Joint Diseases and Related Surgery

Jt Dis Relat Surg
2025;36(3):562-576

ORIGINAL ARTICLE

The efficacy and safety of different doses of febuxostat and allopurinol: A meta-analysis

Feng Zhang, Yanyan Wang

Department of Medicament, The First College of Clinical Medical Science, China Three Gorges University, Yichang, China

ABSTRACT

Objectives: This meta-analysis aims to explore the treatment effects and safety of different doses of febuxostat and allopurinol in patients with gout.

Materials and methods: We systematically searched electronic databases and included randomized-controlled trials (RCTs) evaluating the effects of different doses of febuxostat and allopurinol on the number of patients with serum uric acid (SUA) levels ≤6.0 mg/dL, as well as on SUA levels, gout attack incidence and adverse events (AEs) in patients with gout. We calculated pooled effect sizes, including standardized mean differences (SMDs), relative risks (RRs) or risk differences (RDs), using a random-effects model, and estimated the range of effects using 95% confidence intervals (CIs). A total of 16 RCTs involving 19,683 patients were included.

Results: The results showed that compared to allopurinol, febuxostat significantly increased the number of patients with SUA levels ≤6.0 mg/dL, particularly at doses of 40-80 mg/day (RR=1.14, 95% CI: 1.00, 1.30) and >80 mg/day (RR=2.75, 95% CI: 1.68, 4.49). Febuxostat also significantly improved SUA levels (SMD=−0.70, 95% CI: −1.02, −0.37), but had no significant effect on gout attack risk (RR=1.13, 95% CI: 0.94, 1.35). The risk of any-grade AEs was lower in the febuxostat group than in the control group (RR=0.95, 95% CI: 0.93, 0.98), but there were no significant differences in treatment-related AEs (RR=0.99, 95% CI: 0.92, 1.07) and serious AEs (RD=−0.01, 95% CI: −0.02, 0.00).

Conclusion: Overall, compared to allopurinol, febuxostat significantly improves SUA levels in patients with gout and has a certain safety profile. However, more high-quality studies are needed to further explore its efficacy.

Keywords: Allopurinol, efficacy, febuxostat, safety, meta-analysis.

Gout, a metabolic arthritis caused by monosodium urate crystal deposition, is directly related to hyperuricemia resulting from abnormal purine metabolism and impaired uric acid excretion.[1] With socioeconomic development and dietary changes, the global gout burden has risen, marked by a 22.5% increase in age-standardized prevalence from 1990 to 2020.[2] The condition exhibits significant aging characteristics, with higher prevalence in older populations.[3] Epidemiological studies also indicate a rising incidence of gout.[4-6] Notably, the impact of gout extends beyond joint disease; it is an independent risk factor for cardiovascular diseases.[7,8] Large-scale cohort studies have shown a 20% increase in coronary heart disease risk with each 1 mg/dL serum uric acid (SUA) rise,[9] and urate-lowering therapy can reduce all-cause mortality by around 22%,[10] underscoring the clinical value of effective urate-lowering treatment.

Current international guidelines recommend the sustained control of SUA below 6 mg/dL as the core goal of gout treatment, a threshold below the saturating concentration of monosodium urate, which effectively promotes crystal dissolution and reduces acute attacks.[11,12] Among the choices of uric acid-lowering drugs, xanthine oxidase inhibitors (XOIs) have become the preferred regimen because of their precise efficacy, with allopurinol having been clinically used as a traditional XOI

Received: March 07, 2025
Accepted: June 27, 2025
Published online: July 21, 2025

Correspondence: Yanyan Wang, MD. Department of Medicament, The First College of Clinical Medical Science, China Three Gorges University, Yichang, Hubei 443000, China.

E-mail: wang_yyan@yeah.net

Citation: Zhang F, Wang Y. The efficacy and safety of different doses of febuxostat and allopurinol: A meta-analysis. Jt Dis Relat Surg 2025;36(3):562-576. doi: 10.52312/jdrs.2025.1976.

©2025 All right reserved by the Turkish Joint Diseases Foundation

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes (http://creativecommons.org/licenses/by-nc/4.0/).

drug for more than half a century. However, pharmacokinetic studies have shown that the uric acid-lowering effect of allopurinol exhibits significant individual differences, and there is a risk of serious hypersensitivity reactions.[13,14] Through dual inhibition of oxidative and reductive xanthine oxidase, febuxostat, a novel selective XOI, is mainly metabolized in the liver and excreted through the kidneys and intestines following oral administration and has shown promising efficacy in lowering uric acid and enhancing renal protection compared with other drugs.[15,16] Several studies have reported the clinical efficacy and safety of different doses of febuxostat compared to allopurinol in the treatment of hyperuricemia; however, the sample sizes included in a single study relatively small and the results were inconsistent across studies.[17-19] Although meta-analyses have compared the efficacy and safety of the two drugs, they have focused mainly on the overall comparison of the drugs themselves, ignoring the importance of dose on treatment efficacy and safety.[20,21] Although two recent meta-analyses examined the clinical efficacy of differential febuxostat dosages, their omission of newly published evidence may introduce potential bias.[22,23] In this meta-analysis, we compare the therapeutic effects and safety of different doses of febuxostat versus allopurinol in patients with gout, clarify the drug dose-efficacy relationship, and provide evidence-based guidance for clinical practice.

MATERIALS AND METHODS

Search strategy

In line with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 Statement,[24] we systematically searched four electronic databases, PubMed, Web of Science, Cochrane Library and Embase, from their inception to 20 April 2025. The search terms included: 'Gout', 'Febuxostat' and 'Allopurinol'. The search strategy was as follows: ('gout'[MeSH Terms] OR 'gout'[All Fields]) AND ('febuxostat'[MeSH Terms] OR 'febuxostat'[All Fields]) AND ('allopurinol'[MeSH Terms] OR 'allopurinol'[All Fields] OR 'allopurinols'[All Fields]). In addition, to expand the scope of included studies, we further screened the target literature by reviewing the references of included studies.

Inclusion and exclusion criteria

Inclusion criteria were as follows: *(i)* peer-reviewed Chinese or English studies on the efficacy and safety of different doses of febuxostat and allopurinol for gout treatment; *(ii)* participants diagnosed with gout or hyperuricemia, based on the American College of Rheumatology criteria or SUA≥480 μmol/L (8.0 mg/dL),[25] with no restrictions on age, sex or disease duration; *(iii)* interventions were febuxostat and allopurinol; *(iv)* at least one outcome indicator was reported: post-treatment SUA level, number of participants with SUA≤6.0 mg/dL or adverse event (AE) rate; and *(v)* study design was a randomized-controlled trial (RCT).

Exclusion criteria included *(i)* non-human studies; *(ii)* conference papers, case reports, systematic reviews, etc.; *(iii)* incomplete outcome data; *(iv)* duplicate reports; and *(v)* unavailable full texts.

Literature screening and data extraction

Two researchers independently screened the literature against the inclusion/exclusion criteria. Initially, titles and abstracts were reviewed, followed by full-text reading of potentially eligible studies. In the case of disagreements, a third researcher was consulted. Following screening, the two researchers separately extracted data using a standardized form, covering literature details, participant demographics, febuxostat/allopurinol doses and duration, and outcome data.

Quality assessment

We assessed literature quality using the Cochrane Collaboration's risk-assessment tool,[26] which evaluates randomization, allocation concealment, blinding, data completeness, outcome reporting and other bias sources.

Statistical analysis

Statistical analysis was performed using the RevMan version 5.3 software (The Cochrane Collaboration, UK). Continuous data were expressed in standardized mean differences (SMDs) and count data as relative risks (RRs). When zero events occurred in included studies,[27] risk differences (RDs) were used for meta-analysis. Effect sizes were estimated using 95% confidence intervals (CIs). Given that the random-effects model is more conservative than the fixed-effects model, we chose the former to address potential cross-study and cross-population effect differences.[26,28] Subgroup analyses were conducted for the following febuxostat doses: ≤40, 40-80 and >80 mg/day. Heterogeneity was assessed using the Q-test and I^2 statistic. If I^2<50% or p>0.05, good homogeneity was assumed.

Sensitivity analysis was performed by excluding the included studies one by one. A p value of <0.05 was considered statistically significant.

RESULTS

Characteristics of included studies

Following a systematic search of Chinese and English databases, 1,768 studies were included in the screening process. After excluding duplicates and irrelevant studies, 72 articles proceeded to full-text review. Ultimately, 16 studies.[17-19,29-42] were included (Figure 1). These studies were published between 2005 and 2024, mainly from China (n=6) and the United States (n=5). All were RCTs, with 14 multi-center and nine double-blinded designs. They involved 19,683 patients, with 11,241 in the febuxostat group (doses: 10-240 mg) and 8,442 in the allopurinol group (doses: 100-300 mg). Most participants were men and had a high body mass index. More details are presented in Table I.

Literature quality assessment

After assessing the literature quality using the Cochrane Collaboration's risk-assessment tool, all 16 included studies were found to be of high quality. However, seven studies had a high risk of bias in blinding due to their open-label design (Figures 2 and 3).

Serum uric acid level ≤6.0 mg/dL

A meta-analysis based on a random-effects model showed a significant increase in the number of patients with SUA levels ≤6.0 mg/dL following treatment with febuxostat compared to allopurinol (RR: 1.65; 95% CI: 1.40, 1.94). The treatment effects varied across different febuxostat dosages. Six studies reporting outcomes with febuxostat ≤40 mg/day showed a 1.14-fold increased likelihood of attaining SUA levels ≤6.0 mg/dL compared to allopurinol (95% CI: 1.00, 1.30). Ten studies evaluating febuxostat 40-80 mg/day demonstrated greater efficacy, with a 1.66-fold higher achievement rate compared to allopurinol (95% CI: 1.45, 1.90). Notably, two studies investigating high-dose febuxostat (>80 mg/day) revealed the most pronounced effect, yielding a 2.75-fold increased probability of reaching target SUA levels compared with allopurinol (95% CI: 1.68, 4.49) (Figure 4). Furthermore, a leave-one-out sensitivity analysis was performed by sequentially excluding each included study. The results demonstrated

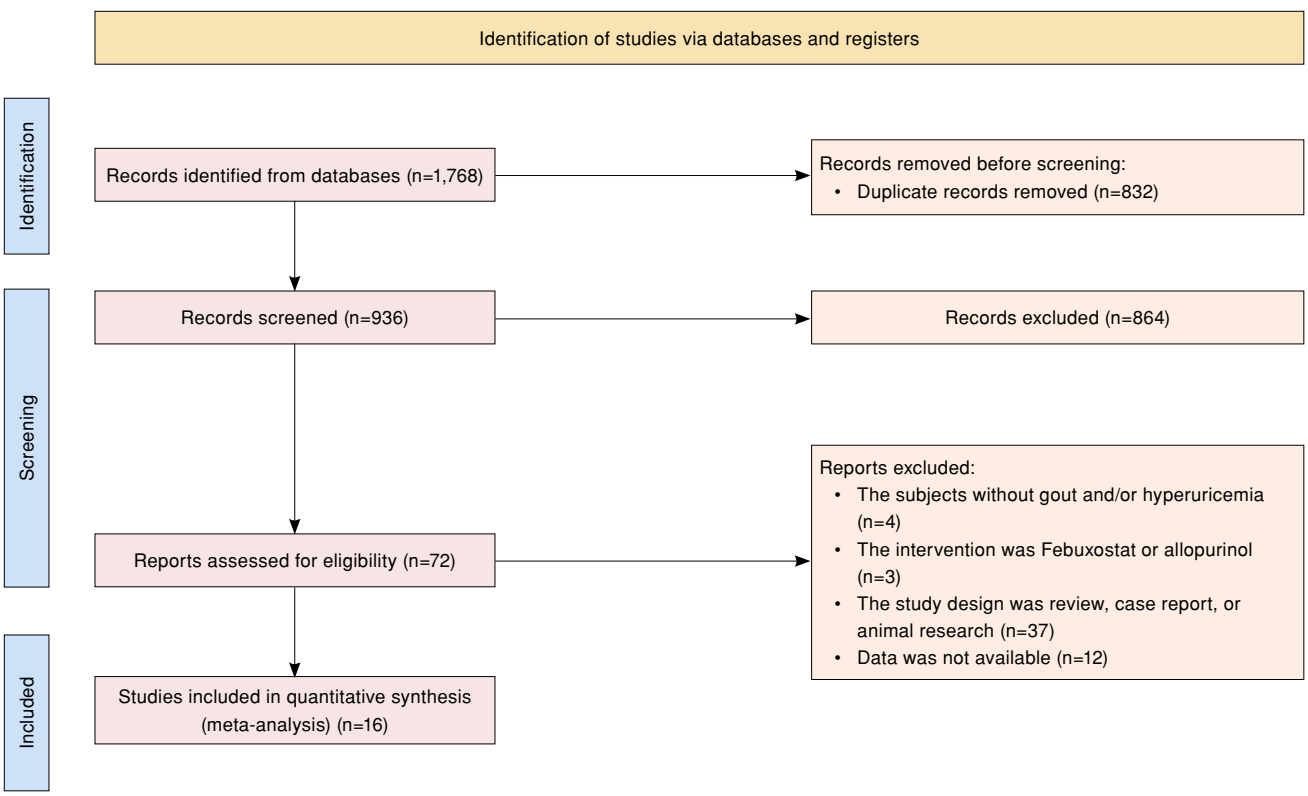


FIGURE 1. Study flowchart.

TABLE I
Basic information of included studies

Study	Location	Study design	Duration	Patients	Intervention	Sample size	Age	Male (%)	BMI	Years with gout	Baseline serum uric acid (mg/dL)
Becker et al.,[17] 2005	USA, Canada	RCT, double-blind, multicenter	52 weeks	Adults patients with gout and with serum urate concentrations of at least 8.0 mg per deciliter	Febuxostat 80 mg/d	256	51.8±11.7	95	32.7±6.1	11.5±9.4	9.80±1.24
					Febuxostat 120 mg/d	251	52.0±12.1	79	32.3±5.7	12.6±9.9	9.84±1.26
					Allopurinol 300 mg/d	253	51.6±12.6	77	32.6±6.1	11.6±9.3	9.90±1.23
Schumacher et al.,[18] 2008	USA	RCT, double-blind, multicenter	28 weeks	Adults (18-85) patients with gout and with serum urate concentrations of at least 8.0 mg per deciliter	Febuxostat 80 mg/d	267	51±12	94	33±6	11±9	9.85±1.263
					Febuxostat 120 mg/d	269	51±12	95	33±7	12±9	9.85±1.263
					Febuxostat 240 mg/d	134	54±13	94	33±7	11±9	9.85±1.263
					Allopurinol 300 mg/d	268	52±12	93	33±6	11±9	9.85±1.263
Becker et al.,[29] 2009	USA, Canada	RCT, open-label, multicenter	6 months	Adults patients with gout and with serum urate concentrations of at least 8.0 mg per deciliter	Febuxostat 80 mg/d	649	51.4±11.95	NA	32.3±5.78	NA	9.83±1.252
					Febuxostat 120 mg/d	292	50.9±11.57	NA	33.2±6.17	NA	9.74±1.281
					Allopurinol 300 mg/d	145	51.0±11.30	NA	33.8±6.79	NA	9.82±1.157
Becker et al.,[30] 2010	USA	RCT, double-blind, multicenter	24 weeks	Adults (18-85) patients with gout and with serum urate concentrations of at least 8.0 mg per deciliter	Febuxostat 40 mg/d	757	52.5±11.68	95.4	32.9±6.37	12.0±9.13	9.6±1.15
					Febuxostat 80 mg/d	756	53.0±11.79	93.9	32.9±6.39	11.7±9.64	9.6±1.20
					Allopurinol 300 mg/d	756	52.9±11.73	93.8	32.7±6.23	11.2±9.14	9.5±1.19

TABLE I
Continued

Study	Location	Study design	Duration	Patients	Intervention	Sample size	Age	Male (%)	BMI	Years with gout	Baseline serum uric acid (mg/dL)
Kamatani et al.,[31] 2011	Japan	RCT, open-label, multicenter	16 weeks	Adults (>=20) patients had hyperuricemia, including gout	Febuxostat 40 mg/d	10	56.0±8.2	100			
					Febuxostat 60 mg/d	10	53.3±11.0	90	NA	NA	NA
					Allopurinol 300 mg/d	20	51.3±12.0	95			
Huang et al.,[32] 2014	China	RCT, double-blind, multicenter	28 weeks	Adults (18-70) patients with gout and with serum urate concentrations of at least 8.0 mg per deciliter	Febuxostat 40 mg/d	172	46.42±10.90	97.1	25.63±2.80	NA	9.89±1.36
					Febuxostat 80 mg/d	172	47.40±11.18	98.3	25.25±2.64	NA	9.98±1.39
					Allopurinol 300 mg/d	172	46.17±11.56	97.7	25.44±2.53	NA	9.95±1.35
Kim et al.,[33] 2014	Korea	RCT, double-blind, multicenter	4 weeks	Male adults with gout with serum urate concentrations of at least 8.0 mg per deciliter	Febuxostat 40 mg/d	35	49.6±11.9	100	26.4±3.5	NA	9.7±1.1
					Febuxostat 80 mg/d	35	49.1±12.4	100	25.4±2.6	NA	9.5±1.3
					Febuxostat 120 mg/d	36	51.2±9.9	100	25.9±2.1	NA	9.5±1.0
					Allopurinol 300 mg/d	36	48.3±11.8	100	25.9±3.2	NA	9.5±1.0
Xuet al.,[34] 2015	China	RCT, double-blind, multicenter	24 weeks	Adults (18-70) patients with gout and with serum urate concentrations of at least 8.0 mg per deciliter	Febuxostat 40 mg/d	160	45.5±11.9	98.8	25.3±2.7	2.7 (1.0-5.8)	560.8±73.3
					Febuxostat 80 mg/d	158	48.2±12.0	92.4	25.1±2.6	3.0 (1.2-5.1)	565.1±75.5
					Allopurinol 300 mg/d	159	46.6±10.7	93.7	25.4±3.3	3.0 (2.0-6.9)	574.2±77.8

TABLE I
Continued

Study	Location	Study design	Duration	Patients	Intervention	Sample size	Age	Male (%)	BMI	Years with gout	Baseline serum uric acid (mg/dL)
Yu et al.,[35] 2016	China, Taiwan	RCT, open-label, multicenter	12 weeks	Adults (20-65) patients with gout and with serum urate concentrations of at least 8.0 mg per deciliter	Febuxostat 80 mg/d	54	46.0±11.0	98.1	26.8±3.7	NA	NA
					Allopurinol 300 mg/d	55	45.2±12.0	96.4	27.8±4.2	NA	NA
Zhang et al.,[19] 2019	China	RCT, double-blind, multicenter	24 weeks	Adults (18-85) with gout and with serum urate concentrations of at least 8.0 mg per deciliter	Febuxostat 40 mg/d	181	46.5±11.9	99.4	26.1±3.2	NA	9.6±1.5
					Febuxostat 80 mg/d	188	47.2±12.9	97.9	25.7±3.2	NA	9.6±1.5
					Allopurinol 300 mg/d	184	48.3±13.1	98.9	26.0±3.4	NA	9.8±1.4
Mackenzie et al.,[37] 2020	UK, Denmark, Sweden	RCT, open-label, multicenter		Adults (≥60) with gout	Febuxostat 80-120 mg/d	3063	71.0±6.4	85.5	31.0±5.1	NA	NA
					Allopurinol 100-300 mg/d	3065	70.9±6.5	85	31.2±5.3	NA	NA
Desideri et al.,[38] 2022	Italy	RCT, open-label, multicenter	36 weeks	Adults with a history of gout and elevated SUA levels	Febuxostat 80 mg/d	98	58.66±10.83	82.7	31.68±5.5	NA	9.47±1.05
					Allopurinol 100 mg/d	98	60.52±10.35	81.6	31.51±4.91	NA	9.19±1.04
Saag et al.,[39] 2022	USA	RCT, double-blind, multicenter	32 months	Adults (male ≥50, female ≥55) with gout	Febuxostat 40-80 mg/d	3098	65 (44-93)	83.9	33.5±6.92	11.8±11.4	8.7±1.7
					Allopurinol 300 mg/d	3092				11.9±11.2	8.7±1.7
Yanget al.,[40] 2022	China	RCT, double-blind, multicenter	6 months	Chronic kidney disease patients complicated with hyperuricemia	Febuxostat 20 mg/d	60	62.2±9.2	75	23.8±2.9	NA	9.06±1.51
					Allopurinol 200 mg/d	60	61.7±6.9	71.7	23.8±2.8		9.19±1.71

no substantial reduction in heterogeneity (I^2 change <10%), and the overall findings remained statistically consistent, indicating the robustness of the analytical outcomes.

Serum uric acid levels

The meta-analysis based on a random-effects model revealed that febuxostat treatment significantly reduced SUA levels compared with allopurinol (SMD: −0.70; 95% CI: −1.02, −0.37). The magnitude of effect varied across different febuxostat dosages. Four studies reporting outcomes with febuxostat ≤40 mg/day showed no statistically significant improvement in SUA levels (SMD: −0.29; 95% CI: −0.93, 0.35). In contrast, febuxostat 40-80 mg/day (n=5; SMD: −0.88; 95% CI: −1.29, −0.87) and febuxostat >80 mg/day (n=2; SMD: −1.04; 95% CI: −1.22, −0.87) demonstrated statistically significant reductions in SUA levels (Figure 5). Furthermore, a leave-one-out sensitivity analysis was performed by sequentially excluding each included study. The results demonstrated no substantial reduction in heterogeneity (I^2 change <15%), and the overall findings remained statistically consistent, indicating the robustness of the analytical outcomes.

Acute gout

The meta-analysis based on a random-effects model demonstrated that febuxostat did not exhibit a statistically significant difference in the risk of acute gout compared to allopurinol (RR: 1.13; 95% CI: 0.94, 1.35). Subgroup analyses stratified by febuxostat dosage revealed similar trends: the ≤40 mg/day subgroup had a RR of 0.85 (95% CI: 0.51-1.40), the 40–80 mg/day subgroup had an RR of 1.04 (95% CI: 0.92-1.18) and the >80 mg/day subgroup demonstrated an RR of 1.63 (95% CI: 0.96-2.75) (Figure 6). Furthermore, a leave-one-out sensitivity analysis was performed by sequentially excluding each included study. The results demonstrated no substantial reduction in heterogeneity (I^2 change <10%) and the overall findings remained statistically consistent, indicating the robustness of the analytical outcomes.

Adverse events

The meta-analysis based on a random-effects model indicated that febuxostat was associated with a slightly lower risk of any-grade AEs compared to allopurinol (RR: 0.95; 95% CI: 0.93, 0.98). This trend was observed only in the febuxostat 40–80 mg/day (RR: 0.95; 95% CI: 0.91, 0.99) and >80 mg/day (RR: 0.95; 95% CI: 0.91, 0.98) subgroups (Figure 7). Furthermore, the effects of febuxostat versus allopurinol on

TABLE I Continued

Study	Location	Study design	Duration	Patients	Intervention	Sample size	Age	Male (%)	BMI	Years with gout	Baseline serum uric acid (mg/dL)
Chen et al.,[41] 2024	China	RCT, open-label, single center	24 weeks	Patients with gout	Febuxostat 80 mg/d	49	52.18±12.38	63.3	22.98±2.32	7.91±2.22	521.91±18.92
					Allopurinol 300 mg/d	49	52.03±12.07	67.3	23.87±2.21	7.65±2.39	519.67±19.38
Nakagomi et al.,[42] 2015	Japan	RCT, open-label, single center	12 months	Patients with chronic heart failure and hyperuricemia	Febuxostat 10-40 mg/d	31	69.3±10.0	71	23.6±2.4	NA	9.4±0.5
					Allopurinol 100-300 mg/d	30	71.8±8.0	69	23.1±3.1	NA	9.3±0.5

RCT: Randomized-controlled trial; BMI: Body mass index; NA: Not available.

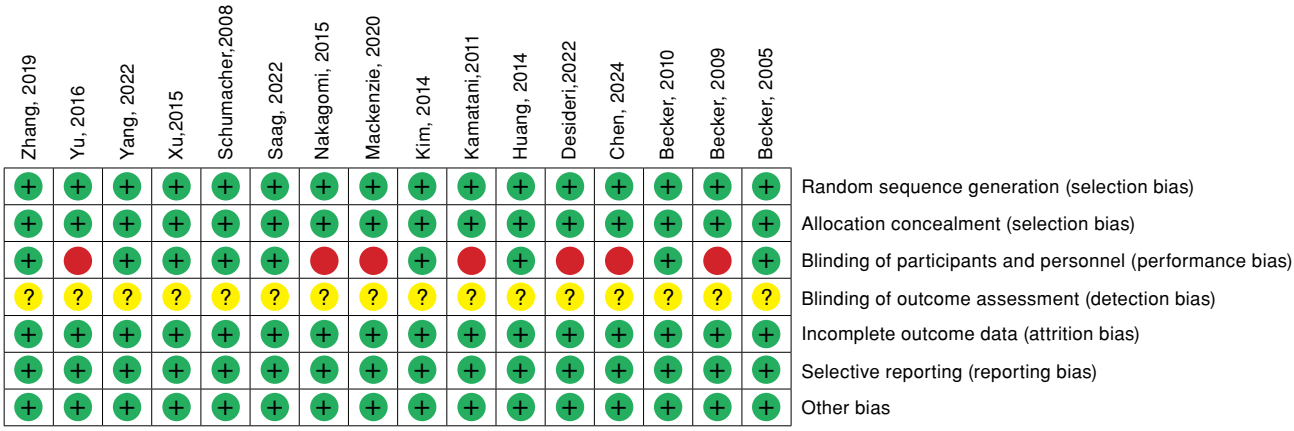


FIGURE 2. Risk of bias summary.

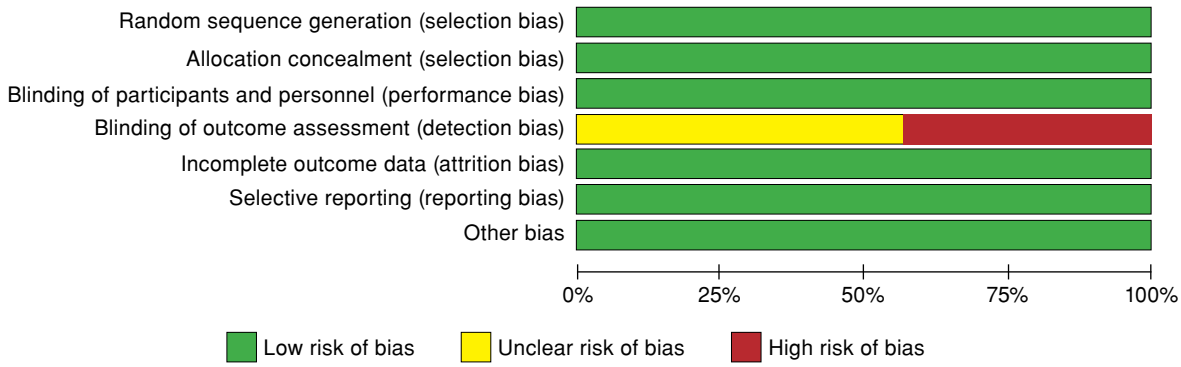


FIGURE 3. Risk of bias graph.

treatment-related AEs (TRAEs) and serious AEs (SAEs) were evaluated. The meta-analysis revealed no statistically significant differences in TRAEs (RR: 0.99; 95% CI: 0.92, 1.07) (Supplementary Figure 1) or SAEs (RD: −0.01; 95% CI: −0.02, 0.00) (Supplementary Figure 2). Subgroup analyses stratified by febuxostat dosage demonstrated consistent results. Additionally, febuxostat demonstrated no significant impact on the risks of hepatic dysfunction (RR: 0.99; 95% CI: 0.92, 1.07) (Supplementary Figure 3) or cardiovascular events (RD: 0.00; 95% CI: −0.01, 0.01) (Supplementary Figure 4).

DISCUSSION

In this meta-analysis of prospective studies, we systematically evaluated the efficacy and safety of febuxostat at different dosages compared to allopurinol. Sixteen studies of moderate to high quality were included, demonstrating that febuxostat significantly outperformed allopurinol in achieving SUA levels ≤6.0 mg/dL, with a potential dose-dependent effect. The impact on SUA reduction varied across dosage groups, with significant improvements observed in higher-dose regimens (40-80 and >80 mg/day). Regarding safety, febuxostat exhibited an acceptable profile, particularly for TRAEs and SAEs. The findings of the present study are consistent with prior research regarding the dose-response relationship of allopurinol in urate-lowering efficacy and safety.[20-23] This updated analysis comprehensively compares the efficacy and safety of febuxostat dosages versus allopurinol in gout patients, incorporating the most recent evidence to inform clinical decision-making.

Febuxostat, approved in the United States in 2009 and in China in 2013, expanded therapeutic options for gout and hyperuricemia, particularly for patients intolerant to conventional urate-lowering

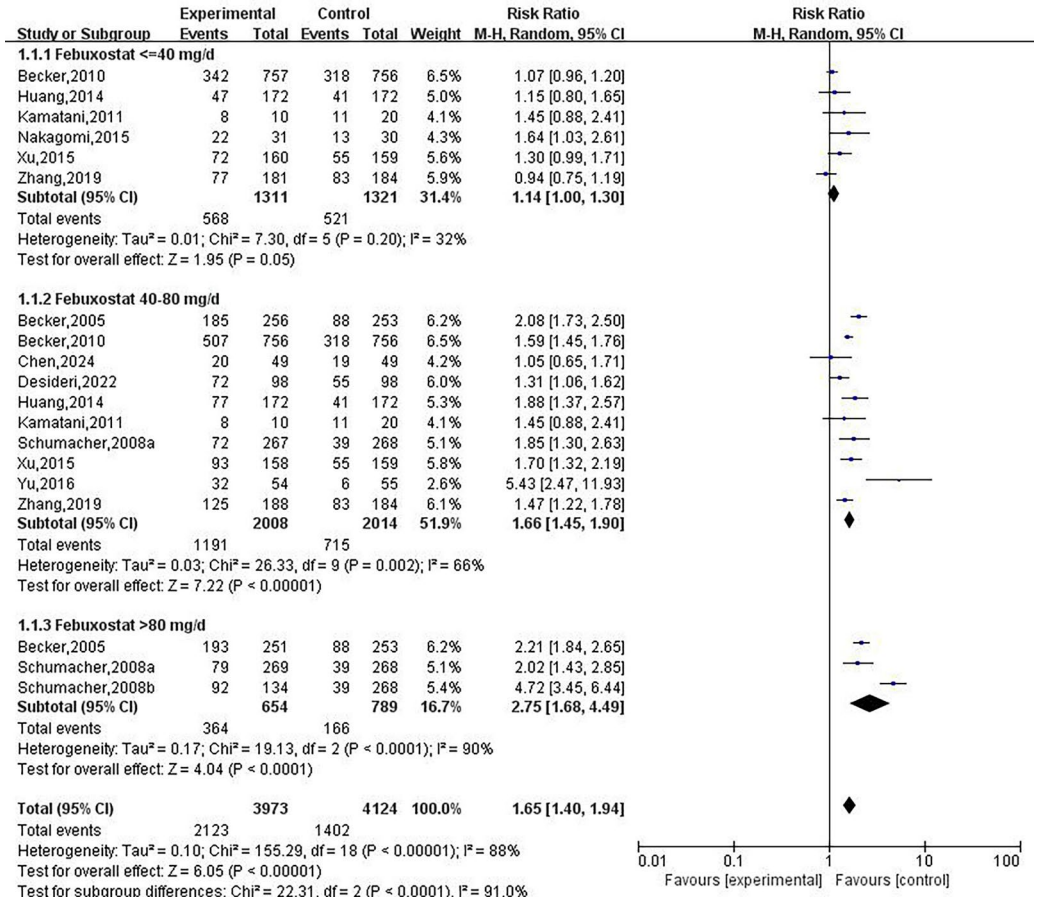


FIGURE 4. Forest plot of different doses of febuxostat on serum uric acid ≤6.0 mg/dL.
CI: Confidence interval.

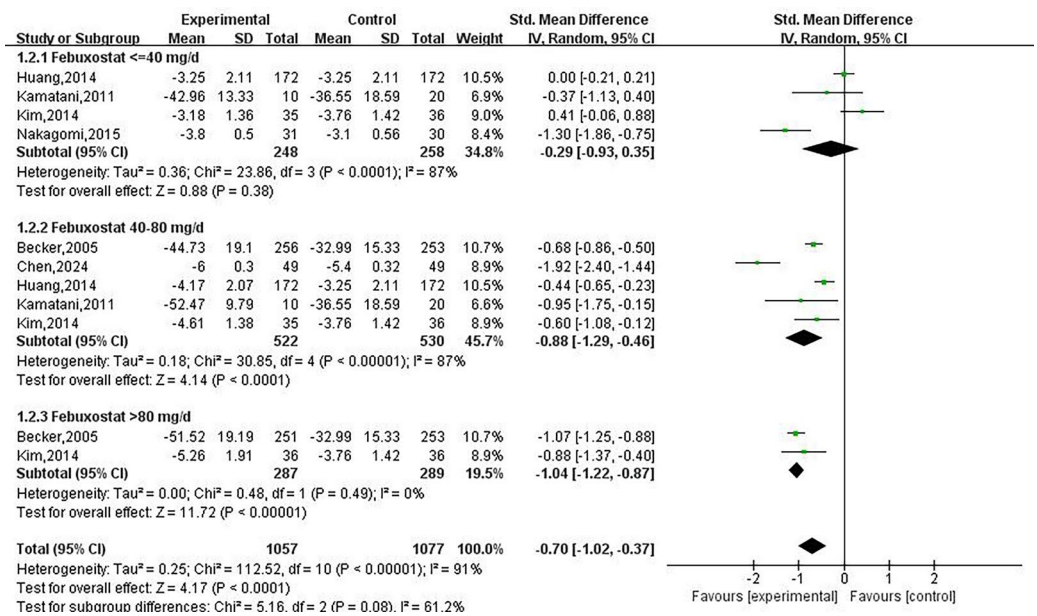


FIGURE 5. Forest plot of different doses of febuxostat on serum uric acid.
CI: Confidence interval.

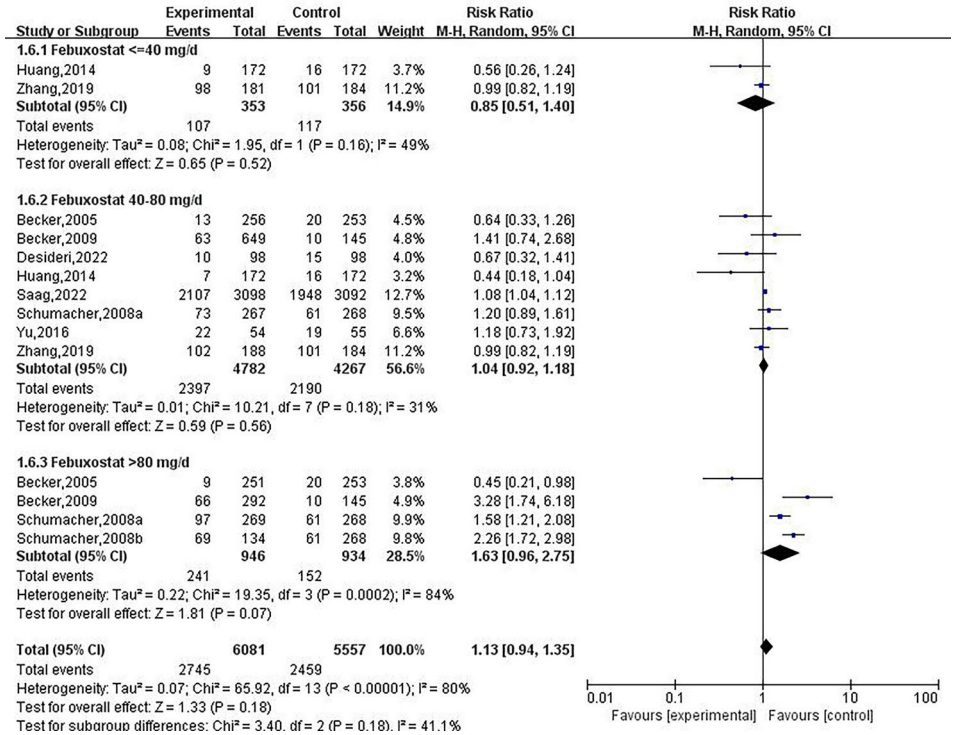


FIGURE 6. Forest plot of different doses of febuxostat on the incidence of gout.
CI: Confidence interval.

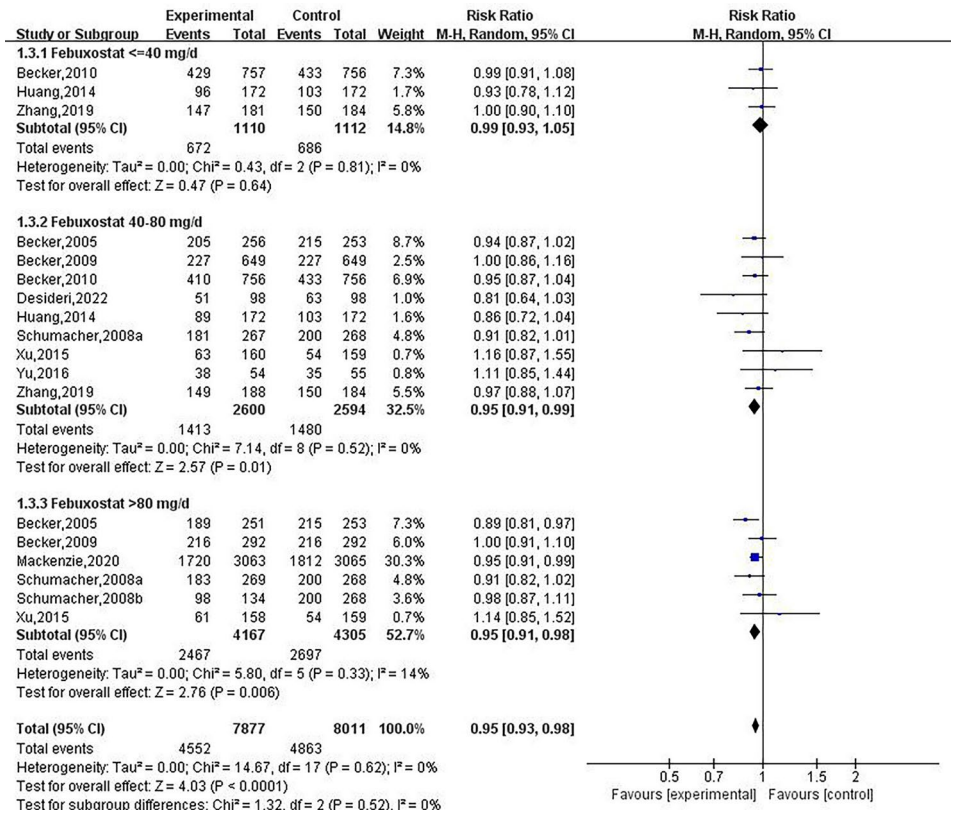


FIGURE 7. Forest plot of different doses of febuxostat on the incidence of any grade AE.
CI: Confidence interval; AE: Adverse events.

therapies.[43] Its superior efficacy in achieving SUA targets may stem from its unique mechanism. As a non-purine selective XOI, febuxostat more precisely inhibits uric acid synthesis compared to allopurinol, a purine analog with non-selective inhibition.[44] Dose-response analyses revealed that SUA-lowering effects intensified with higher doses. The lack of significant improvement with ≤40 mg/day may reflect insufficient xanthine oxidase inhibition to reach therapeutic thresholds, whereas 40-80 and >80 mg/day regimens achieved adequate enzyme suppression for clinically meaningful reductions.[17] Notably, the neutral effect of febuxostat on acute gout risk (RR=1.13) likely involves multifactorial interactions. Rapid SUA decline may dissolve urate crystals, releasing free urate and triggering transient inflammation (e.g., NOD-like receptor protein 3 [NLRP3] inflammasome-mediated interleukin [IL]-1β activation), potentially counteracting long-term prophylaxis.[45] Additionally, short follow-up periods in some studies may have missed delayed flares (occurring months after treatment initiation), as urate crystal redistribution can provoke late-phase inflammation unaccounted for in current trial designs.[46]

Safety analyses showed a marginally lower risk of any-grade AEs with febuxostat compared to allopurinol, though this trend was restricted to 40-80 and >80 mg/day subgroups, possibly due to limited statistical power in lower-dose groups. No significant differences were observed for TRAEs, SAEs, hepatic dysfunction or cardiovascular events. However, the Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial highlighted elevated cardiovascular mortality risk with febuxostat in elderly patients (>65 years) with pre-existing severe cardiovascular disease.[47] The absence of such signals in our analysis may reflect differences in baseline population characteristics and shorter follow-up durations, which may dilute long-term risk detection. While uric acid reduction remains a therapeutic priority, cardiovascular outcomes are multifactorial, influenced by lipid profiles, blood pressure, glucose metabolism and inflammatory status, which are factors not fully adjusted for in this meta-analysis.

In the present study, several limitations warrant consideration. First, the included studies primarily involved Chinese and American populations, which limits generalizability to other ethnic groups, and pharmacogenetic variations in drug metabolism across races may further influence interethnic heterogeneity in drug efficacy and safety profiles. Second, daily febuxostat doses were predominantly 40, 80 or 120 mg, with only one trial testing 240 mg/day, precluding exploration of higher-dose effects. Finally, heterogeneity in baseline SUA levels, comorbidities and concomitant medications may confound dose-response relationships; insufficient data precluded stratified analyses to address these variables. While most studies assessed outcomes at ≥4 months, one trial reported efficacy data at one month. Sensitivity analysis confirmed this did not substantially influence pooled effects. Nevertheless, heterogeneity in follow-up durations may affect longitudinal safety assessments, and findings should be interpreted with consideration of the treatment timeframe. Additionally, only RCTs were included in this study.

In conclusion, febuxostat demonstrates superior efficacy compared to allopurinol in achieving SUA targets, with a dose-dependent effect and acceptable safety. However, clinicians should remain vigilant regarding long-term outcomes, particularly cardiovascular risks in high-risk populations. Further multi-center, large-scale, prospective studies are needed to confirm these findings, optimize dosing strategies, and clarify the role of febuxostat in diverse clinical contexts.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Conceptualization, data curation, methodology, project administration, writing-original draft, writing-review & editing: F.Z.; Conceptualization, investigation, methodology, validation, writing-original draft, writing-review & editing, project administration, resources, supervision: Y.W.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

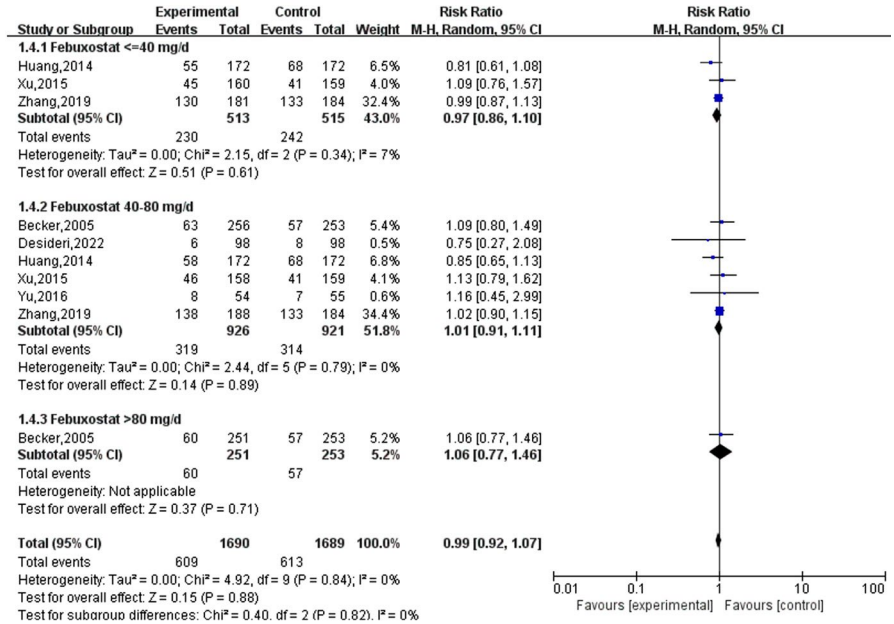
Funding: The authors received no financial support for the research and/or authorship of this article.

REFERENCES

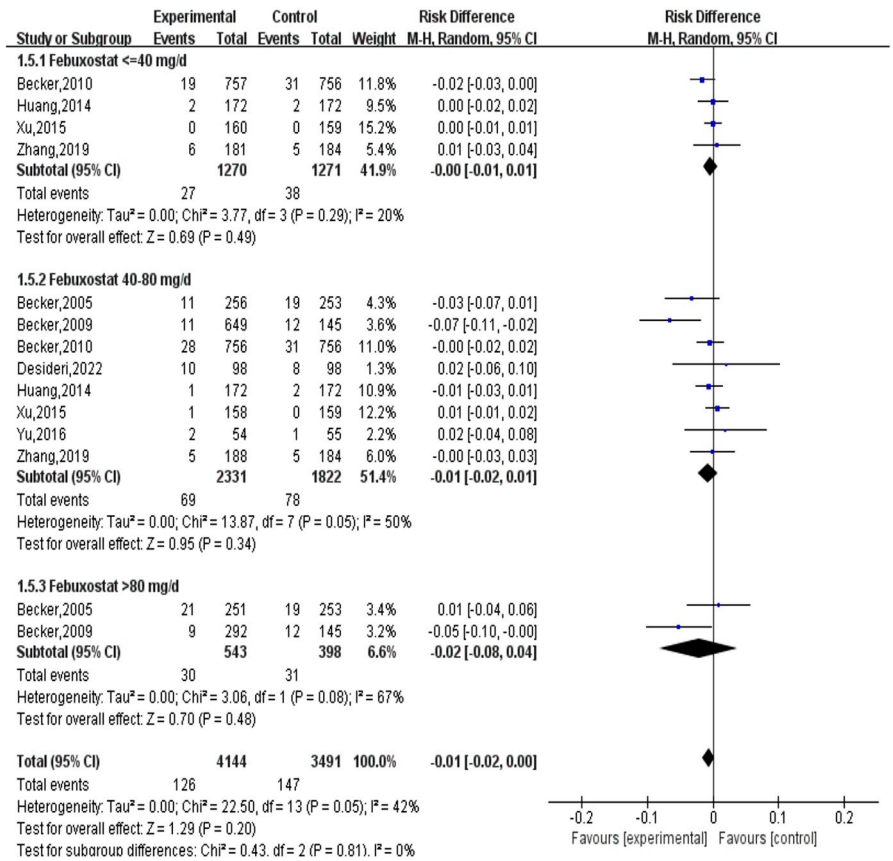
1. Ragab G, Elshahaly M, Bardin T. Gout: An old disease in new perspective - A review. J Adv Res 2017;8:495-511. doi: 10.1016/j.jare.2017.04.008.
2. GBD 2021 Gout Collaborators. Global, regional, and national burden of gout, 1990-2020, and projections to 2050: A systematic analysis of the Global Burden of Disease Study 2021. Lancet Rheumatol 2024;6:e507-17. doi: 10.1016/S2665-9913(24)00117-6.
3. Kuo CF, Grainge MJ, Zhang W, Doherty M. Global epidemiology of gout: Prevalence, incidence and risk factors. Nat Rev Rheumatol 2015;11:649-62. doi: 10.1038/nrrheum.2015.91.

4. Cea Soriano L, Rothenbacher D, Choi HK, García Rodríguez LA. Contemporary epidemiology of gout in the UK general population. Arthritis Res Ther 2011;13:R39. doi: 10.1186/ar3272.
5. Trifirò G, Morabito P, Cavagna L, Ferrajolo C, Pecchioli S, Simonetti M, et al. Epidemiology of gout and hyperuricaemia in Italy during the years 2005-2009: A nationwide population-based study. Ann Rheum Dis 2013;72:694-700. doi: 10.1136/annrheumdis-2011-201254.
6. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: The National Health and Nutrition Examination Survey 2007-2008. Arthritis Rheum 2011;63:3136-41. doi: 10.1002/art.30520.
7. Choi HK, Ford ES, Li C, Curhan G. Prevalence of the metabolic syndrome in patients with gout: The Third National Health and Nutrition Examination Survey. Arthritis Rheum 2007;57:109-15. doi: 10.1002/art.22466.
8. Annemans L, Spaepen E, Gaskin M, Bonnemaire M, Malier V, Gilbert T, et al. Gout in the UK and Germany: Prevalence, comorbidities and management in general practice 2000-2005. Ann Rheum Dis 2008;67:960-6. doi: 10.1136/ard.2007.076232.
9. Zuo T, Liu X, Jiang L, Mao S, Yin X, Guo L. Hyperuricemia and coronary heart disease mortality: A meta-analysis of prospective cohort studies. BMC Cardiovasc Disord 2016;16:207. doi: 10.1186/s12872-016-0379-z.
10. Lee YH, Song GG. Effect of urate-lowering therapy on all-cause and CVD-specific mortality in gout and hyperuricemia: A meta-analysis. Z Rheumatol 2024;83:338-44. doi: 10.1007/s00393-024-01600-0.
11. NICE guideline. Gout: diagnosis and management (NG219). Published: 9 June 2022. Available at: https://www.nice.org.uk/guidance/ng219
12. Gout: Diagnosis and management. London: National Institute for Health and Care Excellence (NICE); 2022 Jun 9.
13. Stamp LK, Day RO, Yun J. Allopurinol hypersensitivity: Investigating the cause and minimizing the risk. Nat Rev Rheumatol 2016;12:235-42. doi: 10.1038/nrrheum.2015.132.
14. Kim SC, Newcomb C, Margolis D, Roy J, Hennessy S. Severe cutaneous reactions requiring hospitalization in allopurinol initiators: A population-based cohort study. Arthritis Care Res (Hoboken) 2013;65:578-84. doi: 10.1002/acr.21817.
15. Yu H, Liu X, Song Y, Cheng J, Bao H, Qin L, et al. Safety and efficacy of benzbromarone and febuxostat in hyperuricemia patients with chronic kidney disease: A prospective pilot study. Clin Exp Nephrol 2018;22:1324-30. doi: 10.1007/s10157-018-1586-y.
16. Kim S, Kim HJ, Ahn HS, Oh SW, Han KH, Um TH, et al. Renoprotective effects of febuxostat compared with allopurinol in patients with hyperuricemia: A systematic review and meta-analysis. Kidney Res Clin Pract 2017;36:274-81. doi: 10.23876/j.krcp.2017.36.3.274.
17. Becker MA, Schumacher HR Jr, Wortmann RL, MacDonald PA, Eustace D, Palo WA, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med 2005;353:2450-61. doi: 10.1056/NEJMoa050373.
18. Schumacher HR Jr, Becker MA, Wortmann RL, Macdonald PA, Hunt B, Streit J, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: A 28-week, phase III, randomized, double-blind, parallel-group trial. Arthritis Rheum 2008;59:1540-8. doi: 10.1002/art.24209.
19. Zhang F, Liu Z, Jiang L, Zhang H, Zhao D, Li Y, et al. A randomized, double-blind, non-inferiority study of febuxostat versus allopurinol in hyperuricemic Chinese subjects with or without gout. Rheumatol Ther 2019;6:543-57. doi: 10.1007/s40744-019-00173-8.
20. Liu CW, Chang WC, Lee CC, Shau WY, Hsu FS, Wang ML, et al. The net clinical benefits of febuxostat versus allopurinol in patients with gout or asymptomatic hyperuricemia - A systematic review and meta-analysis. Nutr Metab Cardiovasc Dis 2019;29:1011-22. doi: 10.1016/j.numecd.2019.06.016.
21. Wang M, Zhang Y, Zhang M, Li H, Wen C, Zhao T, et al. The major cardiovascular events of febuxostat versus allopurinol in treating gout or asymptomatic hyperuricemia: A systematic review and meta-analysis. Ann Palliat Med 2021;10:10327-37. doi: 10.21037/apm-21-1564.
22. Fan M, Liu J, Zhao B, Wu X, Li X, Gu J, et al. Comparison of efficacy and safety of urate-lowering therapies for hyperuricemic patients with gout: A meta-analysis of randomized, controlled trials. Clin Rheumatol 2021;40:683-92. doi: 10.1007/s10067-020-05272-4.
23. Xie H, Hu N, Pan T, Wu JC, Yu M, Wang DC. Effectiveness and safety of different doses of febuxostat compared with allopurinol in the treatment of hyperuricemia: A meta-analysis of randomized controlled trials. BMC Pharmacol Toxicol 2023;24:79. doi: 10.1186/s40360-023-00723-5.
24. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.
25. Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken) 2012;64:1431-46. doi: 10.1002/acr.21772.
26. Higgins J, Altman DG. Assessing risk of biasin included studies. In: Higgins J Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0. Chapter 8: 2008. Available at: http://www.cochrane-handbook.org [Accessed: 20.07.2010]
27. Xu C, Furuya-Kanamori L, Zorzela L, Lin L, Vohra S. A proposed framework to guide evidence synthesis practice for meta-analysis with zero-events studies. J Clin Epidemiol 2021;135:70-8. doi: 10.1016/j.jclinepi.2021.02.012.
28. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88. doi: 10.1016/0197-2456(86)90046-2.
29. Becker MA, Schumacher HR, MacDonald PA, Lloyd E, Lademacher C. Clinical efficacy and safety of successful longterm urate lowering with febuxostat or allopurinol in subjects with gout. J Rheumatol 2009;36:1273-82. doi: 10.3899/jrheum.080814.
30. Becker MA, Schumacher HR, Espinoza LR, Wells AF, MacDonald P, Lloyd E, et al. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: The CONFIRMS trial. Arthritis Res Ther 2010;12:R63. doi: 10.1186/ar2978.
31. Kamatani N, Fujimori S, Hada T, Hosoya T, Kohri K, Nakamura T, et al. An allopurinol-controlled, multicenter, randomized, open-label, parallel between-group, comparative study of febuxostat (TMX-67), a non-purine-selective inhibitor of xanthine oxidase, in patients with

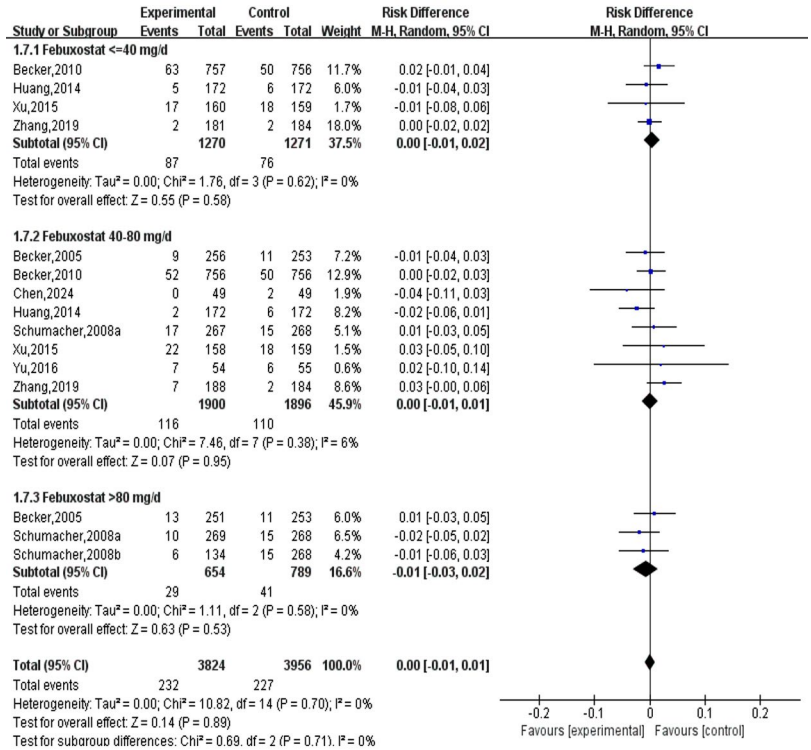
hyperuricemia including those with gout in Japan: Phase 2 exploratory clinical study. J Clin Rheumatol 2011;17:S44-9. doi: 10.1097/RHU.0b013e31821d352f.
32. Huang X, Du H, Gu J, Zhao D, Jiang L, Li X, et al. An allopurinol-controlled, multicenter, randomized, double-blind, parallel between-group, comparative study of febuxostat in Chinese patients with gout and hyperuricemia. Int J Rheum Dis 2014;17:679-86. doi: 10.1111/1756-185X.12266.
33. Kim HA, Seo YI, Song YW. Four-week effects of allopurinol and febuxostat treatments on blood pressure and serum creatinine level in gouty men. J Korean Med Sci 2014;29:1077-81. doi: 10.3346/jkms.2014.29.8.1077.
34. Xu S, Liu X, Ming J, Chen S, Wang Y, Liu X, et al. A phase 3, multicenter, randomized, allopurinol-controlled study assessing the safety and efficacy of oral febuxostat in Chinese gout patients with hyperuricemia. Int J Rheum Dis 2015;18:669-78. doi: 10.1111/1756-185X.12648.
35. Yu KH, Lai JH, Hsu PN, Chen DY, Chen CJ, Lin HY. Safety and efficacy of oral febuxostat for treatment of HLA-B*5801-negative gout: A randomized, open-label, multicentre, allopurinol-controlled study. Scand J Rheumatol 2016;45:304-11. doi: 10.3109/03009742.2015.1099729.
36. Tanaka A, Taguchi I, Teragawa H, Ishizaka N, Kanzaki Y, Tomiyama H, et al. Febuxostat does not delay progression of carotid atherosclerosis in patients with asymptomatic hyperuricemia: A randomized, controlled trial. PLoS Med 2020;17:e1003095. doi: 10.1371/journal.pmed.1003095.
37. Mackenzie IS, Ford I, Nuki G, Hallas J, Hawkey CJ, Webster J, et al. Long-term cardiovascular safety of febuxostat compared with allopurinol in patients with gout (FAST): A multicentre, prospective, randomised, open-label, non-inferiority trial. Lancet 2020;396:1745-57. doi: 10.1016/S0140-6736(20)32234-0.
38. Desideri G, Rajzer M, Gerritsen M, Nurmohamed MT, Giannattasio C, Tausche AK, et al. Effects of intensive urate lowering therapy with febuxostat in comparison with allopurinol on pulse wave velocity in patients with gout and increased cardiovascular risk: The FORWARD study. Eur Heart J Cardiovasc Pharmacother 2022;8:236-42. doi: 10.1093/ehjcvp/pvaa144.
39. Saag KG, Becker MA, White WB, Whelton A, Borer JS, Gorelick PB, et al. Evaluation of the relationship between serum urate levels, clinical manifestations of gout, and death from cardiovascular causes in patients receiving febuxostat or allopurinol in an outcomes trial. Arthritis Rheumatol 2022;74:1593-601. doi: 10.1002/art.42160.
40. Yang N, Cao B. Low-dose febuxostat exhibits a superior renal-protective effect and non-inferior safety profile compared to allopurinol in chronic kidney disease patients complicated with hyperuricemia: A double-centre, randomized, controlled study. J Clin Pharm Ther 2022;47:2214-22. doi: 10.1111/jcpt.13794.
41. Chen X, Ye T, Dai Y, Li P, Zhao X, Yu Y, et al. Comparison of the therapeutic effects of febuxostat combined with a low-purine diet and allopurinol combined with a low-purine diet on the improvement of gout patients. Int J Rheum Dis 2024;27:e15165. doi: 10.1111/1756-185X.15165.
42. Nakagomi A, Saiki Y, Noma S, Kohashi K, Morisawa T, Kosugi M, et al. Effects of febuxostat and allopurinol on the inflammation and cardiac function in chronic heart failure patients with hyperuricemia. IJC Metabolic & Endocrine 2015;8:46-55.
43. Bardin T, Richette P. The role of febuxostat in gout. Curr Opin Rheumatol. 2019;31:152-8. doi: 10.1097/BOR.0000000000000573.
44. Yu KH. Febuxostat: A novel non-purine selective inhibitor of xanthine oxidase for the treatment of hyperuricemia in gout. Recent Pat Inflamm Allergy Drug Discov 2007;1:69-75. doi: 10.2174/187221307779815020.
45. Kim SK. The mechanism of the NLRP3 inflammasome activation and pathogenic implication in the pathogenesis of gout. J Rheum Dis 2022;29:140-53. doi: 10.4078/jrd.2022.29.3.140.
46. FitzGerald JD, Dalbeth N, Mikuls T, Brignardello-Petersen R, Guyatt G, Abeles AM, et al. 2020 American College of Rheumatology Guideline for the Management of Gout. Arthritis Care Res (Hoboken) 2020;72:744-60. doi: 10.1002/acr.24180.
47. White WB, Saag KG, Becker MA, Borer JS, Gorelick PB, Whelton A, et al. Cardiovascular safety of febuxostat or allopurinol in patients with gout. N Engl J Med 2018;378:1200-10. doi: 10.1056/NEJMoa1710895.



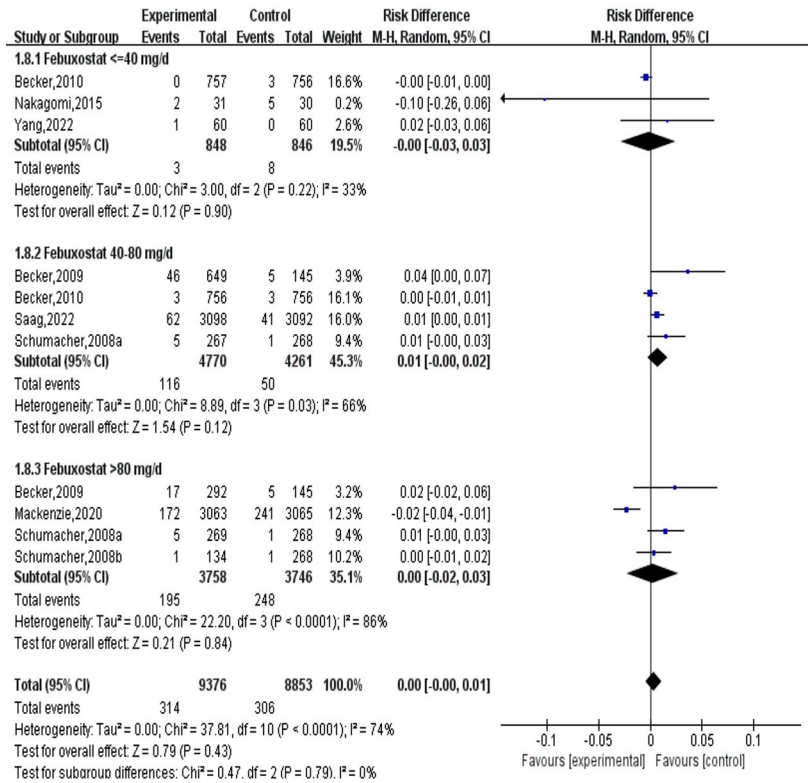
SUPPLEMENTARY FIGURE 1. Forest plot of different doses of febuxostat on the incidence of treatment-related AE.
CI: Confidence interval; AE: Adverse events.



SUPPLEMENTARY FIGURE 2. Forest plot of different doses of febuxostat on the incidence of serious AE.



SUPPLEMENTARY FIGURE 3. Forest plot of different doses of febuxostat on the incidence of hepatic dysfunction.



SUPPLEMENTARY FIGURE 4. Forest plot of different doses of febuxostat on the incidence of cardiovascular events.