

ORIGINAL ARTICLE

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

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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

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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 $\leq 6.0 \text{ mg/dL}$, 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 $\leq 6.0 \text{ mg/dL}$, 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.

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

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 μ mol/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 O-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 $\leq 6.0 \text{ mg/dL}$ 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



	Baseline serum uric acid (mg/dL)	9.80±1.24	9.84±1.26	9.90±1.23	9.85±1.263	9.85±1.26 3	9.85±1.263	9.85±1.263	9.83±1.252	9.74±1.281	9.82±1.157	9.6±1.15	9.6±1.20	9.5±1.19
	Years with gout	11.5±9.4	12.6±9.9	11.6±9.3	11±9	12±9	11±9	11±9	Υ N	NA	NA	12.0±9.13	11.7±9.64	11.2±9.14
	BMI	32.7±6.1	32.3±5.7	32.6±6.1	33±6	33±7	33±7	33±6	32.3±5.78	33.2±6.17	33.8±6.79	32.9±6.37	32.9±6.39	32.7±6.23
	Male (%)	95	79	77	94	95	94	63	Ч И	NA	NA	95.4	93.9	93.8
	Age	51.8±11.7	52.0±12.1	51.6±12.6	51±12	51±12	54±13	52±12	51.4±11.95	50.9±11.57	51.0±11.30	52.5±11.68	53.0±11.79	52.9±11.73
d studies	Sample size	256	251	253	267	269	134	268	649	292	145	757	756	756
TABLE I mation of included	Intervention	Febuxostat 80 mg/d	Febuxostat 120 mg/d	Allopurinol 300 mg/d	Febuxostat 80 mg/d	Febuxostat 120 mg/d	Febuxostat 240 mg/d	Allopurinol 300 mg/d	Febuxostat 80 mg/d	Febuxostat 120 mg/d	Allopurinol 300 mg/d	Febuxostat 40 mg/d	Febuxostat 80 mg/d	Allopurinol 300 mg/d
Basic infor	Patients	Adults patients with gout and with serum urate concentrations of at least 8.0 mg per deciliter			Adults (18-85) patients with gout and with serum urate concentrations of at least 8.0 mg per deciliter				Adults patients with gout and with serum urate concentrations of at least 8.0 mg per deciliter			Adults (18-85) patients with gout and with serum urate concentrations of at least 8.0 mg per deciliter		
	Duration	52 weeks			28 weeks				6 months			24 weeks		
	Study design	RCT, double-blind, multicenter			RCT, double-blind, multicenter				RCT, open-label, multicenter			RCT, double-blind, multicenter		
	Location	USA, Canada			USA				USA, Canada			USA		
	Study	Becker et al., ^{ir7]} 2005			Schumacher et al., ^{tiel} 2008				Becker et al., ^{i29]} 2009			Becker et al., ³⁰¹ 2010		

	Baseline serum uric acid (mg/dL)		NA		9.89±1.36	9.98±1.39	9.95±1.35	9.7±1.1	9.5±1.3	9.5±1.0	9.5±1.0	560.8±73.3	565.1±75.5	574.2±77.8
	Years with gout		NA		A	NA	NA	Ч И	NA	NA	NA	2.7 (1.0-5.8)	3.0 (1.2-5.1)	3.0 (2.0-6.9)
	BMI		NA		25.63±2.80	25.25±2.64	25.44±2.53	26.4±3.5	25.4±2.6	25.9±2.1	25.9±3.2	25.3±2.7	25.1±2.6	25.4±3.3
	Male (%)	100	06	95	97.1	98.3	97.7	100	100	100	100	8. 8	92.4	93.7
	Age	56.0±8.2	53.3±11.0	51.3±12.0	46.42±10.90	47.40±11.18	46.17±11.56	49.6±11.9	49.1±12.4	51.2±9.9	48.3±11.8	45.5±11.9	48.2±12.0	46.6±10.7
	Sample size	10	10	20	172	172	172	35	35	36	36	160	158	159
TABLE I Continued	Intervention	Febuxostat 40 mg/d	Febuxostat 60 mg/d	Allopurinol 300 mg/d	Febuxostat 40 mg/d	Febuxostat 80 mg/d	Allopurinol 300 mg/d	Febuxostat 40 mg/d	Febuxostat 80 mg/d	Febuxostat 120 mg/d	Allopurinol 300 mg/d	Febuxostat 40 mg/d	Febuxostat 80 mg/d	Allopurinol 300 mg/d
	Patients	Adults (>=20) patients had hyperuricemia, including gout			Adults (18-70) patients with gout and with serum urate concentrations of at least 8.0 mg per deciliter			Male adults with gout with serum urate concentrations of at least 8.0 mg per deciliter				Adults (18-70) patients with gout and with serum urate concentrations of at least 8.0 mg per deciliter		
	Duration	16 weeks			28 weeks			4 weeks				24 weeks		
	Study design	RCT, open-label, multicenter			RCT, double-blind, multicenter			RCT, double-blind, multicenter				RCT, double-blind, multicenter		
	Location	Japan			China			Korea				China		
	Study	Kamatani et al., ^[31] 2011			Huang et al., ¹³² 2014			Kim et al., ¹³⁹ 2014				Xuet al., ¹²⁴¹ 2015		

	Baseline serum uric acid (mg/dL)	NA	ΝA	9.6±1.5	9.6±1.5	9.8±1.4	ΥN	ΝA	9.47±1.05	9.19±1.04	8.7±1.7	8.7±1.7	9.06±1.51	9.19±1.71
	Years with gout	٩Z	NA	۲ Z	NA	NA	AN	NA	AN	NA	11.8±11.4	11.9±11.2	AN	
	BMI	26.8±3.7	27.8±4.2	26.1±3.2	25.7±3.2	26.0±3.4	31.0±5.1	31.2±5.3	31.68±5.5	31.51±4.91	33.5±6.92		23.8±2.9	23.8±2.8
	Male (%)	98.1	96.4	99.4	97.9	98.9	85.5	85	82.7	81.6	83.9		75	71.7
	Age	46.0±11.0	45.2±12.0	46.5±11.9	47.2±12.9	48.3±13.1	71.0±6.4	70.9±6.5	58.66±10.83	60.52±10.35	65 (44-93)		62.2±9.2	61.7±6.9
	Sample size	54	55	181	188	184	3063	3065	86	98	3098	3092	09	60
TABLE I Continued	Intervention	Febuxostat 80 mg/d	Allopurinol 300 mg/d	Febuxostat 40 mg/d	Febuxostat 80 mg/d	Allopurinol 300 mg/d	Febuxostat 80-120 mg/d	Allopurinol 100-300 mg/d	Febuxostat 80 mg/d	Allopurinol 100 mg/d	Febuxostat 40-80 mg/d	Allopurinol 300 mg/d	Febuxostat 20 mg/d	Allopurinol 200 mg/d
	Patients	Adults (20-65) patients with gout and with serum urate concentrations of at least 8.0 mg per deciliter		Adults (18-85) with gout and with serum urate concentrations of at least 8.0 mg per deciliter			Adults (≥60) with gout		Adults with a history of gout and elevated SUA levels		Adults (male ≥50, female ≥55) with gout		Chronic kidney disease patients complicated with hyperuricemia	
	Duration	12 weeks		24 weeks					36 weeks		32 months		6 months	
	Study design	RCT, open-label, multicenter		RCT, double-blind, multicenter			RCT, open-label, multicenter		RCT, open-label, multicenter		RCT, double-blind, multicenter		RCT, double-blind, multicenter	
	Location	China, Taiwan		China			UK, Denmark, Sweden		Italy		NSA		China	
	Study	Yu et al., ^{135]} 2016		Zhang et al., ^{it9]} 2019			Mackenzie et al., ^[37] 2020		Desideri et al., ^[38] 2022		Saag et al., ^[39] 2022		Yanget al., ^{40]} 2022	

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 randomeffects 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 $\leq 40 \text{ mg/day}$ 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 (I² 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., ⁱ⁴² 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	۲	23.6±2.4	AN	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-controll	led trial; BMI: E	Body mass index;	NA: Not availabl	e.							





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 $\leq 6.0 \text{ mg/dL}$, 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 decisionmaking.

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

Study or Subarcum	Experim	Total	Evente	Total	Moinht	M LI Dandom OFM CL	
Study of Subgroup	Events	Total	Events	Total	weight	M-H, Kandom, 95% CI	M-H, Random, 95% CI
1.1.1 Febuxostat <=4	u mg/a						
Becker,2010	342	151	318	756	6.5%	1.07 [0.96, 1.20]	
Huang,2014	47	172	41	172	5.0%	1.15 [0.80, 1.65]	
Kamatani,2011	8	10	11	20	4.1%	1.45 [0.88, 2.41]	
Nakagomi,2015	22	31	13	30	4.3%	1.64 [1.03, 2.61]	
Xu,2015	72	160	55	159	5.6%	1.30 [0.99, 1.71]	
Zhang,2019	77	181	83	184	5.9%	0.94 [0.75, 1.19]	
Subtotal (95% CI)		1311		1321	31.4%	1.14 [1.00, 1.30]	•
Total events	568		521				
Heterogeneity: Tau ² =	0.01; Chi2	= 7.30,	df = 5 (P)	= 0.20);	I= 32%		
Test for overall effect:	Z = 1.95 (F	P = 0.05)					
1.1.2 Febuxostat 40-	80 ma/d						
Becker 2005	185	256	88	253	6.2%	2.08 [1.73. 2.50]	-
Becker 2010	507	756	318	756	6.5%	1.59 [1.45 1.76]	-
Chen 2024	20	19	19	19	1 296	1.05 [0.65, 1.71]	
Decideri 2022	72	99	55	99	6.0%	1 31 [1 06 1 62]	
Luona 2014	77	172	41	172	5 20%	1.00 [1.00, 1.02]	
Vomotoni 2011		10	41	20	4 1 0%	1 46 10 00 0 441	
Rahumashar 2000a	70	267	20	20	4.1 70	1.40 [0.00, 2.41]	
Schumacher,2006a	12	207	59	200	5.00	1.00 [1.30, 2.03]	
Xu,2015	93	158	55	159	5.8%	1.70 [1.32, 2.19]	108-000
YU,2016	32	54	0	55	2.0%	5.43 [2.47, 11.93]	100
Zhang,2019	125	188	83	184	6.1%	1.47 [1.22, 1.78]	
Subtotal (95% CI)		2008	12.50	2014	51.9%	1.66 [1.45, 1.90]	•
Total events	1191		715			10	
Heterogeneity: Tau ² = Test for overall effect:	0.03; Chi ² 7 = 7 22 (F	= 26.33 < 0 000	, df = 9 (F 101)	P = 0.00	12); 1 ² = 66	%	
Nerroscana recordor							
1.1.3 Febuxostat >80	mg/d	1226.0	0.03	3.254			1000
Becker,2005	193	251	88	253	6.2%	2.21 [1.84, 2.65]	
Schumacher,2008a	79	269	39	268	5.1%	2.02 [1.43, 2.85]	Contraction of the second
Schumacher,2008b	92	134	39	268	5.4%	4.72 [3.45, 6.44]	
Subtotal (95% CI)		654		789	16.7%	2.75 [1.68, 4.49]	-
Total events	364		166				
Heterogeneity: Tau ² = Test for overall effect:	0.17; Chi ² Z = 4.04 (F	= 19.13 P < 0.000	, df = 2 (F)1)	° < 0.00	101); I² = 9	0%	
Total (95% Cl)		3973		4124	100.0%	1.65 [1.40, 1.94]	•
Total events	2123		1402				
Heterogeneity: Tau ² =	0.10; Chi2	= 155.2	9, df = 18	B (P < 0.	.00001); P	= 88%	
Test for overall effect:	Z = 6.05 (F	< 0.000	001)				Course (experimentel) Feveres (centre)
			24 46	-	00041 12	- 01 00	Favours (experimental) Favours (control)

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

	Expe	eriment	al	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% CI
1.2.1 Febuxostat <=.	40 mg/d								
Huang,2014	-3.25	2.11	172	-3.25	2.11	172	10.5%	0.00 [-0.21, 0.21]	+
Kamatani,2011	-42.96	13.33	10	-36.55	18.59	20	6.9%	-0.37 [-1.13, 0.40]	and the second s
Kim,2014	-3.18	1.36	35	-3.76	1.42	36	9.0%	0.41 [-0.06, 0.88]	
Nakagomi,2015	-3.8	0.5	31	-3.1	0.56	30	8.4%	-1.30 [-1.86, -0.75]	
Subtotal (95% CI)			248			258	34.8%	-0.29 [-0.93, 0.35]	-
Heterogeneity: Tau ²	= 0.36; Ch	ni ² = 23.	86, df =	3 (P < 0	.0001);	12 = 879	%		
Test for overall effect	t: Z = 0.88	(P = 0.3	88)						
1.2.2 Febuxostat 40	-80 mg/d								
Becker 2005	-44.73	19.1	256	-32.99	15.33	253	10.7%	-0.68 [-0.86, -0.50]	+
Chen.2024	-6	0.3	49	-5.4	0.32	49	8.9%	-1.92 [-2.40, -1.44]	
Huang 2014	-4.17	2.07	172	-3.25	2.11	172	10.5%	-0.44 [-0.65, -0.23]	-
Kamatani.2011	-52.47	9.79	10	-36.55	18.59	20	6.6%	-0.95 [-1.75, -0.15]	
Kim.2014	-4.61	1.38	35	-3.76	1.42	36	8.9%	-0.60 [-1.08, -0.12]	
Subtotal (95% CI)			522			530	45.7%	-0.88 [-1.29, -0.46]	•
Heterogeneity: Tau ²	= 0.18; Ch	ni ² = 30.1	85. df =	4 (P < 0	.00001)); ² = 8;	7%		
Test for overall effect	t: Z = 4.14	(P < 0.0	0001)						
1.2.3 Febuxostat >8	0 mg/d								
Becker,2005	-51.52	19.19	251	-32.99	15.33	253	10.7%	-1.07 [-1.25, -0.88]	+
Kim.2014	-5.26	1.91	36	-3.76	1.42	36	8.9%	-0.88 [-1.37, -0.40]	
Subtotal (95% CI)			287			289	19.5%	-1.04 [-1.22, -0.87]	•
Heterogeneity: Tau ²	= 0.00; Ch	ni ² = 0.4	8, df = 1	(P = 0.4)	19); I ² =	0%			
Test for overall effect	t: Z = 11.7:	2 (P < 0	.00001)					
Fotal (95% CI)			1057			1077	100.0%	-0.70 [-1.02, -0.37]	•
Heterogeneity: Tau ²	= 0.25; Ch	ni ² = 112	.52, df	= 10 (P	< 0.000	01); I ² =	91%		
Test for overall effect	t: Z = 4.17	(P < 0.0	0001)			10.5			-2 -1 0 1 2
	ferences	Chi ² =	5.16. di	= 2 (P =	0.08). [² = 61.2	96		Favours (experimental) Favours (control)

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.6.1 Febuxostat <=4	0 mg/d						
Huang,2014	9	172	16	172	3.7%	0.56 [0.26, 1.24]	the second s
Zhang,2019	98	181	101	184	11.2%	0.99 [0.82, 1.19]	
Subtotal (95% CI)		353		356	14.9%	0.85 [0.51, 1.40]	-
Total events	107		117				
Heterogeneity: Tau ² =	0.08; Chi ²	= 1.95,	df = 1 (P	= 0.16)	² = 49%		
Test for overall effect:	Z = 0.65 (F	P = 0.52))				
1.6.2 Febuxostat 40-8	80 mg/d						
Becker,2005	13	256	20	253	4.5%	0.64 [0.33, 1.26]	
Becker,2009	63	649	10	145	4.8%	1.41 [0.74, 2.68]	
Desideri,2022	10	98	15	98	4.0%	0.67 [0.32, 1.41]	the second se
Huang,2014	7	172	16	172	3.2%	0.44 [0.18, 1.04]	and the second sec
Saag,2022	2107	3098	1948	3092	12.7%	1.08 [1.04, 1.12]	•
Schumacher,2008a	73	267	61	268	9.5%	1.20 [0.89, 1.61]	+-
Yu,2016	22	54	19	55	6.6%	1.18 [0.73, 1.92]	
Zhang,2019	102	188	101	184	11.2%	0.99 [0.82, 1.19]	+
Subtotal (95% CI)		4782		4267	56.6%	1.04 [0.92, 1.18]	•
Total events	2397		2190				
Heterogeneity: Tau ² = Test for overall effect:	0.01; Chi² Z = 0.59 (F	= 10.21 P = 0.56)	, df = 7 (F	P = 0.18	l); I² = 31	%	
1.6.3 Febuxostat >80	ma/d						
Becker 2005	9	251	20	253	3.8%	0.45 (0.21 0.98)	
Becker.2009	66	292	10	145	4.9%	3.28 [1.74, 6,18]	
Schumacher,2008a	97	269	61	268	9.9%	1.58 [1.21, 2.08]	
Schumacher, 2008b	69	134	61	268	9.8%	2.26 [1.72, 2.98]	-
Subtotal (95% CI)		946		934	28.5%	1.63 [0.96, 2.75]	◆
Total events	241		152				
Heterogeneity: Tau ² =	0.22; Chi ²	= 19.35	, df = 3 (F	e = 0.00	$102); I^2 = 1$	34%	
Test for overall effect:	Z = 1.81 (F	P = 0.07))		ų.		
Total (95% CI)		6081		5557	100.0%	1.13 [0.94, 1.35]	•
Total events	2745		2459				
Heterogeneity: Tau ² =	0.07; Chi2	= 65.92	, df = 13	(P < 0.0	10001); l²	= 80%	
Test for overall effect:	Z = 1.33 (F	P = 0.18)				Favours (experimental) Favours (control)
Test for subaroup diffe	erences: C	hi ² = 3.4	40. df = 2	(P = 0.1	18). $ ^2 = 4$	1.1%	r avours texperimentalit i r avours teoritiolit

FIGURE 6. Forest plot of different doses of febuxostat on the incidence of gout.

	Experim	ental	Conti	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.3.1 Febuxostat <=4	0 mg/d						
Becker,2010	429	757	433	756	7.3%	0.99 [0.91, 1.08]	
Huang,2014	96	172	103	172	1.7%	0.93 [0.78, 1.12]	Concerning and the
Zhang,2019	147	181	150	184	5.8%	1.00 [0.90, 1.10]	
Subtotal (95% CI)		1110		1112	14.8%	0.99 [0.93, 1.05]	•
Total events	672		686				
Heterogeneity: Tau ² =	0.00; Chi2	= 0.43,	df = 2 (P	= 0.81)	; I ² = 0%		
Test for overall effect:	Z=0.47 (F	P = 0.64)					
1.3.2 Febuxostat 40-	80 mg/d						
Becker,2005	205	256	215	253	8.7%	0.94 [0.87, 1.02]	
Becker,2009	227	649	227	649	2.5%	1.00 [0.86, 1.16]	1
Becker,2010	410	756	433	756	6.9%	0.95 [0.87, 1.04]	-++
Desideri,2022	51	98	63	98	1.0%	0.81 [0.64, 1.03]	
Huang,2014	89	172	103	172	1.6%	0.86 [0.72, 1.04]	+
Schumacher,2008a	181	267	200	268	4.8%	0.91 [0.82, 1.01]	
Xu.2015	63	160	54	159	0.7%	1.16 [0.87, 1.55]	
Yu.2016	38	54	35	55	0.8%	1.11 [0.85, 1.44]	
Zhang,2019	149	188	150	184	5.5%	0.97 [0.88, 1.07]	
Subtotal (95% CI)		2600		2594	32.5%	0.95 [0.91, 0.99]	•
Total events	1413		1480				
Heterogeneity: Tau ² =	0.00; Chi ²	= 7.14,	df = 8 (P	= 0.52)	; I ² = 0%		
Test for overall effect:	Z = 2.57 (F	P = 0.01)					
1.3.3 Febuxostat >80	mg/d						
Becker,2005	189	251	215	253	7.3%	0.89 [0.81, 0.97]	
Becker,2009	216	292	216	292	6.0%	1.00 [0.91, 1.10]	
Mackenzie,2020	1720	3063	1812	3065	30.3%	0.95 [0.91, 0.99]	-
Schumacher,2008a	183	269	200	268	4.8%	0.91 [0.82, 1.02]	
Schumacher,2008b	98	134	200	268	3.6%	0.98 [0.87, 1.11]	
Xu,2015	61	158	54	159	0.7%	1.14 [0.85, 1.52]	
Subtotal (95% CI)		4167		4305	52.7%	0.95 [0.91, 0.98]	•
Total events	2467		2697				
Heterogeneity: Tau ² =	0.00; Chi ²	= 5.80,	df = 5 (P	= 0.33)	; I= 14%		
Test for overall effect:	Z= 2.76 (F	P = 0.000	3)				
Total (95% CI)		7877		8011	100.0%	0.95 [0.93, 0.98]	•
Total events	4552		4863				
Heterogeneity: Tau ² =	0.00; Chi ²	= 14.67	. df = 17	(P = 0.8)	52); I ² = 09	% -	
Test for overall effect:	Z = 4.03 (F	< 0.000	01)	,			0.5 0.7 1 1.5 2
To at fay and many diff	aranaaa: C	hiz - 1 1	2 45-2	/D = 0	CON 18 - 0	ov.	Favours [experimental] Favours [control]

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]-1 β 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 \geq 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.

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	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.4.1 Febuxostat <=4	40 mg/d						
Huang,2014	55	172	68	172	6.5%	0.81 [0.61, 1.08]	
Xu,2015	45	160	41	159	4.0%	1.09 [0.76, 1.57]	+
Zhang,2019	130	181	133	184	32.4%	0.99 [0.87, 1.13]	•
Subtotal (95% CI)		513		515	43.0%	0.97 [0.86, 1.10]	•
Total events	230		242				
Heterogeneity: Tau ² =	= 0.00; Chi ^a	² = 2.15,	df = 2 (P	= 0.34)); I ² = 7%		
Test for overall effect	: Z = 0.51 (P = 0.61)				
1.4.2 Febuxostat 40-	80 mg/d						
Becker,2005	63	256	57	253	5.4%	1.09 [0.80, 1.49]	+
Desideri,2022	6	98	8	98	0.5%	0.75 [0.27, 2.08]	
Huang,2014	58	172	68	172	6.8%	0.85 (0.65, 1.13)	
Xu,2015	46	158	41	159	4.1%	1.13 [0.79, 1.62]	
Yu,2016	8	54	7	55	0.6%	1.16 [0.45, 2.99]	
Zhang,2019	138	188	133	184	34.4%	1.02 [0.90, 1.15]	•
Subtotal (95% CI)		926		921	51.8%	1.01 [0.91, 1.11]	•
Total events	319		314				
Heterogeneity: Tau ² =	= 0.00; Chi ^a	= 2.44.	df = 5 (P	= 0.79	; I ² = 0%		
Test for overall effect	: Z = 0.14 (P = 0.89)				
1.4.3 Febuxostat >80) mg/d						
Becker,2005	60	251	57	253	5.2%	1.06 [0.77, 1.46]	+
Subtotal (95% CI)		251		253	5.2%	1.06 [0.77, 1.46]	◆
Total events	60		57				
Heterogeneity: Not a	pplicable						
Test for overall effect	Z = 0.37 (P = 0.71)				
Total (95% CI)		1690		1689	100.0%	0.99 [0.92, 1.07]	4
Total events	609		613				
Heterogeneity Tau ² :	= 0 00° Chi ²	= 4 92	df = 9 (P)	= 0.84): I ² = 0%		⊢ ⊢ ⊢ ⊢
Test for overall effect	Z = 0.15 (P = 0.88	0	0.04,			0.01 0.1 1 10 10
Test for subgroup dif	Terences: ($chi^2 = 0$	40 df = 2	(P = 0)	82) F= 0	196	Favours [experimental] Favours [control]
reerier cabaroab an			10. di - 2				

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.

	Experim	ental	Contr	ol		Risk Difference	Risk Difference
Study or Subaroup	Events	Total	Events	Total	Weight	M-H. Random. 95% Cl	M-H. Random, 95% Cl
1.7.1 Febuxostat <=4	0 mg/d						
Becker,2010	63	757	50	756	11.7%	0.02 [-0.01, 0.04]	+
Huang,2014	5	172	6	172	6.0%	-0.01 [-0.04, 0.03]	
Xu,2015	17	160	18	159	1.7%	-0.01 [-0.08, 0.06]	
Zhang,2019	2	181	2	184	18.0%	0.00 [-0.02, 0.02]	+
Subtotal (95% CI)		1270		1271	37.5%	0.00 [-0.01, 0.02]	•
Total events	87		76				
Heterogeneity: Tau ² =	0.00; Chi ²	= 1.76,	df = 3 (P :	= 0.62)	; I² = 0%		
Test for overall effect:	Z = 0.55 (P	= 0.58))				
1.7.2 Febuxostat 40-8	80 mg/d						
Becker,2005	9	256	11	253	7.2%	-0.01 [-0.04, 0.03]	
Becker,2010	52	756	50	756	12.9%	0.00 [-0.02, 0.03]	+
Chen,2024	0	49	2	49	1.9%	-0.04 [-0.11, 0.03]	
Huang,2014	2	172	6	172	8.2%	-0.02 [-0.06, 0.01]	
Schumacher,2008a	17	267	15	268	5.1%	0.01 [-0.03, 0.05]	_
Xu,2015	22	158	18	159	1.5%	0.03 [-0.05, 0.10]	
Yu,2016	7	54	6	55	0.6%	0.02 [-0.10, 0.14]	
Zhang,2019	7	188	2	184	8.6%	0.03 [-0.00, 0.06]	
Subtotal (95% CI)		1900		1896	45.9%	0.00 [-0.01, 0.01]	•
Total events	116		110				
Heterogeneity: Tau ² =	0.00; Chi ²	= 7.46,	df = 7 (P :	= 0.38)	; l² = 6%		
Test for overall effect:	Z = 0.07 (P	P = 0.95))				
1.7.3 Febuxostat >80	mg/d						
Becker,2005	13	251	11	253	6.0%	0.01 [-0.03, 0.05]	
Schumacher,2008a	10	269	15	268	6.5%	-0.02 [-0.05, 0.02]	
Schumacher,2008b	6	134	15	268	4.2%	-0.01 [-0.06, 0.03]	
Subtotal (95% CI)		654		789	16.6%	-0.01 [-0.03, 0.02]	T
Total events	29		41				
Heterogeneity: Tau* =	0.00; Chi*	= 1.11,	df = 2 (P :	= 0.58)	; I* = 0%		
Test for overall effect:	Z = 0.63 (F	' = 0.53))				
Total (95% CI)		3824		3956	100.0%	0.001.0.01.0.011	•
Total evente	222	3024	227	5550	100.070	0.00[-0.01, 0.01]	I
Hotorogonoity Tou2-	232 0.00: Chiž	- 10.92	227 df=14	(P - 0 7	201 - 1 2 - 00	×	
Test for overall effect:	$7 = 0.14 / \Box$	= 10.02 = 0.80	, ui – 14 i	()	0,1 = 0		-0.2 -0.1 0 0.1 0.2
Test for subgroup diffe	2 - 0.14 (F	-0.09, hi≊-0.0	/ 80 df - 2	(P = 0	71) 12 - 0	96	Favours [experimental] Favours [control]
reation suburoub unit	cicilites. U	- 0.0	55. ui – Z	u [*] = 0.	(1), 1 = 0	10	

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

	Experim	ental	Contr	ol		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.8.1 Febuxostat <=4	0 mg/d						
Becker,2010	0	757	3	756	16.6%	-0.00 [-0.01, 0.00]	
Nakagomi,2015	2	31	5	30	0.2%	-0.10 [-0.26, 0.06]	• • • • • • • • • • • • • • • • • • • •
Yang,2022	1	60	0	60	2.6%	0.02 [-0.03, 0.06]	
Subtotal (95% CI)		848		846	19.5%	-0.00 [-0.03, 0.03]	-
Total events	3		8				
Heterogeneity: Tau ² =	0.00; Chi ²	= 3.00,	df = 2 (P :	= 0.22)	; I² = 33%		
Test for overall effect.	Z = 0.12 (F	P = 0.90))				
4.0.2 Februartet 40.0	0						
1.8.2 Feblixostal 40-8	o mg/a	640	5	4.45	2.00	0.04/0.00.0.071	
Becker,2009	40	049	5	140	3.9%	0.04 [0.00, 0.07]	1
Becker,2010	3	000	3	100	10.1%	0.00 [-0.01, 0.01]	1
Saay,2022	62	3098	41	3092	10.0%	0.01 [0.00, 0.01]	
Schumacher,2008a	5	20/	1	208	9.4%	0.01 [-0.00, 0.03]	
Subtotal (95% CI)	440	4//0	50	4201	45.5%	0.01[-0.00, 0.02]	•
Tutal events	110	- 0.00	00 	- 0.02	12 - 000		
Test for suprell offect	0.00, CHF	= 0.09,	ui = 3 (P :	= 0.03)	, I- = 00%		
restion overall ellect.	2 - 1.34 (r	- 0.12,					
1.8.3 Febuxostat >80	mg/d						
Becker,2009	17	292	5	145	3.2%	0.02 [-0.02, 0.06]	
Mackenzie,2020	172	3063	241	3065	12.3%	-0.02 [-0.04, -0.01]	
Schumacher,2008a	5	269	1	268	9.4%	0.01 [-0.00, 0.03]	
Schumacher,2008b	1	134	1	268	10.2%	0.00 [-0.01, 0.02]	+
Subtotal (95% CI)		3758		3746	35.1%	0.00 [-0.02, 0.03]	•
Total events	195		248				
Heterogeneity: Tau ² =	0.00; Chi ²	= 22.20	, df = 3 (F	o < 0.00	001); l ² = 8	36%	
Test for overall effect:	Z = 0.21 (F	P = 0.84)					
Total (05% CI)		0376		9953	100.0%	0.001.0.00.0.011	•
Total avante	214	3310	206	0000	100.070	0.00[-0.00, 0.01]	
Hotorogonoity Tou? -	0.00 · Chia	- 27 01	JUD	0~00	0011-12-	740	
Tect for overall effect	0.00, CIII ⁻ 7 – 0 70 /0	- 37.01 - 0.40	, ui – 101	(r ≤ 0.0	, in the second s	140	-0.1 -0.05 0 0.05 0.1
Test for cubarous diff.	2 - 0.79 (F	- 0.43) hiž - 0	17 df - 0	/P = 0	70) 12 - 0	04	Favours [experimental] Favours [control]
restion subdroub dille	erences. C	10 = 0.4	+7. ul = 2	ιr = 0.	/ 9). ["= 0	70	

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