effect on lowering diastolic BP in long-term follow-up. ULT does not result in a higher risk of impaired liver function, gastrointestinal event, CV event, skin reaction, and musculoskeletal event. According to the above results, patients with AH may be treated with ULT to benefit from renal protection, and the use of allopurinol should be considered a priority.

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Appendices

Appendix 1. Literature search strategy

Appendix 2. Data extraction from included trials-Details of secondary outcomes

Appendix 3. Summary of the risks of bias in every included trial

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Appendix 5. League table of the network meta-analysis comparing the events of secondary outcomes of all drugs

Appendix 6. Result of pairwise meta-analyses of all directly compared interventions

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1. Embase

No.	Query	Results
#10	#8 AND #9	493
#9	#3 OR #4 OR #5 OR #6 OR #7	47551
#8	#1 AND #2	1574
#7	'urate lowering therapy'/exp OR 'urate lowering therapy' OR (('urate'/exp OR urate) AND lowering AND ('therapy'/exp OR therapy))	1979
#6	'urate oxidase'/exp OR 'urate oxidase' OR (('urate'/exp OR urate) AND ('oxidase'/exp OR oxidase)) OR 'pegloticase'/exp OR pegloticase OR 'rasburicase'/exp OR rasburicase	5573
#5	'selective uric acid reabsorption inhibitor' OR (selective AND uric AND ('acid'/exp OR acid) AND reabsorption AND ('inhibitor'/exp OR inhibitor)) OR 'lesinurad'/exp OR lesinurad	364
#4	'uricosuric agent'/exp OR 'uricosuric agent' OR (('uricosuric'/exp OR uricosuric) AND ('agent'/exp OR agent)) OR 'probenecid'/exp OR probenecid OR 'benzbromarone'/exp OR benzbromarone OR 'sulfinpyrazone'/exp OR sulfinpyrazone	18373
#3	'xanthine oxidase inhibitor'/exp OR 'xanthine oxidase inhibitor' OR 'allopurinol'/exp OR allopurinol OR 'febuxostat'/exp OR febuxostat OR feburic	27770
#2	asymptomatic	245443
#1	'hyperuricemia'/exp OR hyperuricemia OR 'uric acid'/exp OR 'uric acid' OR (uric AND ('acid'/exp OR acid))	72592

2. Pubmed

Search	Actions	Details	Query	Results	Time
#10	•••	›	Search: **(((hyperuricemia) OR (uric acid)) AND (asymptomatic)) AND (((((((xanthine oxidase inhibitor) OR (allopurinol)) OR (febuxostat OR feburic)) OR ((((uricosuric agent) OR (probenecid)) OR (benzbromarone)) OR (sulfinpyrazone))) OR ((selective uric acid reabsorption inhibitor) OR (lesinurad))) OR (((urate oxidase enzyme) OR (pegloticase)) OR (rasburicase))) OR (urate lowering therapy))**	281	20:40:22
#9	•••	›	Search: **((((((xanthine oxidase inhibitor) OR (allopurinol)) OR (febuxostat OR feburic)) OR ((((uricosuric agent) OR (probenecid)) OR (benzbromarone)) OR (sulfinpyrazone))) OR ((selective uric acid reabsorption inhibitor) OR (lesinurad))) OR (((urate oxidase enzyme) OR (pegloticase)) OR (rasburicase))) OR (urate lowering therapy)**	25,899	20:40:09
#8	•••	›	Search: **((hyperuricemia) OR (uric acid)) AND (asymptomatic)**	819	20:39:45
#7	•••	›	Search: **urate lowering therapy**	3,314	20:39:30
#6	•••	›	Search: **((urate oxidase enzyme) OR (pegloticase)) OR (rasburicase)**	2,347	20:38:37
#5	•••	›	Search: **(selective uric acid reabsorption inhibitor) OR (lesinurad)**	171	20:37:56
#4	•••	›	Search: **(((uricosuric agent) OR (probenecid)) OR (benzbromarone)) OR (sulfinpyrazone)**	8,810	20:37:17
#3	•••	›	Search: **((xanthine oxidase inhibitor) OR (allopurinol)) OR (febuxostat OR feburic)**	13,911	20:36:31
#2	•••	›	Search: **asymptomatic**	167,625	20:35:45
#1	•••	›	Search: **(hyperuricemia) OR (uric acid)**	43,504	20:35:13

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Appendix 1. Literature search strategy

Impaired liver function
Liver dysfunction
Abnormal liver function test results
Gastrointestinal events
Vomiting
Diarrhea
Gastroenteritis
Loss of appetite
Melena
Nausea
Other gastrointestinal symptom or sign
CV events
Arrhythmia
Angina
Aortic aneurysm
Myocardial infarction
Heart failure
Other events related to CV system
Skin reactions
Skin eruption
Rash
Hypersensitivity
Dermatologic events
Musculoskeletal events
Joint pain
Fracture
Pain in back
Any musculoskeletal events

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Appendix 2. Data extraction from included trials: Details of secondary outcomes

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Siu, 2005	Low	Unclear	Unclear	Unclear	Low	Low
Ogino, 2010	Low	Unclear	Low	Low	Low	Low
Kanbay, 2011	Low	Unclear	Unclear	Low	Low	Low
Liu, 2015b	Low	High	High	Low	Low	Low
Sircar, 2015	Low	Unclear	Low	Low	Low	Low
Takir, 2015	Unclear	Unclear	Unclear	Unclear	Low	Low
Beddhu, 2016	Low	Low	Low	Low	unclear	Low
Jalal, 2017	Low	Low	Low	Low	Low	Low
Kimura, 2018	Low	Unclear	Low	Unclear	Low	Low
Mukri, 2018	Low	High	High	Low	Low	Low
Kojima, 2019	Low	High	High	Low	Low	Low
Perrenoud, 2020	Low	Unclear	Low	Unclear	Low	Low
Tanaka, 2020	Low	High	High	Low	Low	Low

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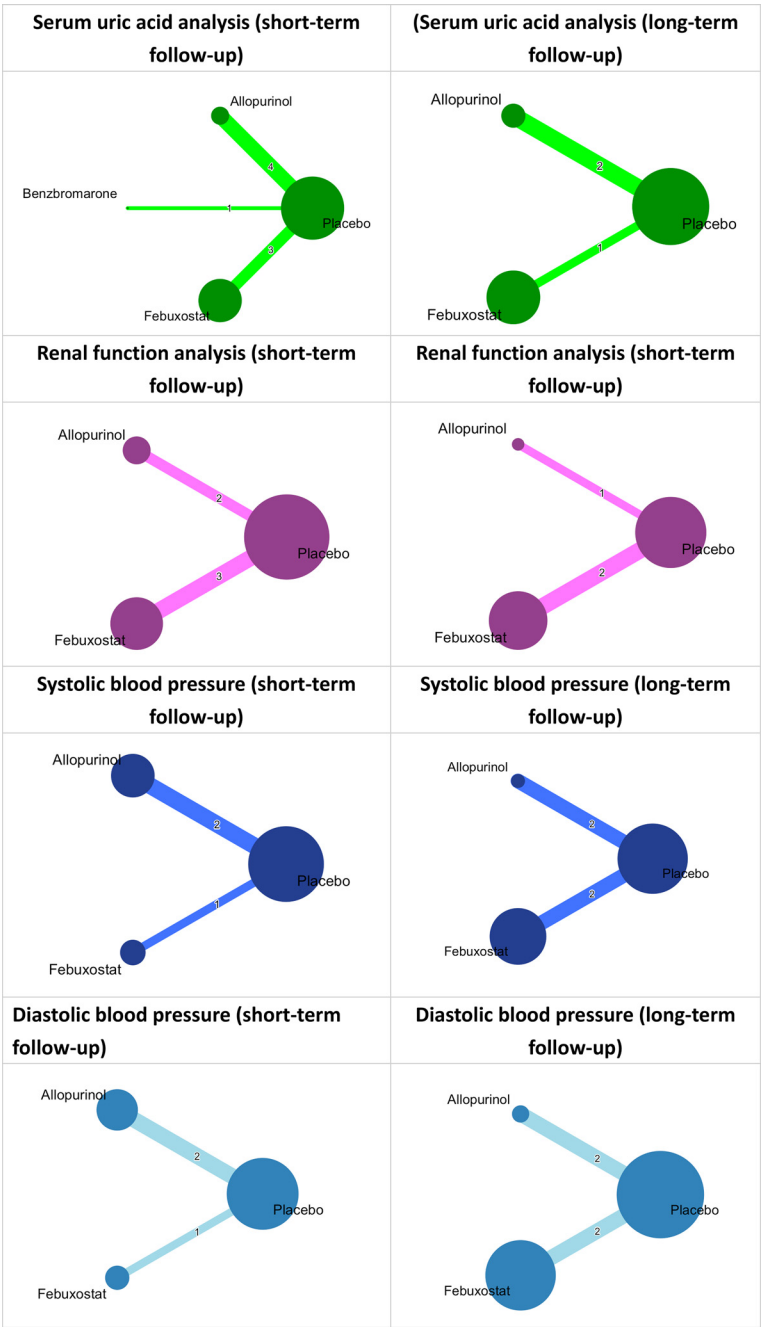
Appendix 3. Summary of the risks of bias in every included trial



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Appendix 4. Network plot for effect of urate-lowering therapy. Each node represents a treatment group, and an edge indicates at least 1 trial comparing the 2 treatments on the ends of the edge. The node size in the network plot is proportional to the number of patients randomized to the treatment group, and the width of an edge is proportional to the number of studies making the pairwise comparison

Impaired liver function		
Allopurinol	-	1.14 (0.09; 15.25)
0.75 (0.03; 18.30)	**Febuxostat**	1.53 (0.23; 9.92)
1.14 (0.09; 15.25)	1.53 (0.23; 9.92)	**Placebo**

Gastrointestinal events		
Allopurinol	-	2.65 (0.53; 13.25)
0.87 (0.10; 7.66)	**Febuxostat**	3.05 (0.70; 13.24)
2.65 (0.53; 13.25)	3.05 (0.70; 13.24)	**Placebo**

Cardiovascular events	
Febuxostat	0.78 (0.29; 2.07)
0.78 (0.29; 2.07)	**Placebo**

Skin reaction		
Allopurinol	-	0.14 (0.00; 6.55)
0.06 (0.00; 4.94)	**Febuxostat**	2.24 (0.28; 17.98)
0.14 (0.00; 6.55)	2.24 (0.28; 17.98)	**Placebo**

Musculoskeletal events	
Febuxostat	2.08 (0.69; 6.25)
2.08 (0.69; 6.25)	**Placebo**

Appendix 5. League table of the network meta-analysis comparing the events of secondary outcomes of all drugs, including odds ratios and 95% confidence intervals

	Benz-Control	P Value	Allop-Control	P Value	Febux-Control	P Value
Ur-Ac	-3.05± 1.09	*-	-2.16± 0.53	< 0.001	-2.71± 0.61	0.0300
GFR	-	-	3.07± 1.47	0.5065	1.07± 1.79	0.4527
SBP	-	-	0.04± 2.71	0.9704	-4.50± 3.94	*-
DBP	-	-	1.58± 1.99	0.8183	0.10± 2.02	*-

DBP, diastolic blood pressure; GFR, glomerular filtration rate; SBP, systemic blood pressure.

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Result of pairwise meta-analyses of all directly compared interventions

Appendix 6.1 Results of pairwise meta-analyses of all directly compared interventions of short-term results. *P* value is obtained from the Cochrane Q test for heterogeneity.

	Allop-Control	*P* Value	Febux-Control	*P* Value
Ur-Ac	-3.17 ± 1.03	0.0001	-2.62 ± 1.41	*-
GFR	4.10 ± 0.73	*-	0.40 ± 0.51	0.3547
SBP	-4.74 ± 3.25	0.6326	-0.78 ± 0.91	0.5233
DBP	0.86 ± 2.42	0.1484	-1.47 ± 0.73	0.8174

*Only 1 trial included in the analysis so heterogeneity could not be evaluated.
†High heterogeneity is defined by P value< 0.1.

Appendix 6.2 Results of pairwise meta-analyses of all directly compared interventions of long-term results. *P* value is obtained from the Cochrane Q test for heterogeneity.

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	File of JABFM_abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	2
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	CRD42021256528
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	3

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		• Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	Appendix 4
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	6-10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	Appendix 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	7- 10
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	Table 2, 3 Appendix 5
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network	NA/ 10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	Appendix 3
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	NA/ 10
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	File of JABFM_title page

PICOS = population, intervention, comparators, outcomes, study design.
* Text in italics indicateS wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.
† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

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