Systematic Review and Meta-Analysis

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Effects of febuxostat on renal function in patients with chronic kidney disease

A systematic review and meta-analysis

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Abstract

Background/Objective: Hyperuricemia has been proven to be an independent risk factor for chronic kidney disease (CKD). However, the role of hyperuricemia in the progression of CKD remains unclear. Thus, we performed a systematic review and meta-analysis to evaluate the efficacy and safety of febuxostat, a first line urate-lowering agent, in CKD patients with hyperuricemia.

Methods: We have systematically searched for randomized controlled trials assessing the efficacy and safety of febuxostat versus control in CKD patients with hyperuricemia through MEDLINE, PubMed, EMBASE, and Cochrane databases. All statistical analyses were conducted by using the statistical package Review Manager, version 5.3.5. Heterogeneity was assessed using the Cochrane Q and I^2 tests and summary statistics were reported with 95% confidence interval. Two-tailed test was used for analysis and a P value of $<.05$ is considered statistically significant.

Results: Eleven eligible trials with 1317 participants were included in the meta-analysis. A significant reduction in serum uric acid was found in the febuxostat treated group. Also, a significant higher eGFR was found in the febuxostat treated group among CKD stage 3 and 4 patients. No significant difference of major complication or death was identified between treatment and control groups.

Conclusions: The meta-analysis showed that other than its urate-lowering effect, febuxostat presented a reno-protective effect in CKD patients. More studies with larger sample sizes and higher quality are required to clarify the role of febuxostat use in the progression of CKD.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, CI = confidence interval, CKD = chronic kidney disease, DBP = diastolic blood pressure, eGFR = estimated Glomerular Filtration Rate, FDA = Food and Drug Administration, hsCRP = high-sensitivity C-Reactive Protein, RCTs = randomized controlled trials, SBP = systolic blood pressure, SUA = serum uric acid.

Keywords: chronic kidney disease, febuxostat, hyperuricemia, meta-analysis, renal function

1. Introduction

Hyperuricemia, commonly defined as an increase in serum urate concentration to greater than 6.8 to 7.0 mg/dL, is associated with many systemic diseases.[1,2] Hyperuricemia is highly prevalent worldwide, with an estimate of over 20% of the US and China population having this condition.[3,4] In a cross-sectional study, hyperuricemia was proven to have a positive association with metabolic syndrome development.[5] It is associated with cardiovascular diseases, including hypertension[4,5] and major cardiovascular events.[6] A meta-analysis showed that asymptomatic hyperuricemia is an independent risk factor for chronic

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kidney disease (CKD), defined as abnormalities in kidney function or structure lasting for >3 months, with implications for health.[7,8]

According to the American College of Rheumatology 2012 guideline, pharmacological urate-lowering treatment is recommended in patients with current hyperuricemia and past gout attacks.[1] However, owing to a lack of studies on the causal relation between hyperuricemia and the progression of systemic diseases including hypertension, cardiovascular disease, and CKD, whether to treat hyperuricemia in non-gout diseases remains unclear.[2] For CKD, animal studies have shown that lowering uric acid concentration can improve kidney function.[9,10] Clinical studies have shown that hyperuricemia is an independent risk factor for kidney disease[11,12] and lowering the uric acid level can slow the progression of kidney disease.[13] Other clinical studies, however, have shown no causal relationship between hyperuricemia and CKD progression.[14,15] Contradictory evidence indicates that an elevated uric acid concentration is related to CKD but not necessarily to the disease progression.[16]

The first line of urate-lowering agent used in patients with gout is xanthine oxidase inhibitor, including allopurinol and febuxostat.[1] The drug allopurinol was introduced in the 1960s and has since been used clinically to treat hyperuricemia, but it has several side effects.[17,18] Apart from minor side effects such as gastrointestinal disorder and mild rash, it can lead to severe conditions, including exfoliative erythroderma, Stevens–Johnson syndrome, and even toxic epidermal necrolysis.[18] Moreover, the risk of allopurinol hypersensitivity reactions is higher in populations with cardiovascular or renal diseases.[19] By contrast, febuxostat is a newer xanthine oxidase inhibitor approved by the Food and Drug Administration (FDA) in 2009. A networking meta-analysis showed that febuxostat has a higher efficacy than allopurinol among hyperuricemia patients with or without gout.[17] Furthermore, studies have shown that febuxostat is less likely to cause adverse events compared with allopurinol.[17,20] Moreover, because allopurinol is mainly excreted through the kidney, whereas febuxostat is mainly metabolized by the liver, dose adjustment of allopurinol might be required in patients with CKD.[21,22] Febuxostat has shown to be safe and effective in patients with moderate to severe renal impairment, and dose adjustment is not required in these patients.[23,24] Thus, we performed a systematic review and meta-analysis to evaluate the efficacy and safety of febuxostat in patients with CKD and hyperuricemia.

2. Methods

2.1. Literature search

We searched randomized controlled trials (RCTs) that assessed the febuxostat efficacy versus control in patients with CKD and hyperuricemia through MEDLINE, PubMed, EMBASE, and Cochrane databases until September 08, 2018. The following keywords and their relevant terms were used: chronic kidney disease, end stage renal disease and febuxostat. (Mesh search headings were listed in Supplemental Digital Content, http://links.lww.com/MD/D123) No language restriction was applied. All the review processes followed registered protocol that was accepted by the online PROSPERO international prospective register of systematic reviews of the National Institute for Health Research (CRD42018090797).

2.2. Inclusion and exclusion criteria

Studies that met the following criteria were included in our analysis:

1. evaluated the efficacy and safety of febuxostat in patients with CKD,
2. clearly documented the inclusion and exclusion criteria for patient selection,
3. adequately documented the dosage and duration of the intervention and control groups, and
4. RCTs.

Studies were excluded from our analysis if

1. the outcomes of interest were not clearly reported or
2. the extraction or calculation of appropriate data from the published results was not possible.

2.3. Study selection and data extraction

Two reviewers (TCL and CHL) independently extracted the following information from each included study: first author, year of publication, study population characteristics, study design, inclusion and exclusion criteria, matching criteria, febuxostat dosage, intervention period, treatment duration, outcomes, and adverse effects. The following outcome measures were used to evaluate the efficacy and safety of febuxostat for hyperuricemia in patients with CKD: changes in serum uric acid (SUA), serum creatinine, estimated glomerular filtration rate (eGFR), high-sensitivity C-reactive protein (hsCRP), systolic blood pressure (SBP), diastolic blood pressure (DBP) and any adverse effect. Any disagreement on data extraction was resolved by a third reviewer (YCC). The authors of the studies were contacted for additional information when necessary. Risk of bias for each study was assessed using the risk of bias assessment tool from the Cochrane Handbook for Systematic Reviews of Intervention.[25]

2.4. Statistical analysis

Meta-analysis using a random-effects model was performed if data on a given outcome were available from more than one study. All statistical analyses were conducted by using the statistical package Review Manager, version 5.3.5. The effect size for each study was defined as the weighted mean difference between the treatment group and the control group. When necessary, standard deviations were estimated from the provided confidence interval (CI) limits, standard error, or range values. The mean and standard error of difference between the 2 groups, if not provided in the article, were estimated using the percentile estimation method (a nonparametric method to simulate a percentage approximated under the normal distribution). Heterogeneity was assessed using the Cochrane Q and I^2 tests and summary statistics were reported with 95% CI. Two-tailed test was used for analysis and a P value of $<.05$ is considered statistically significant.

3. Results

3.1. Characteristics of the trials

Figure 1 shows a flow chart for trial selection. Our initial search yielded 528 studies; of these, 124 were duplicates and 342 were

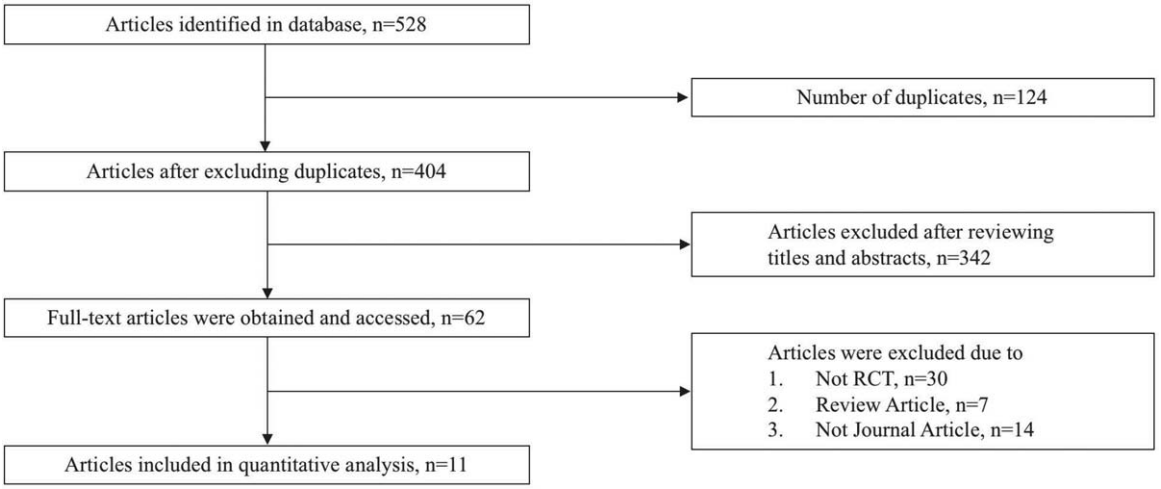

Figure 1. Flow diagram of articles considered for inclusion.

ineligible based on our screening of titles and abstracts. Thus, we retrieved full texts of 62 studies. Of these, 30 were not RCT, 14 were not journal articles, and 7 were review articles. In total, 11 eligible trials with 1317 participants were obtained and included in the meta-analysis.[26–36] Characteristics and patient demographic data from each of the 11 trials included in our review are listed in Table 1. These studies were published between 2015 and 2018 and had sample sizes ranging from 40 to 441. All trials had evaluated patients with CKD and hyperuricemia, defined differently according to each study. Most trials defined hyperuricemia as SUA ≥7.0 mg/dL. Patients who were pregnant, used medications metabolized by xanthine oxidase enzyme, or were involved in another clinical trial within 4 weeks were excluded from most trials. Baseline characteristics, mean uric acid, and renal function (if available) were similar between the intervention and control groups, except for the studies by Sircar et al[27] and Kimura et al,[33] which had a higher baseline uric acid level (the former) in the intervention group and a higher baseline systolic blood pressure (the latter) in the intervention group.

In the 11 included trials, febuxostat dosage in the treatment group ranged from 10 to 80 mg/day. The control group in most trials was administered placebos. Two studies compared the efficacy and safety of febuxostat with allopurinol[26,28] and 1 study compared with benzbromarone.[36] Efficacy of febuxostat was assessed by measuring the changes in SUA, serum creatinine, eGFR, hsCRP, SBP, and DBP. The safety of the treatment and control groups was assessed based on adverse effects reported during the treatment and follow-up periods.

3.2. Changes in SUA

All RCTs investigated the change in SUA of the treatment group versus the control group. However, results of the changes in SUA were only able to be extracted from 9 studies.[26–29,31–34,36] A significant difference was found between the 2 groups, with a greater decrease in SUA in the febuxostat group (weighted mean difference, –2.50; 95% CI, –3.35 to –1.66; I^2: 97%). A subgroup analysis performed in 3 studies comparing febuxostat with other uric acid lowering agents showed a significant difference with a greater decrease in the febuxostat group (weighted mean difference, –1.16; 95% CI, –1.92 to –0.40; I^2: 83%).[26,28,36]

3.3. Changes in hsCRP

The change in hsCRP was reported in 5 RCTs.[26,28,29,31,32] No significant difference was found between the treatment and control groups (weighted mean difference, 0.05; 95% CI, –0.42 to 0.51; I^2: 91%). Only 2 of the 5 studies showed a significant difference in the change of hsCRP between the febuxostat and allopurinol groups ($P < .05$).[26,32]

3.4. Changes in renal function

Renal function, assessed by the change in eGFR and serum creatinine, has been evaluated in the included studies. Seven studies evaluated the change in eGFR.[26–28,30,33,34,36] We used data from 6 studies and excluded 1 study because it had inadequate information and the author was not available for clarification.[30] The results from the 6 studies were in favor of febuxostat treatment; however, they showed no statistically significant difference between the 2 groups (weighted mean difference, 2.05; 95% CI, –0.24 to 4.34; I^2: 34%). We have performed subgroup analyses on studies comparing febuxostat and placebo and studies with CKD stage 3 and 4 participants. After subgroup analysis on studies comparing febuxostat and placebo, a result in favor of febuxostat was shown (weighted mean difference, 2.36; 95% CI, −1.62 to 6.33; I^2: 63%). We have also performed subgroup analysis of studies with CKD stage 3 and 4 participants and showed a statistically significant higher eGFR was observed in the febuxostat group (weighted mean difference, 3.66; 95% CI, 0.76 to 6.55; I^2: 15%). As for serum creatinine, 3 studies evaluated the change in serum creatinine between the febuxostat and control groups.[26,28,36] These studies compared the febuxostat group with other uric acid lowering agents. No significant difference was observed between the results of the studies (weighted mean difference, –0.06; 95% CI, –0.21 to 0.09; I^2: 73%). However, a statistically significant lower serum creatinine was seen in the febuxostat group after sub-group analysis of studies with treatment duration greater or equal to

Table 1

Characteristics of patients a nd intervention in included studies.

Study	Inclusion Criteria	Baseline Uric Acid (mg/dL)	Baseline eGFR (ml/min/1.73 m^2)	No. of patient (% of male)	Age, (yr) mean ± SD	Treatment Duration	Intervention
Alshahewey et al [2017]	Patients on HD with SUA≥7.0mg/dL	I: 7.5±0.8 C: 7.5±0.7	Not available	I: 28 (57%) C: 29 (58%)	I: 47±12.25 C: 47±13.83	2 months	I: 40 mg febuxostat thrice weekly C: placebo
Beddhu et al [2016]	Patients with CKD stage 1–3 with hyperuricemia (male-SUA≥5.50mg/dL, female-SUA≥4.61mg/dL)	I: 7.16±1.50 C: 7.09±1.19	I: 52.2±15.3 C: 54.8±19.0	I: 40 (60.0%) C: 40 (70.0%)	I: 67±10 C: 68±11	24 weeks	I: 80 mg febuxostat/day C: placebo
Gunawardhana et al [2018]	Patients with eGFR 30–60 ml/min with SUA≥8.0mg/dL	I1: 9.8±1.4 I2: 9.6±1.3 I3: 9.6±1.1 I4: 9.8±1.4 C: 9.7±1.2	I1: 46.0±8.3 I2: 43.3±6.7 I3: 48.2±7.5 I4: 48.3±8.8 C: 47.3±9.4	I1: 37 (67.6%) I2: 39 (66.7%) I3: 37 (75.7%) I4: 38 (76.3%) C: 38 (68.4%)	I1: 61.3±10.1 I2: 64.4±11.2 I3: 63.5±10.3 I4: 61.4±12.2 C: 64.6±12.8	3 months	I1: 40 mg IR febuxostat I2: 40 mg XR febuxostat I3: 80 mg IR febuxostat I4: 80 mg XR febuxostat C: placebo
Kimura et al [2018]	Patients with CKD stage 3 with SUA > 7.0–10.0mg/dl	I: 7.8±0.9 C: 7.8±0.9	I: 45.2±9.5 C: 44.9±9.7	I: 219 (77.0%) C: 222 (77.6%)	I: 65.3±11.8 C: 65.4±12.3	108 weeks	I: febuxostat days 1–28: 10mg/day weeks 4–7: 20mg/day weeks 8–108: 40mg/day C: placebo
Mukri et al [2018]	Patients with CKD stage 3–4 with SUA≥6.72mg/dL	I: 9.1±1.7 C: 9.0±1.2	I: 26.2±10.6 C: 28.2±14.67	I: 47 (53%) C: 46 (54%)	I: 64±7.4 C: 67±4.4	6 months	I: febuxostat 40mg/day C: placebo
Saag et al [2016]	Patients with eGFR 15–50 ml/minute/1.73m^2 with SUA≥7.0mg/dL	I1: 10.4±1.43 I2: 10.4±1.70 C: 10.8±1.96	Not available	I1: 32 (78.1%) I2: 32 (81.3%) C: 32 (81.3%)	I1: 67.3±11.11 I2: 63.6±8.15 C: 66.3±12.05	12 months	I1: 30 mg febuxostat twice/day I2: 40 or 80 mg febuxostat/day (to reach SUA<6.0mg/dL) C: placebo
Sezai et al [2015]	Patients with CKD stage 3–4 with SUA≥8.0mg/dL	I: 8.73±0.90 C: 8.63±1.00	I: 40.11±10.4 C: 41.5±10.6	I: 56 (76.8%) C: 53 (79.2%)	I: 69.4±10.0 C: 69.1±9.2	6 months	I: max. 60 mg/day for febuxostat (to reach SUA ≤6.0mg/dL) C: max. 300mg/day for allopurinol (to reach SUA ≤6.0mg/dL)
Sircar et al [2015]	Patients with CKD stage 3–4 with SUA≥7.0mg/dL	I: 9.0±2.0 C: 8.2±1.1	I: 31.5±13.6 C: 32.6±11.4	I: 45 (64%) C: 48 (77%)	I:56.22±10.87 C:58.42±14.52	6 months	I: 40 mg febuxostat/day C: placebo
Tanaka et al [2015]	CKD stage 3 with SUA≥7.0mg/dL	I: 7.75±0.84 C: 8.18±1.11	I: 41.8±12.0 C: 47.4±11.0	I: 21 (90.5%) C: 19 (84.2%)	I: 70.1±9.5 C: 66.1±7.0	12 weeks	I: 10mg-40mg febuxostat/day (to reach SUA ≤6.0mg/dL) C: placebo/ allopurinol according to the baseline
Tsuruta et al [2015]	Patients on HD with SUA≥7.0mg/dL	I: 8.2±0.8 C: 8.3±0.9	Not available	I: 27 (63%) C: 26 (65.4%)	I: 67.7±12.4 C: 68.9±12.7	4 weeks	I: 10 mg febuxostat/day C: placebo
Yu et al [2018]	Patients with eGFR 20–60 ml/minute/1.73 m^2 with SUA≥8.0mg/dL	I: 9.61±1.86 C: 8.87±1.32	I: 38.5±13.1 C: 41.2±14.22	I: 33 (75.8%) C: 33 (63.6%)	I: 59.5±9.0 C: 63.2±7.6	12 months	I: 20–80 mg febuxostat/day C: 25–100mg benzbromarone /day (to reach SUA ≤6.0mg/dL (female) or 7.0mg/dL (male))

C = control, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, HD = hemodialysis, I = intervention, IR = immediate release, Max. = maximum, No. = number, SUA = serum uric acid, XR = extended release.

6 months (weighted mean difference, −0.14; 95% CI, −0.24 to −0.04; I^2: 0%).

3.5. Changes in blood pressure

Four studies have evaluated the change in blood pressure.[28,29,32,33] They provided data on the change in the SBP between the treatment and control groups. A significant lower systolic blood pressure was observed in the febuxostat group (weighted mean difference, –4.44; 95% CI, –8.08 to −0.80; I^2: 12%). These 4 studies also compared the change in the DBP between the 2 groups. However, no significant difference between the 2 groups was seen (weighted mean difference, –3.08; 95% CI, –6.25 to 0.08; I^2: 34%).

3.6. Adverse effects

Nine of the 11 included trials assessed the safety of febuxostat.[27,28,30–36] Safety was commonly assessed by evaluating serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), and occurrence of pancytopenia, cardiovascular disorder, death, or any adverse events related to febuxostat use. No significant between-group difference on major complication or death was found or to be determined to be related to the treatment drug during the follow-up periods.[30,33,35] One study did not discover any reported adverse event during the follow period.[32] Other studies discovered adverse events in the febuxostat group, including 1 case of elevated liver function, 1 case of a decrease in SBP, 1 case of rash and 2 cases of mild diarrhea.[27,28,31] Two studies showed a significantly higher incidence of adverse events in the febuxostat group: a significantly higher incidence of joint pain[34] and a significant increase in AST and haemoglobin.[36] The rest of the studies did not report any adverse effects with febuxostat use during the follow-up period.

3.7. Risk of bias assessment

The methodological quality assessment of the 11 included RCTs is presented in Figure 6. Six of the included studies were

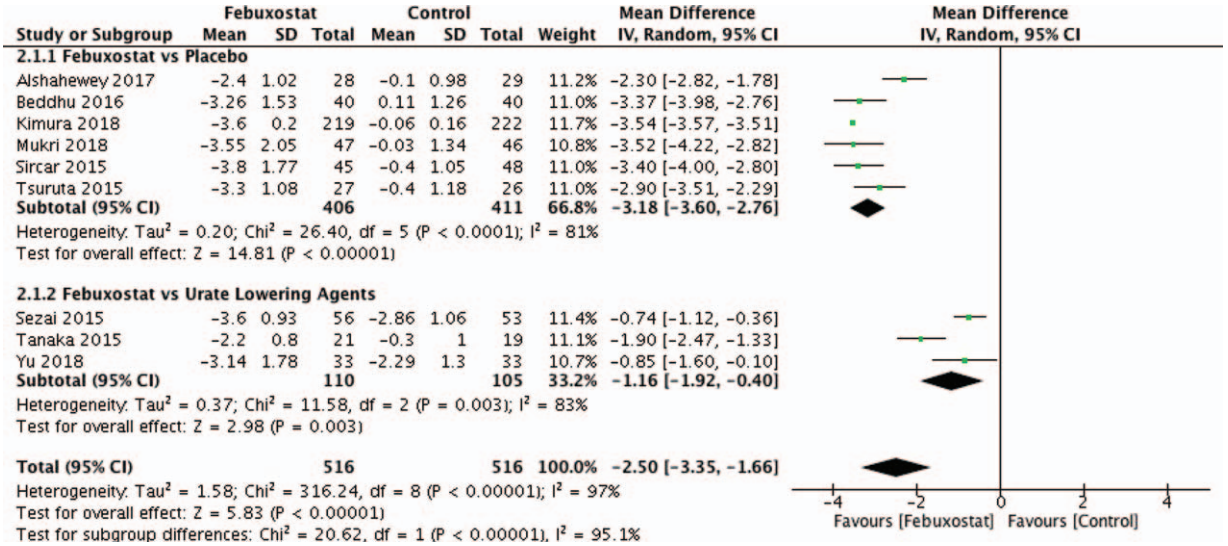

Figure 2. The effect of febuxostat on serum uric acid. (2.1.1) Febuxostat compared with placebo. (2.1.2) Febuxostat compared with urate lowering agents.

double-blind RCTs,[27,30–33,35] whereas one was a single-blind RCT.[26] Four studies used the open-label method in designing the RCTs,[28,29,34,36] where all the outcomes except for adverse outcome reporting and blood pressure were measured through lab tests using blood and urine. One study was a sub-analysis of patients with CKD from a RCT (NU-FLASH trial) in 2013.[26] Three studies described the allocation concealment methods used.[27,28,35] Methods used for outcome analysis were intention to treat (ITT) in three studies,[32–34] modified ITT in 4 studies,[27,30,31,35] and per protocol in 4 studies.[26,28,29,36] Safety outcomes were reported in nine RCTs comparing febuxostat with control.

Regarding the risk of bias for each RCT, some of them had high risk of certain biases. Two studies were funded by Takeda Pharmaceuticals,[30,35] and the sponsoring authors were involved in designing and writing the study manuscript in one of the study.[30] One study was funded by Teijin Pharma Limited,[33] and the other was partly supported by Teijin Pharma Limited.[26] One study used a single-blind design; the lack of blinding of participants and personnel may result in high risk of bias.[26] Furthermore, high risk resulted from utilizing the study method of performing sub-analysis of the RCT.[26] Four studies used an open-label design, which also produces high risk from the lack of blinding of participants and personnel.[28,29,34,36] Three studies employed no blinding in their adverse outcome assessment, which may result in a high risk of bias.[28,34,36] Furthermore, the sample sizes of the studies were relatively small, which may limit the generalizability. The overall quality of all trials was fair after risk of bias assessment.

4. Discussion

We performed a systematic review and meta-analysis to assess the efficacy, reno-protective effect, and safety of febuxostat in patients with CKD. We included eleven studies with 1317 participants.[26–36] Patients on febuxostat showed a superior SUA-lowering effect compared with those in the control group. No statistically significant difference in the biomarkers of renal function, including eGFR and serum creatinine, was observed when comparing patients on febuxostat treatment with those in the control group. However, after subgroup analysis of changes in eGFR in three studies with study participants of CKD stage 3 and 4, a significant reno-protective effect was observed in the febuxostat group.[26,27,34] When analyzing the changes in serum creatinine, no significant difference was seen. However, after subgroup analysis of studies with treatment duration greater or equal to 6 months, a significantly lower serum creatinine in the patients with febuxostat treatment compared with those in the control group were observed.[26,36] In terms of the safety of febuxostat, nine trials reported different outcomes of adverse events.

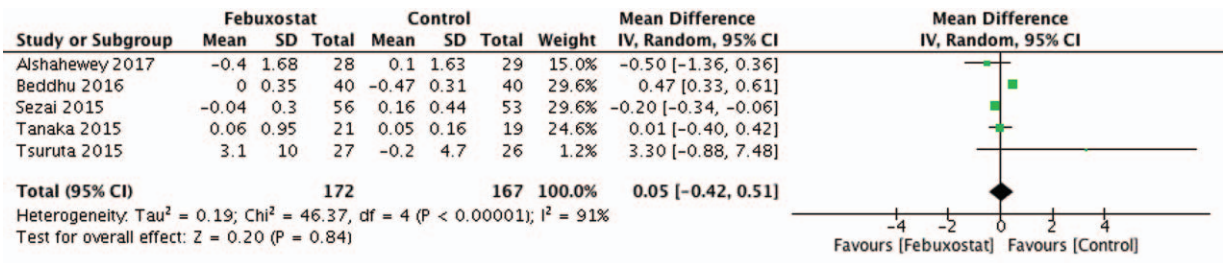

Figure 3. The effect of febuxostat compared with control group on high-sensitivity C-reactive protein (hsCRP).

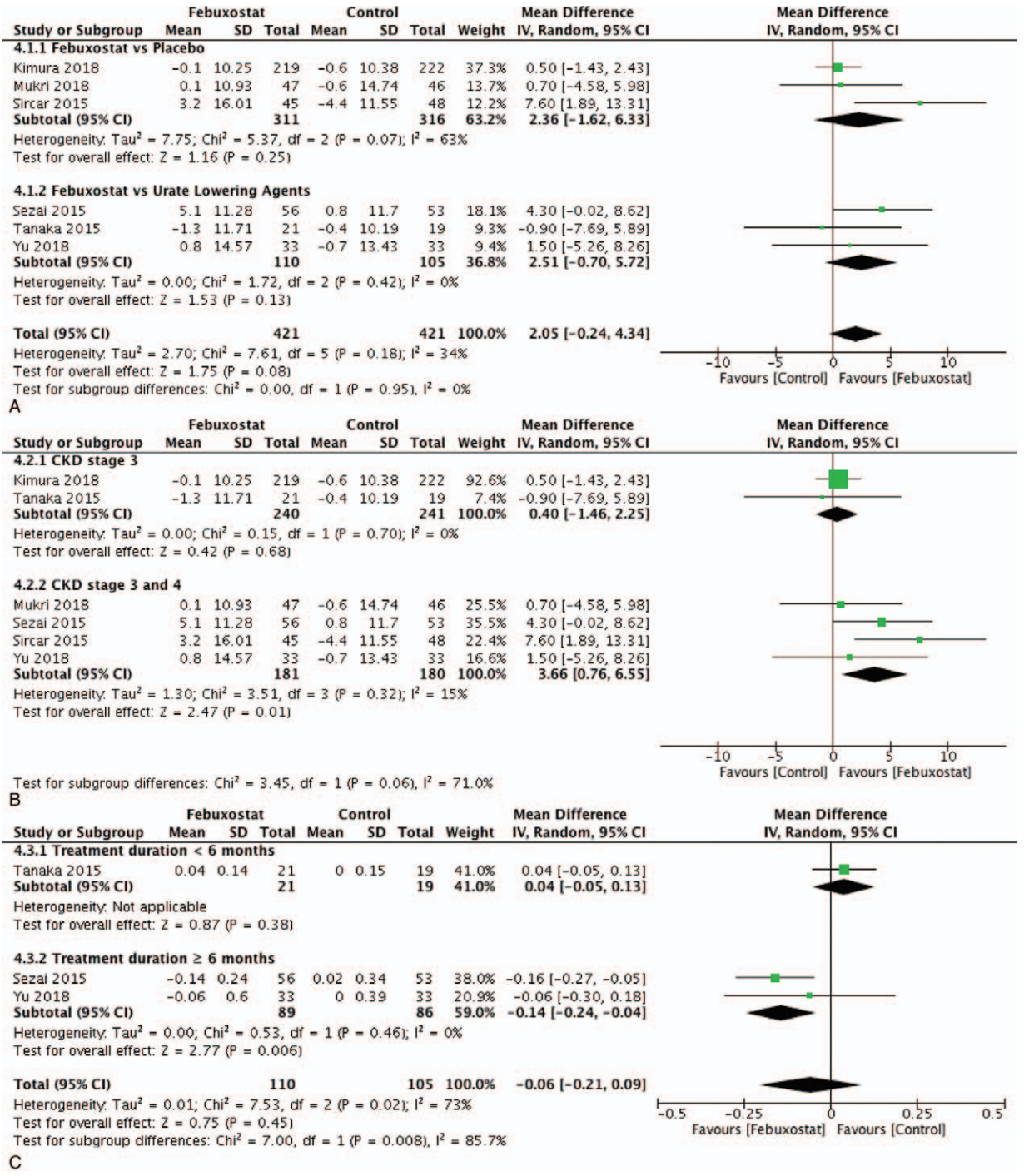

Figure 4. 4.1. The effect of febuxostat on estimated Glomerular Filtration Rate (eGFR). (4.1.1) Febuxostat compared with placebo. (4.1.2) Febuxostat compared with urate lowering agents. 4.2. The effect of febuxostat compared with control group on eGFR. (4.2.1) studies with only chronic kidney disease (CKD) stage 3 participants. (4.2.2) studies with both CKD stage 3 and 4 participants. 4.3. The effect of febuxostat compared with control group on serum creatinine. (4.3.1) Treatment duration less than 6 months. (4.3.2) treatment duration greater or equal to 6 months.

Outcomes including rash, diarrhea, change in blood pressure, joint pain and increase in liver function were noted. Mukri et al also noted a trend of higher incidence of cardiovascular events with the use of febuxostat; however, no significant difference was observed.[34]

Previous studies have performed systemic review and meta-analysis on randomized controlled trials on urate-lowering therapies and assessed their effects on kidney function.[37–43] Wang et al analyzed 11 trials with 753 patients and also evaluated the effect of urate-lowering agents, including allopurinol, rasburicase and benzbromarone, which showed a decrease in serum creatinine and increase in eGFR in the treatment arm, thereby proposing the beneficial effect of urate-lowering therapy in renal function.[37] Meanwhile, Bose et al analyzed 8 trials with

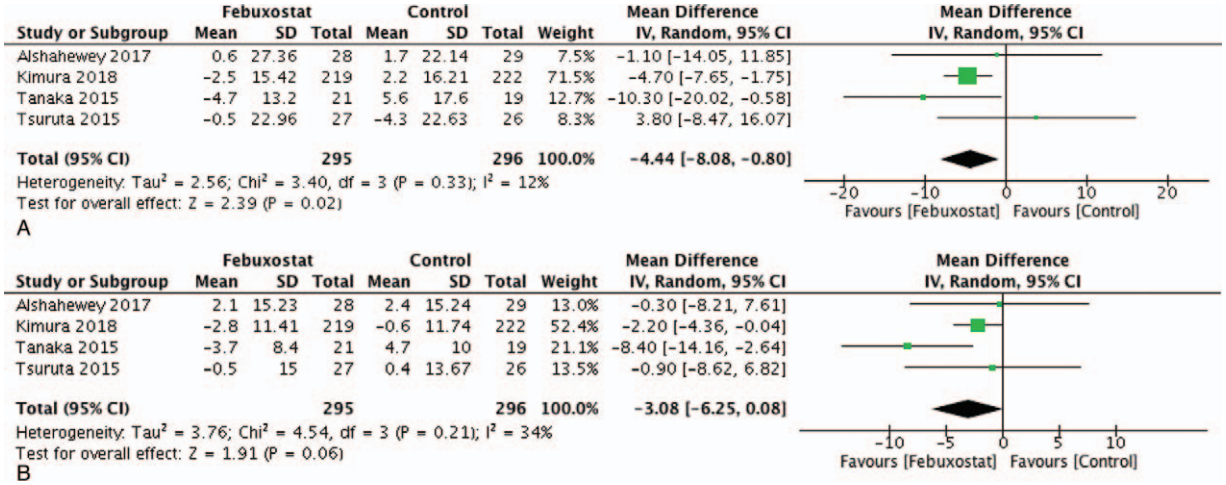

Figure 5. 5.1. The effect of febuxostat compared with control group on Systolic Blood Pressure (SBP). 5.2. The effect of febuxostat compared with control group on diastolic blood pressure (DBP).

476 participants and evaluated the effect of allopurinol in patients with or without CKD, and showed that allopurinol may retard CKD progression.[38] Kanji et al also analyzed 19 trials with 992 participants with stage 3 to 5 CKD and evaluated the effect of urate-lowering therapies, including allopurinol, benzbromarone, losartan, amlodipine, and rasburicase; they showed a statistically significant improvement in serum creatinine and eGFR, favoring allopurinol.[39] Kim et al analyzed 4 studies with 157 participants and evaluated the effect of febuxostat compared with allopurinol.[40] A possible reno-protective effect in febuxostat over allopurinol was seen. Su et al analyzed 16 trials with 1211 patients with CKD and evaluated the effect of allopurinol, pegloticase, and febuxostat.[41] They showed that an effect of uric acid-lowering therapy on improvement of kidney outcomes in adults with CKD may be seen. Sampson et al analyzed 12 studies with 1187 participants with or without CKD and evaluated the effect of allopurinol and oxypurinol.[42] A possible effect of uric acid-lowering therapy on CKD progression prevention may be seen. Pisano et al analyzed nine trials with 695 participants with or without CKD and evaluated the effect of allopurinol, topiroxstat, and febuxostat, and showed that xanthine oxidase inhibitors may be used in retarding CKD progression.[43] However, our study assessed the efficacy and safety of solely febuxostat in patients with CKD. Our results showed a trend towards a reno-protective effect when assessing the eGFR of the patients. Moreover, the results of studies including CKD stage 4 patients showed a significantly higher eGFR in the febuxostat group compared with the control group.

Febuxostat is a nonpurine analogue inhibitor of xanthine oxidase.[44] It was approved by the US FDA in 2009 for gout treatment.[22] It is mainly metabolized to acyl-glucuronide metabolites in the liver,[44] and is well-tolerated in patients with moderate to severe renal impairment.[24] Conversely, allopurinol is mainly excreted through urine and may cause toxicity if used in patients with renal dysfunction.[45] Moreover, compared with allopurinol, febuxostat is a more selective and potent urate-lowering drug.[44,46] Febuxostat selectively inhibits only xanthine oxidase and no other purine-metabolising enzymes. In addition, allopurinol inhibits other enzymes such as purine nucleoside phosphorylase and orotidine-5′-monophosphate decarboxylase.[44] As for potency, febuxostat can inhibit both the oxidized and reduced forms of xanthine oxidase.[44,47] However, allopurinol and its metabolite, oxypurinol, can inhibit only the oxidized form and the reduced form of xanthine oxidase, respectively. A recent network meta-analysis showed a positive effect in the febuxostat group, particularly at a 120 mg dosage of QD when compared with other urate-lowering therapies.[17] Thus, febuxostat is a more competent uric acid-lowering agent.[17,44,46]

When compared with benzbromarone, febuxostat may also be a more suitable choice for patients with chronic kidney disease. Although benzbromarone has been proven to be effective in patients with mild to moderate CKD patients,[48] it is not recommended in patients with eGFR < 30 mL/min.[49] Moreover, severe adverse effects for benzbromarone, including hepatotoxic effects, have been reported, leading to it being withdrawn from US and several European countries.[50]

Hyperuricemia occurs in 25.3% of the population.[4] Its association with CKD development has been well-illustrated. Animal studies have shown that hyperuricmeia can cause CKD progression.[9,10] Furthermore, clinical studies have shown a clear association of hyperuricemia with CKD,[51–53] but the causal relationship has been poorly illustrated.[16] Our study showed a significant decrease in SUA in patients with CKD using febuxostat and a slowed eGFR deterioration in patients with more severe CKD. This might provide some insight on the causal relationship of hyperuricemia and CKD progression. Febuxostat, a well-tolerated drug in patients with renal insufficiency,[23,24,54] might be a treatment option in patients with CKD and hyperuricemia.

The strengths of this review include a comprehensive search for relevant studies, systematic and explicit application of eligibility criteria, careful consideration of study quality, and a rigorous analytical approach. We analyzed detailed relevant outcomes including change of SUA, hsCRP, eGFR, serum creatinine, blood pressure and any adverse effect. However, as with all other meta-analyses, our study has some limitations. First, the number of studies included was relatively small. We found only 11 relevant RCTs despite our comprehensive search strategy. Second, the studies that we included used relatively small sample sizes,

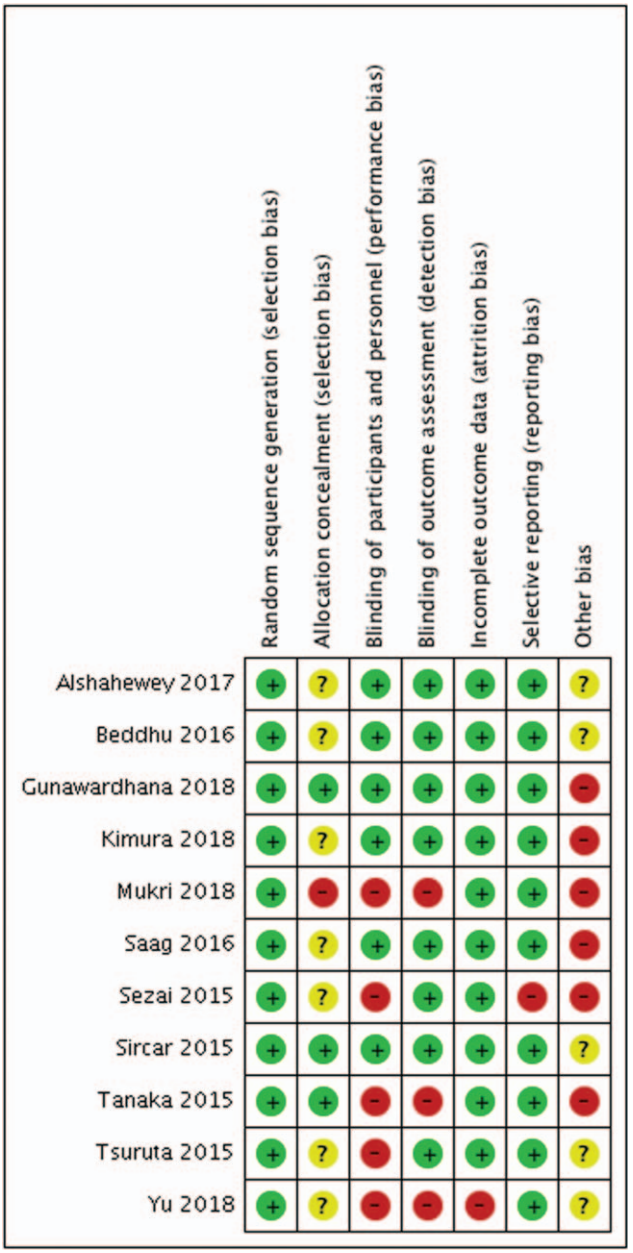

Figure 6. Assessment of the methodological quality of the included studies.

ranging from 40 to 441 participants. Third, the follow-up time in the 11 studies was relatively short with large variation, ranging from 1 to 24 months. When analyzing the safety profile of febuxostat treatment, we assessed various outcomes. Moreover, the differences in febuxostat dosage, the regimen, and the follow-up time contributed to heterogeneity.

In conclusion, our meta-analysis shows that other than its urate-lowering effect, febuxostat has a reno-protective effect in CKD patients. This study has provided us with greater insight into the causal relationship of hyperuricemia and CKD progression, and indicates a possible treatment for the aforementioned population. Febuxostat, apart from its urate-lowering effect, may be used in slowing the deterioration of patients with CKD. More RCTs with larger sample sizes and higher quality are required to clarify the role of febuxostat use in the progression of CKD.

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