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Comparison of the efficacy of febuxostat *vs.* benzbromarone in the treatment of gout: a meta-analysis in Chinese gout patients

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Abstract. – OBJECTIVE: Febuxostat and benzbromarone are two common drugs for the treatment of gout, but the clinical efficacy of these two drugs is controversial. This meta-analysis aimed to compare the efficacy of febuxostat and benzbromarone in the treatment of gout.

MATERIALS AND METHODS: PubMed, Embase, and the Cochrane Library were searched for articles related to febuxostat and benzbromarone in the treatment of gout from inception to January 7, 2023. Titles and abstracts were reviewed in accordance with predesigned inclusion and exclusion criteria, and data were extracted independently. The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the studies, and the continuous variables were expressed as the standard mean square error (SMD) by STATA 16 (Stata Corp., College Station, TX, USA). The sensitivity analysis was conducted by randomly removing a study, and the heterogeneity was analyzed by funnel plots and Egger's test.

RESULTS: According to the search strategy, a total of 1,043 publications were retrieved from the three aforementioned databases, of which 45 publications were excluded due to duplication. Fourteen studies remained after screening titles and abstracts, and a total of 7 studies met the inclusion criteria after a comprehensive evaluation of the 14 studies. Meta-analysis showed that the uric acid (UA)-reducing effect of febuxostat is better than that of benzbromarone, while febuxostat showed a better ability to improve the estimated glomerular filtration rate (eGFR) and reduce Cr and blood urea nitrogen (BUN). In terms of hepatotoxicity, benzbromarone was not as potent as febuxostat in increasing alanine transaminase (ALT) and aspartate transaminase (AST), suggesting that benzbromarone has less hepatotoxicity. Moreover, there was no significant difference in the effect on blood lipid levels between the two drugs.

CONCLUSIONS: The beneficial effect of febuxostat on renal function-related indexes such as the eGFR, Cr and BUN is significant, while benzbromarone is more effective in reducing UA and has relatively less hepatotoxicity. The specific efficacy of the two drugs needs to be confirmed by further research.

Key Words:
Febuxostat, Benzbromarone, Gout, Meta-analysis.

Introduction

Gout is a common inflammatory arthropathy caused by the deposition of monosodium urate (MSU) crystals in and around the joints and soft tissues[1,2]. It often occurs in people over 40 years old and results in stabbing pain, gnawing, burning, or throbbing of the joints. It can resolve spontaneously after 7-14 days and enter the asymptomatic period until the next attack of gout. With the prolongation of the course of the disease, it may develop into gouty arthritis, chronic gouty arthritis, or structural joint injury[3]. The latest survey shows that the incidence of gout in Asia, Europe, and North America has reached 0.6 to 0.9 per thousand, and the incidence in adults has reached 0.68% to 3.90%[3].

Febuxostat is a 2-arylthiazole derivative that reduces uric acid (UA) production primarily by inhibiting the effectiveness and selectivity of two forms of xanthine oxidase (XO). It noncompetitively

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blocks the activity of both enzymes by binding to their active sites. As a nonpurine xanthine oxidase inhibitor, it can selectively inhibit the oxidation and reduction form of xanthine oxidase and reduce the production of UA to treat gout[4,5]. Thus, febuxostat has an excellent UA-lowering effect in patients with overproduction of urate secretion[6]. Approximately 49% of febuxostat is recycled in urine and 45% in stool, so febuxostat is not approved in patients whose creatinine (Cr) clearance rate is less than 30 ml/min. The most common clinical side effects of febuxostat are cutaneous side effects. In addition, it is generally not recommended for patients with ischemic or congestive heart disease[5].

Benzbromarone is a benzofuran derivative that can control the apical (luminal) urate exchanger in the human proximal tubule URAT1[7], increase urate excretion in proximal tubules, and reduce urate reabsorption, thereby increasing the excretion of UA by the kidneys and reducing serum and urinary UA in patients with hyperuricemia and gout[8,9]. Therefore, benzbromarone is more suitable for patients who have abnormal urate excretion[6]. Benzbromarone is mainly metabolized by cytochrome P450 2C9 (CYP2C9) in the liver, and the main metabolites, which are excreted through bile and feces, are 6-hydroxybenzbromarone, which is related to its uricosuric effect, and 1'-hydroxybenzbromarone. Benzbromarone has a half-life of approximately 3 hours, and the active metabolites can last for 30 hours to prolong the curative effect. In light of previous reports[9] of hepatotoxicity and experimental evidence collected thus far, it is recommended to use it in patients with mild to moderate chronic kidney disease and it should be avoided in patients with known liver disease or asymptomatic hyperuricemia. In addition, benzbromarone is not suitable for patients with urinary calculus or crystal deposition[10].

However, the clinical efficacy of these two drugs in the treatment of gout has been controversial, according to the results of previous studies in the literature. In terms of renal function, some studies[6,11-13] have suggested that febuxostat is considered superior to benzbromarone in reducing UA and Cr and increasing the estimated glomerular filtration rate (eGFR). However, Yan et al[14] concluded that benzbromarone is advantageous for reducing UA. In terms of hepatotoxicity, some recent studies[6,14] have shown that febuxostat has a more significant effect on increasing aspartate transaminase (AST) and alanine transaminase (ALT). Zhou et al[10] concluded that febuxostat could lead to abnormal liver function. However, some studies[12,13] suggest that there is no significant difference in the effects of the two drugs on AST. In terms of reducing blood lipids, Wu et al[15] concluded that febuxostat reduces cholesterol (TC) and triglycerides (TG) more effectively than benzbromarone. However, some previous studies[6,10] have suggested that the effects of febuxostat use in the treatment of gout may be more closely related to hyperlipidemia. Nevertheless, Yan et al[14] concluded that there is no significant difference in the effect of the two drugs on blood lipid levels.

Among previous studies, there is no consensus on the effects of the two drugs on the human body. There has not been a meta-analysis with a separate comparison of the efficacy of febuxostat and benzbromarone in the treatment of gout. To systematically compare the effects of these two drugs on human liver function, renal function and blood lipids, we carried out this meta-analysis and compared the therapeutic effects and influence of the two drugs more comprehensively in different post-treatment time periods.

Materials and Methods

Standard Protocol Approvals, Registrations

This meta-analysis was conducted and reported in accordance with Cochrane recommendations[16], the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[17], and the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) guidelines[18], and the protocol was registered in PROSPERO with the registration unique identifying number (UIN) of CRD42023406675. Because of the nature of the study, informed consent and Institutional Review Board approval are not required.

Search Strategy

PubMed, Embase, and the Cochrane Library were searched for articles related to febuxostat and benzbromarone in the treatment of gout from inception to January 7, 2023. There were no restrictions on language or publication time. A total of two individuals with retrieval experience conducted the literature review. Medical Subject Headings (MeSH) in Cochrane Library or PubMed and subject headings (Emtree) in Embase were used for the controlled vocabulary. Search terms included the following: "Gout" or "Hyperuricemia" or "Uric Acid" or "Arthritis, Gouty"; "Febuxostat" or "Xanthine Oxidase"; and "Benzbromarone". By manually searching

for systematic reviews and meta-analyses with similar terms and referencing the citations of those studies, we were able to identify potentially relevant articles to the greatest possible extent. All literature downloaded from the three databases was integrated into Endnote X9 software, and duplicate literature was identified and manually deleted.

Selection Criteria

In accordance with the principles of the PICOS, strict inclusion and exclusion criteria were established.

The inclusion criteria were as follows:

(1) Participants: patients with gout were included.
(2) Intervention: febuxostat was used as a treatment medicine.
(3) Comparison: benzbromarone was used as a treatment medicine.
(4) Outcome: the evaluation included outcomes of the efficacy of both drugs, such as renal function indexes, including UA, Cr, eGFR, and blood urea nitrogen (BUN); indexes for evaluating liver function, including ALT and AST; and indexes for evaluating blood lipid levels, including TC and TG.
(5) Study design: prospective or retrospective cohort study.

The exclusion criteria were as follows:

(1) The efficacy of febuxostat and benzbromarone in the treatment of gout was not assessed.
(2) Conference proceedings, case reports, clinical trial protocols, letters, correspondence, and reviews were excluded.
(3) The results of the study on the clinical efficacy of these two drugs have not been reported, or the reported data are insufficient.

Two investigators reviewed the titles and abstracts independently in accordance with the inclusion and exclusion criteria discussed above. We also performed cross-checks to ensure accuracy. Any differences were resolved through discussion and consensus with a third reviewer. Finally, 7[6,10-15] studies that met the requirements were included (Table I).

Data Extraction

Three investigators used predesigned data extraction tables to extract data from the included articles. Extracted data included first author, publication year, study design, region of study, study period, sample size, age, sex, follow-up period, type of treatment, renal function, serum urate, serum Cr, outcomes, and adjusted variables. At the same time, these articles were screened again for eligibility. Any inconsistencies were resolved through information review and discussion among the authors.

Quality Assessment

Two investigators used the Newcastle-Ottawa scale (NOS) to assess the methodological quality of the included studies independently (Table II)[19].

Table I. Characteristics of studies included in the meta-analysis.

First author	Year	Study Design	Region	Observation Period	Sample size	Average age (years)	Follow-up period (months)	Intervention+Drug dosing (mg/d)
Zhou et al[10]	2017	Retrospective cohort study	China	2011.11-2014.12	G1: 60 G2: 30	G1: 45.55 G2: 46.5	G1: 6 G2: 6	G1: Febuxostat 40 Febuxostat 80 G2: Benzbromarone 50
Liang et al[6]	2019	Prospective cohort study	China	2015.11-2017.9	G1: 105 G2: 109	G1: 52.42 G2: 50.27	G1: 2.8 G2: 2.8	G1: Febuxostat 20 m Sodium Bicarbonate 3,000 G2: Benzbromarone 25 Sodium Bicarbonate 3,000
Chou et al[11]	2017	Inception cohort study	China	2003.1-2015.12	G1: 138 G2: 399	G1: 65.8 G2: 65.8	G1: 7 G2: 14.6	G1: Febuxostat 40.0 G2: Benzbromarone 88.9
Liu et al[12]	2022	Retrospective study	China	2018.1-2020.9	G1: 23 G2: 50	G1: 48.3 G2: 47.68	G1: 0.93 G2: 0.93	G1: Febuxostat 20 G2: Benzbromarone 25
Wu et al[15]	2019	Retrospective study	China	2015.1-2017.12	G1: 52 G2: 43	G1: 48.37 G2: 44.84	G1: 0 G2: 0	G1: Febuxostat 40 G2: Benzbromarone 50
Yu et al[13]	2018	Prospective cohort study	China	2014.10-2017.10	G1: 33 G2: 33	G1: 59.5 G2: 63.2	G1: 12 G2: 12	G1: Febuxostat 22.3 G2: Benzbromarone 35.9
Yan et al[14]	2022	Prospective cohort study	China	2019.5-2021.1	G1: 98 G2: 98	G1: 43.29 G2: 43.89	G1: 2.8 G2: 2.8	G1: Febuxostat 20 G2: Benzbromarone 25

Table continued

Table I *(continued)*. Characteristics of studies included in the meta-analysis.

First author	Renal function	Mean serum (mg/dL)	Mean serum creatinine (μmol/L)	Outcomes	Adjusted variables
Zhou et al[10]	G1: UA: 10.27 mg/dL G2: UA: 10.94 mg/dL	G1: 10.27 G2: 10.94	G1: 64.71 G2: 65.42	UA, ALT, Cr, AST	covariates
Liang et al[6]	G1: Cr: 84.21 μmol/L CCr: 105.93 mL/min sUA: 561.10 μmol/L G2: Cr: 81.13 μmol/L CCr: 108.86 mL/min sUA: 554.90 μmol/L	G1: 9.43 G2: 9.32	G1: 84.21 G2: 81.13	sUA, CCr, Cr	NR
Chou et al[11]	G1: sUA: 9.5 mg/dL G2: sUA: 9.4 mg/dL	G1: 9.5 G2: 9.4	G1: 265.2 G2: 150.28	sUA, eGFR, Cr	Propensity score, eGFR
Liu et al[12]	G1: eGFR: 72.31 mL/min/1.73 m^2 G2: eGFR: 87.79 mL/min/1.73 m^2	G1: 9.36 G2: 8.72	G1: 109.62 G2: 89.28	sUA, sCr, Aspartate amino-transferase, eGFR, 24 h urinary uric acid, 24 h Urinary creatinine, FEUA, Alanine transaminase	eGRF
Wu et al[15]	G1: NR G2: NR	G1: 9.72 G2: 9.97	G1: NR G2:NR	UA, TC, TG	NR
Yu et al[13]	G1: eGFR: 38.5 mL/min/1.73 m^2 BUN: 10.4 mmol/L ACR: 39.3 mg/mmol G2: eGFR: 41.2 mL/min/1.73 m^2 BUN: 9.1 mmol/L ACR: 38.2 mg/mmol	G1: 9.6 G2: 8.87	G1: 169.1 G2: 151.5	UUA, BUN, NAG, Urine IgG, AST, HDL, Hemoglobin, Myoglobin, Albumin	NR
Yan et al[14]	G1: eGFR: 94.6 mL/min/1.73 m^2 Cr: 85 μmol/L G2: eGFR: 96.3 mL/min/1.73 m^2 Cr: 82 μmol/L	G1: 8.77 G2: 8.7	G1: 85 G2: 82	Fasting glucose, TG, TC, AST, ALT, eGFR, sCr	NR

ACR: Albumin to creatinine ratio; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; CCr: creatinine clearance rate; Cr: Creatinine; eGFR: Estimated glomerular filtration rate; FEUA: Fraction excretion of uric acid; HDL: High-density lipoprotein; IgG: Immunoglobulin G; NAG: N-acetyl-beta-d-glucosaminidase; NR: Not Reported; SCr: Serum Creatinine; sUA: Serum uric acid; TC: Cholesterol; TG: Triglyceride; UA: Uric acid; UUA: Urine uric acid.

The scale included selection (4 scores), comparability (2 scores), and exposure/outcome (3 scores), with a total of 9 points. Scores ≥ 8 were considered of high quality[20].

Statistical Analysis

The results were divided into baseline (before medication), short-term (less than 5 weeks), mid-term (6-10 weeks), and long-term (10 weeks or more) by researchers. Statistical analysis was performed using STATA 16 (Stata Corp, College Station, TX, USA), and the standard mean difference (SMD) was used to analyze continuous data. The researchers also performed a sensitivity analysis and used a funnel plot to evaluate publication bias. Publication bias was evaluated using Egger's test and funnel plot symmetry. $p < 0.05$ indicated that there was publication bias. The heterogeneity between studies was evaluated by the Cochrane Q test and I^2 test, and $I^2 \geq 50\%$ or $p < 0.05$ was used as the criterion for judging the statistical significance of heterogeneity[20].

Results

Search Results

According to the search strategy, a total of 1,043 publications were retrieved from the three aforementioned databases, of which 45 publications were excluded due to duplication. Fourteen studies remained after a screening of titles and abstracts, and a total of 7[6,10-15] studies met the inclusion criteria after a comprehensive evaluation of the 14 studies. The detailed process is shown in Figure 1.

Table II. The methodological quality score of the included studies based on the Newcastle-Ottawa Scale (NOS).

			Selection				Comparability	Exposure/Outcome			Total Score	
Author	year	Study Design	Representativeness of cohort *	Selection of control cohort *	Ascertainment of exposure *	Outcome not present at start *	Comparability of cohorts **	Assessment of outcome *	Length of follow-up *	Adequacy of follow-up *	Total score 9 *	Risk of Bias
Zhou et al[10]	2017	Retrospective cohort study	*	*	*	*	**	*	*	*	9	Low
Liang et al[6]	2019	Prospective cohort study	*	*	*	*	**	*	*	*	8	Low
Chou et al[11]	2017	Retrospective cohort study	*	*	*	*	**	*	*	*	8	Low
Liu et al[12]	2022	Retrospective study	*	*	*	*	**	*		*	8	Low
Wu et al[15]	2019	Retrospective study	*	*	*	*	*	*			6	High
Yu et al[13]	2018	Prospective cohort study	*	*	*	*	**	*	*	*	9	Low
Yan et al[14]	2022	Prospective cohort study	*	*	*	*	**	*	*	*	9	Low

*: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories, which means one point. **: A maximum of two stars can be given for comparability, which means two points.

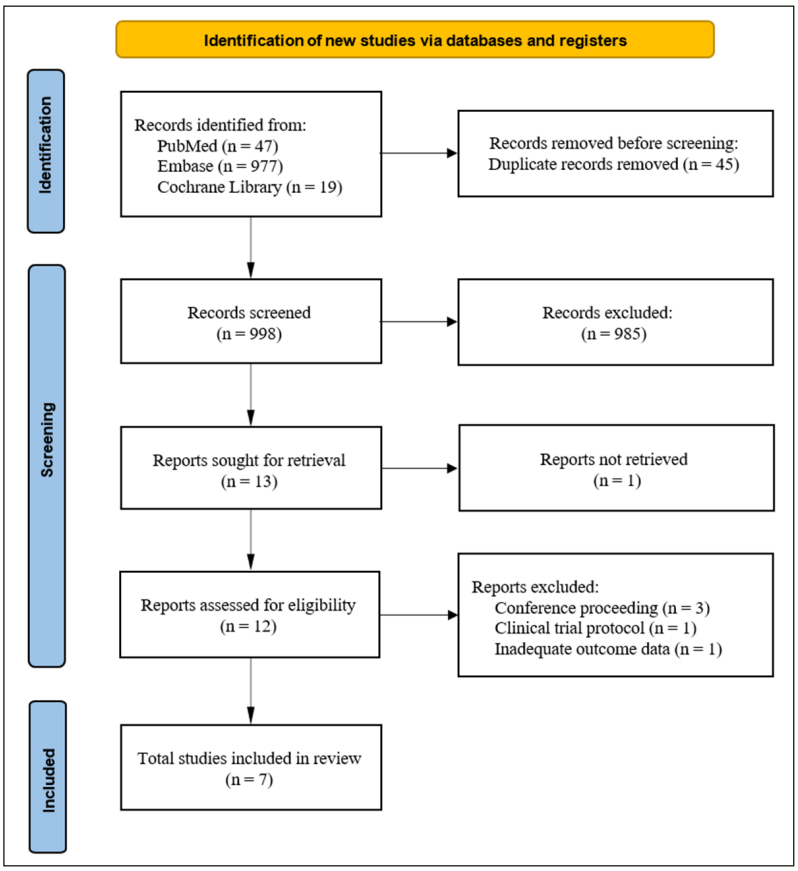

Figure 1. PRISMA Flowchart

Baseline Characteristics

Seven[6,10-15] cohort studies published between 2017 and 2020 were included, of which 85.71% (6/7) were rated as "high quality" (Table II). Treatment was administered to 1,271 patients with gout, of which 509 patients received febuxostat treatment and 762 patients received benzbromarone treatment, with mean ages of 55.34 years and 57.52 years, respectively. Among the seven included studies, three were prospective cohort studies[6,13,14], and four were retrospective cohort studies[10-12,15], all of which were conducted in China[6,10-15]. The specific demographic characteristics are shown in Table I.

Outcomes

Renal function

By analyzing the UA, Cr, eGFR, and BUN of gout patients in different periods, the efficacy of the two drugs in improving renal function was compared.

UA

A total of 7 studies[6,10-15] analyzed UA (n = 1,271 patients; 509 in the febuxostat group and 762 in the benzbromarone group; Figure 2). All studies[6,10-15] reported baseline data (SMD = 0.06, 95% CI: -0.11 to 0.23). Four studies[6,12,14,15] reported short-term follow-up data (SMD = 0.26, 95% CI: -0.08 to 0.60). Three studies[6,14,15] reported mid-term follow-up data (SMD = 0.30, 95% CI: -0.14 to 0.74). Three studies[6,13,14] reported long-term follow-up data (SMD = 0.33, 95% CI: -0.22 to 0.89). The data for each period showed that there was no significant difference in UA between the two groups.

Cr

Six studies[6,10-14] analyzed the Cr of two groups of patients (n = 1,176 patients; 457 in the febuxostat group and 719 in the benzbromarone group; Figure 3), and all 6 studies[6,10-14] reported baseline data showing that the Cr of the febuxostat group was higher than that of the benzbromarone group before treatment (SMD = 0.32, 95% CI: 0.07 to 0.56). However, 3 studies[6,12,14] with short-term follow-up data (SMD = 0.25, 95% CI: -0.09 to 0.58), 2 studies[6,14] with mid-term follow-up data (SMD = 0.08, 95% CI: -0.33 to 0.49), and 3 studies[6,13,14] with long-term follow-up data (SMD = 0.06, 95% CI: -0.14 to 0.27) showed no significant differences in Cr between the two groups.

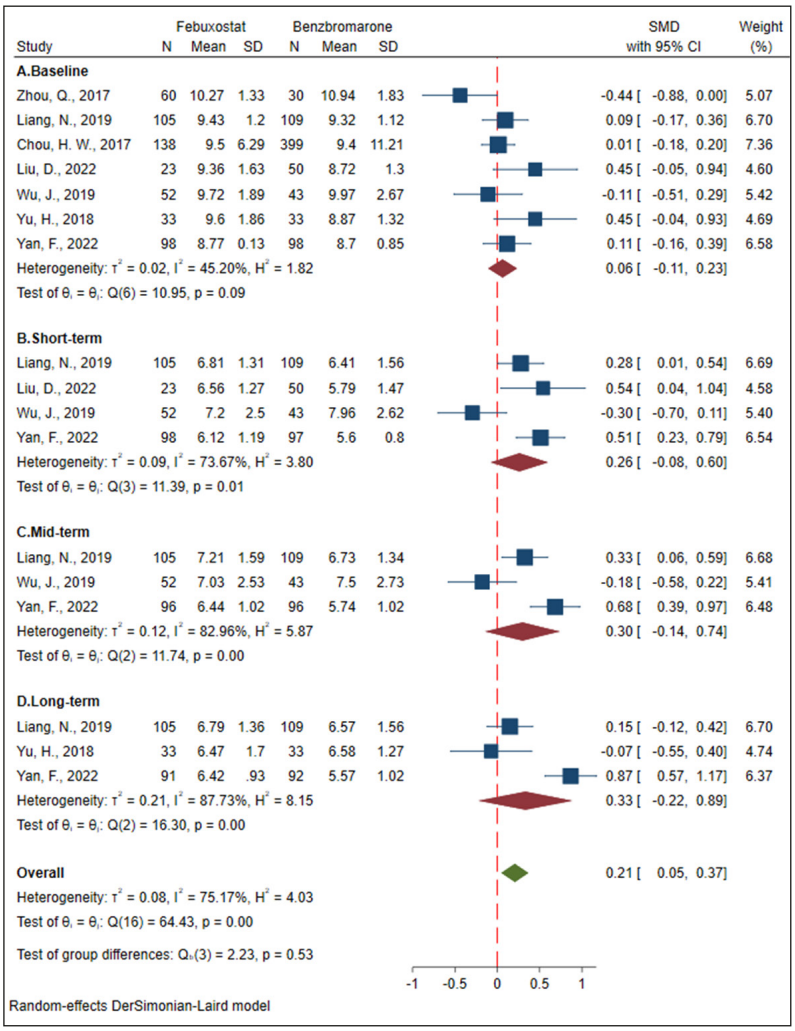

Figure 2. Forest plots comparing UA in patients with gout after treatment with febuxostat or benzbromarone during the baseline, short-term, mid-term and long-term.

eGFR

Data from 4 studies[11-14] that analyzed eGFR were integrated (n = 872 patients; 292 in the febuxostat group and 580 in the benzbromarone group; Figure 4). Baseline data were reported in all 4 studies[11-14] (SMD = -0.22, 95% CI: -0.43 to -0.01), showing that the eGFR of the febuxostat group was higher than that of the benzbromarone group before treatment. However, 2 studies[12,14] reported short-term follow-up data (SMD = -0.24, 95% CI: -0.49 to 0.00), one study[14] reported medium-term follow-up data (SMD = 0.06, 95% CI: -0.22 to 0.35), and two studies[13,14] reported long-term follow-up data (SMD =-0.07, 95% CI: -0.32 to 0.18) and showed no significant difference in eGFR between the two groups.

BUN

A total of two studies[6,13] analyzed BUN (n = 280 patients; 138 in the febuxostat group and 142 in the benzbromarone group; Figure 5). Two studies[6,13] reported baseline data (SMD = 0.42, 95% CI: 0.18 to 0.65), 1 study[6] reported short-term follow-up data (SMD = 0.65, 95% CI: 0.37 to 0.92), and 1 study[6] reported mid-term follow-up data (SMD = 0.50, 95% CI: 0.23 to 0.77), showing that the febuxostat group had a higher BUN level than the benzbromarone group. However, data from 2 studies[6,13] reporting long-term follow-up showed that there was no significant difference in BUN between the two groups (SMD = 0.240.14, 95% CI: -0.38 to 0.86).

Liver function

To compare the hepatotoxicity of the two drugs, ALT and AST in patients with gout were analyzed at different time periods.

ALT

A total of 4 included studies[6,10,13,14] analyzed ALT (n = 566 patients; 296 in the febuxostat

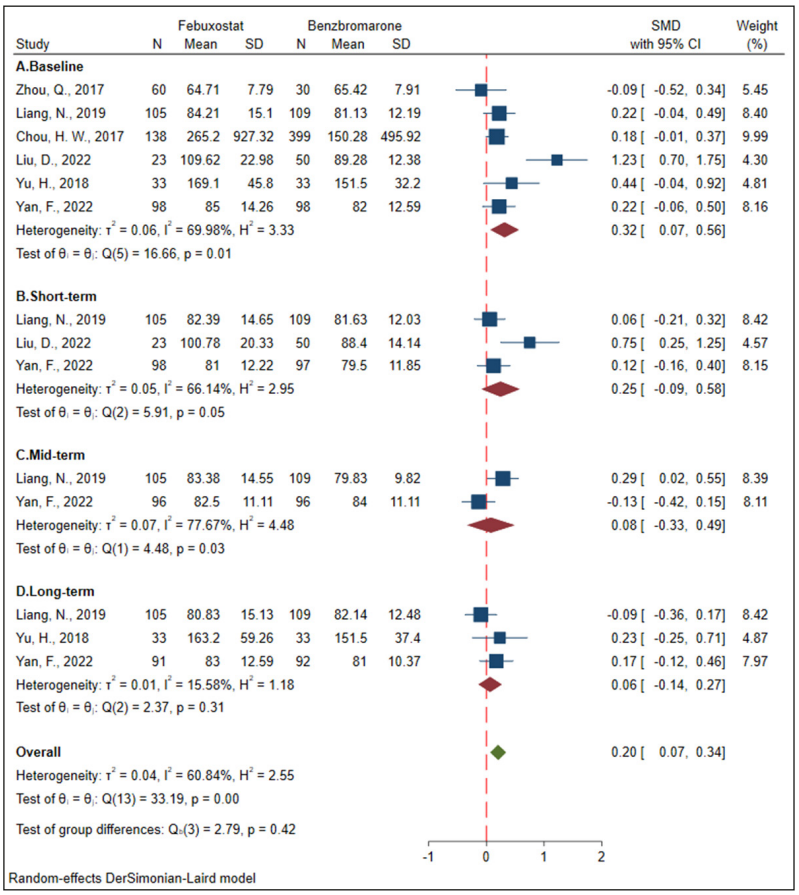

Figure 3. Forest plots comparing Cr in patients with gout after treatment with febuxostat or benzbromarone during the baseline, short-term, mid-term and long-term.

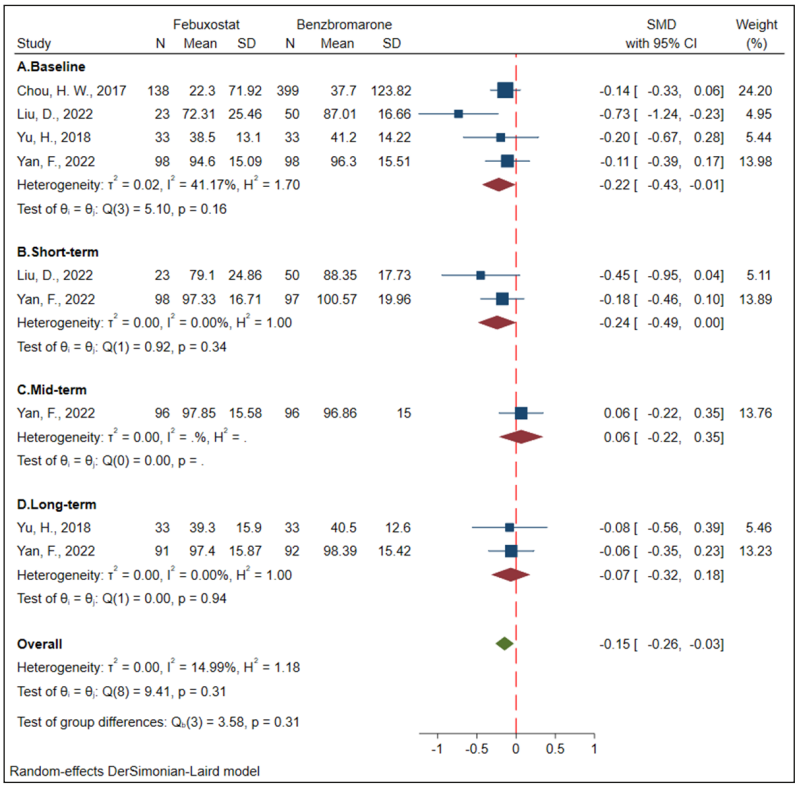

Figure 4. Forest plots comparing the eGFR in patients with gout after treatment with febuxostat or benzbromarone at baseline and in the short-term, mid-term and long-term.

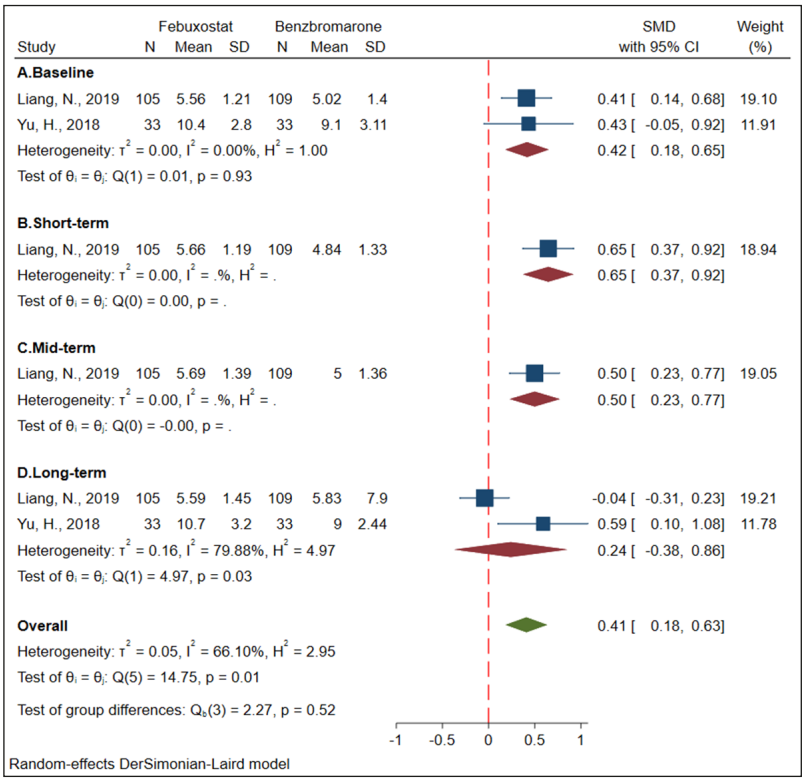

Figure 5. Forest plots comparing BUN in patients with gout after treatment with febuxostat or benzbromarone during the baseline, short-term, mid-term and long-term.

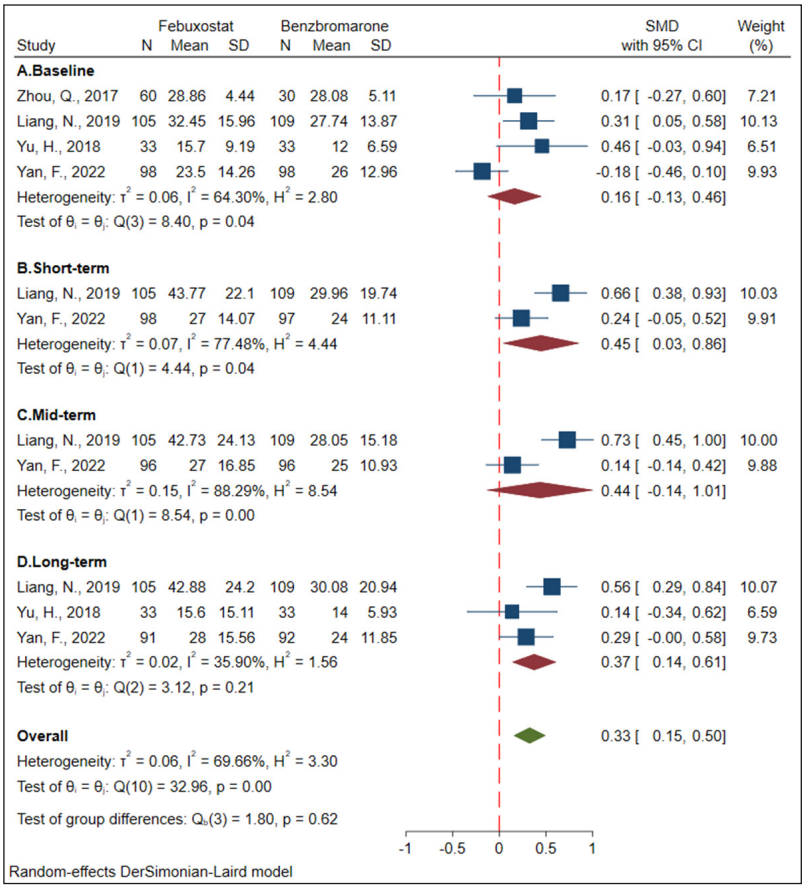

Figure 6. Forest plots comparing ALT in patients with gout after treatment with febuxostat or benzbromarone during the baseline, short-term, mid-term and long-term.

group and 270 in the benzbromarone group; Figure 6). All of these studies[6,10,13,14] reported baseline data (SMD = 0.16, 95% CI: -0.13 to 0.46), and 2 studies[6,14] reported mid-term follow-up data (SMD = 0.44, 95% CI: -0.14 to 1.01). Baseline and mid-term follow-up results showed that there was no significant difference in ALT between the two groups. However, 2 studies[6,14] reported short-term follow-up data (SMD = 0.45, 95% CI: 0.03 to 0.86), and 3 studies[6,13,14] reported long-term follow-up data (SMD = 0.37, 95% CI: 0.14 to 0.61), showing that ALT in the febuxostat group was higher than that in the benzbromarone group.

AST

Four studies[6,10,13,14] analyzed AST (n = 566 patients; 296 in the febuxostat group and 270 in the benzbromarone group; Figure 7). All 4 studies[6,10,13,14] reported baseline data (SMD = -0.03, 95% CI: -0.33 to 0.27), and 2 studies[6,14] reported mid-term follow-up data (SMD = 0.20, 95% CI: -0.19 to 0.60). The results showed that there was no significant difference in AST between the two groups at baseline and mid-term follow-up. However, 2 studies[6,14] reported short-term follow-up data (SMD = 0.37, 95% CI: 0.18 to 0.57), and 3 studies[6,13,14] reported long-term follow-up (SMD = 0.32, 95% CI: 0.13 to 0.50), showing that AST in the febuxostat group was higher than that in the benzbromarone group.

Blood lipids

The TC and TG levels of gout patients in different periods were analyzed to compare the efficacy of the two drugs in improving the level of blood lipids.

TC

A total of 4 studies[6,13-15] were conducted to analyze TC (n = 511 patients; 255 in the febuxostat group and 256 in the benzbromarone group; Figure 8). Four studies[6,13-15] reported baseline data (SMD = -0.11, 95% CI: -0.29 to 0.06), 3 studies[6,14,15] reported short-term follow-up data (SMD = -0.14, 95% CI: -0.33 to 0.04), 3 studies[6,14,15] reported mid-term follow-up data (SMD = -0.25, 95% CI: -0.55 to 0.06), and 3 studies[6,13,14] reported long-term follow-up data (SMD = -0.15, 95% CI: -0.34 to 0.03). The results for each period showed that there was no significant difference in TC between the two groups.

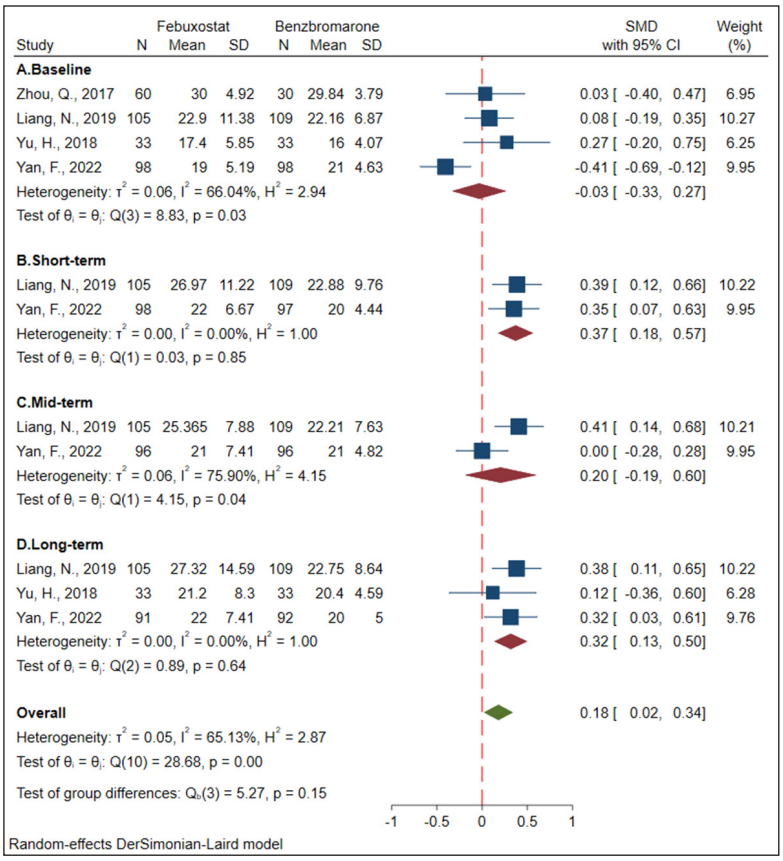

Figure 7. Forest plots comparing AST in patients with gout after treatment with febuxostat or benzbromarone during the baseline, short-term, mid-term and long-term.

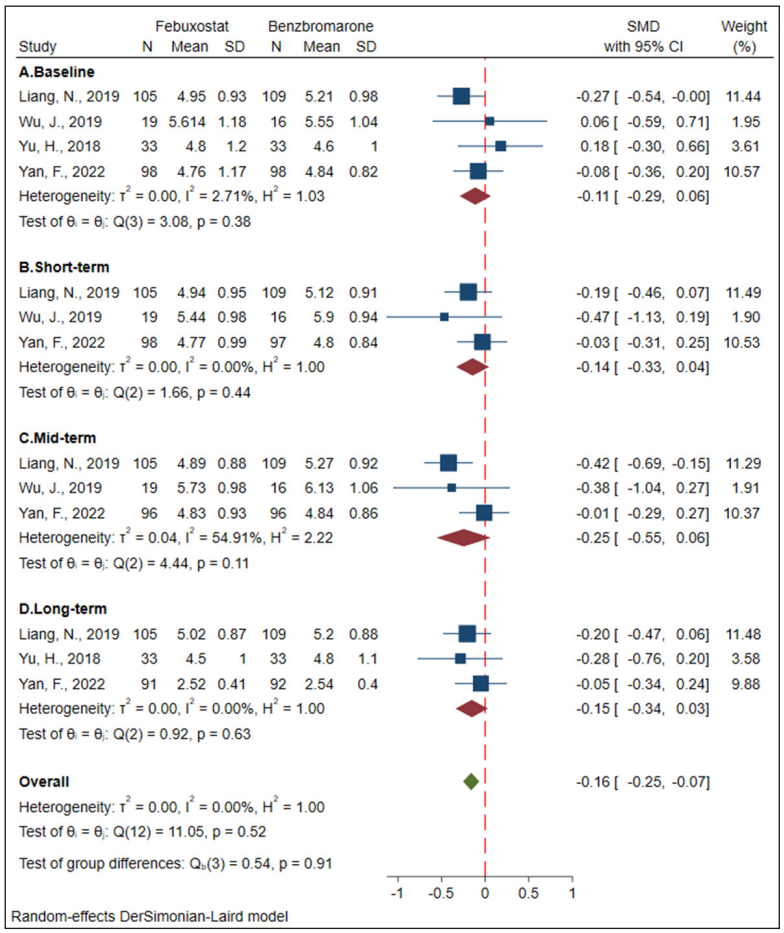

Figure 8. Forest plots comparing TC in patients with gout after treatment with febuxostat or benzbromarone during the baseline, short-term, mid-term and long-term.

TG

Three studies[6,13,14] analyzed TG data for each period (n = 511,255 in the febuxostat group and 256 in the benzbromarone group; Figure 9). Three studies[6,13,14] reported baseline data (SMD = -0.15, 95% CI: -0.32 to 0.02), 2 studies[6,14] reported short-term follow-up data (SMD = 0.11, 95% CI: -0.15 to 0.37), 2 studies[6,14] reported medium-term follow-up data (SMD = 0.08, 95% CI: -0.10 to 0.27), and 3 studies[6,13,14] reported long-term follow-up data (SMD = 0.13, 95% CI: -0.09 to 0.34). Data from each period showed that there was no significant difference in TG between the two groups.

Publication Bias and Sensitivity Analysis

A sensitivity analysis of these outcomes was conducted by randomly removing a study to evaluate the stability of the results (**Supplementary Table**). The study of Wu et al[15] provided poor evidence, and there are limitations, such as the fact that the therapies were not randomized or double-blinded, the sample size of the study was small, and confounding factors were not considered. After exclusion, the short-term follow-up data (SMD = 0.41, 95% CI: 0.23 to 0.59) and the mid-term follow-up data (SMD = 0.49, 95% CI: 0.29 to 0.69) of UA showed that the UA of the febuxostat group was significantly higher than that of the benzbromarone group.

In addition, the combined data related to renal function, hepatotoxicity and blood lipids remained similar after exclusion.

Funnel plots were constructed to assess publication bias (**Supplementary Table**). All the outcome data were basically symmetrical, indicating that the outcome basically had no publication bias. All the outcome indexes were tested by Egger's test, which confirmed that the short-term follow-up result of TG was unstable ($p < 0.05$) (Table III), thus indicating that the results should be treated with caution. In addition, due to the limited sample sizes of the included studies, the detection of publication bias may not be sufficient.

Adopting the method of pruning and filling to adjust the publication bias of all outcomes, it was found that there was one potential deletion study

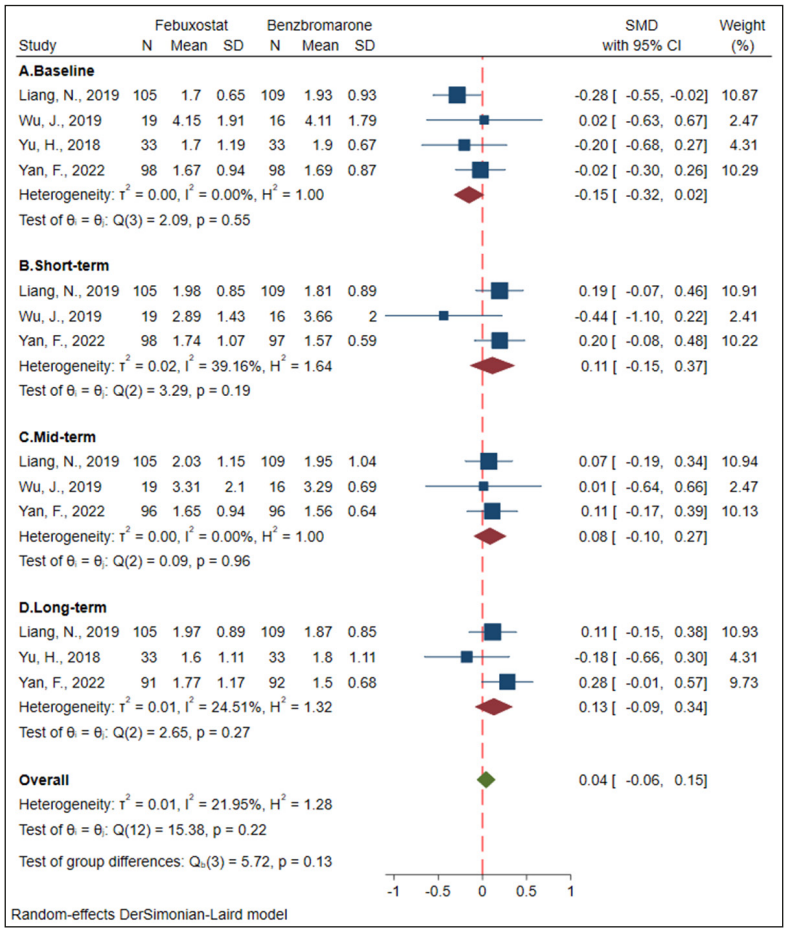

Figure 9. Forest plots comparing TG in patients with gout after treatment with febuxostat or benzbromarone at baseline and in the short-term, mid-term and long-term.

at the short-term follow-up of UA, the baseline of eGFR, the baseline and long-term follow-up of BUN, the baseline of AST and the baseline of TG, and two potential deletion studies in the long-term follow-up of Cr, the baseline of ALT and the baseline of TG, which were consistent with the preliminary results after publication bias correction (**Supplementary Table**).

Discussion

Principal Findings

Febuxostat and benzbromarone are two common drugs for the treatment of gout, but the clinical efficacy of these two drugs is controversial. To compare the efficacy of the two drugs in the treatment of gout, we conducted this meta-analysis, which included 7 studies. Among the renal function-related indicators, the study of Wu et al[15] had a great impact on the outcome of UA, did not use random or double-blind treatment, had a small sample size, and did not consider confounding factors and other limitations; thus, the study of Wu et al[15] was excluded from the analysis of short- and medium-term data. The results showed that benzbromarone was better than febuxostat in reducing UA, while febuxostat had a better effect in improving eGFR and reducing Cr and BUN. In terms of hepatotoxicity, benzbromarone is not as strong as febuxostat in increasing ALT and AST, suggesting that benzbromarone has less hepatotoxicity. In addition, there was no significant difference in the effect on blood lipid levels between the two drugs.

Comparison with Other Studies and Potential Mechanisms

To our knowledge, there is no other meta-analysis comparing the efficacy of febuxostat and benzbromarone in the treatment of gout. The difference in the efficacy of the two drugs in patients with gout is related to the different mechanisms of gout. Studies[6] have shown that benzbromarone can reduce UA by inhibiting UA reabsorption in renal proximal tubules to increase renal UA excretion. The data show that the increasing UA of 80 to 90%

Table III. Summary of results.

Outcome	No. of trials	No. of participants	Mean difference/ Odds Ratio (95% CI)	*p*-value	Heterogeneity	Egger's test *p*-value
UA						
Baseline	7	1,271	0.06 (-0.11, 0.23)	0.09	45.20%	0.997
Short-term	4	577	0.26 (-0.08, 0.60)	0.01	73.67%	0.641
Mid-term	3	501	0.30 (-0.14, 0.74)	0.00	82.96%	0.224
Long-term	3	463	0.33 (-0.22, 0.89)	0.00	87.73%	0.341
Cr						
Baseline	6	1,176	0.32 (0.07, 0.56)	0.01	69.98%	0.166
Short-term	3	482	0.25 (-0.09, 0.58)	0.05	66.14%	0.132
Mid-term	2	406	0.08 (-0.33, 0.49)	0.03	77.67%	NR
Long-term	3	463	0.06 (-0.14, 0.27)	0.31	15.58%	0.489
eGFR						
Baseline	4	872	-0.22 (-0.43, -0.01)	0.16	41.17%	0.501
Short-term	2	268	-0.24 (-0.49, 0.00)	0.34	0.00%	NR
Mid-term	1	192	0.06 (-0.22, 0.35)	NR	NR	NR
Long-term	2	249	-0.07 (-0.32, 0.18)	0.94	0.00%	NR
BUN						
Baseline	2	280	0.42 (0.18, 0.65)	0.93	0.00%	NR
Short-term	1	214	0.65 (0.37, 0.92)	NR	NR	NR
Mid-term	1	214	0.50 (0.23, 0.77)	NR	NR	NR
Long-term	2	280	0.24 (-0.38, 0.86)	0.03	79.88%	NR
ALT						
Baseline	4	566	0.16 (-0.13, 0.46)	0.04	64.30%	0.380
Short-term	2	409	0.45 (0.03, 0.86)	0.04	77.48%	NR
Mid-term	2	406	0.44 (-0.14, 1.01)	0.00	88.29%	NR
Long-term	3	463	0.37 (0.14, 0.61)	0.21	35.90%	0.322
AST						
Baseline	4	566	-0.03 (-0.33, 0.27)	0.03	66.04%	0.853
Short-term	2	409	0.37 (0.18, 0.57)	0.85	0.00%	NR
Mid-term	2	406	0.20 (-0.19, 0.60)	0.04	75.90%	NR
Long-term	3	463	0.32 (0.13, 0.50)	0.64	0.00%	0.064
TC						
Baseline	4	511	-0.11 (-0.29, 0.06)	0.38	2.71%	0.220
Short-term	3	444	-0.14 (-0.33, 0.04)	0.44	0.00%	0.512
Mid-term	3	441	-0.25 (-0.55, 0.06)	0.11	54.91%	0.519
Long-term	3	463	-0.15 (-0.34, 0.03)	0.63	0.00%	0.574
TG						
Baseline	4	511	-0.15 (-0.32, 0.02)	0.55	0.00%	0.265
Short-term	3	444	0.11 (-0.15, 0.37)	0.19	39.16%	0.037
Mid-term	3	441	0.08 (-0.10, 0.27)	0.96	0.00%	0.168
Long-term	3	463	0.13 (-0.09, 0.34)	0.27	24.51%	0.267

p-value < 0.05: statistical significance. I^2 describes the proportion of variation estimated to be due to heterogeneity. I^2 value < 25%: minimal heterogeneity, 25% ≤ I^2 value < 50: moderate heterogeneity, I^2 value ≥ 50%: substantial heterogeneity. Baseline: before medication; Short-term: ≤ 5 weeks; Mid-term: 5-10 weeks; Long-term: > 10 weeks. CI: confidence interval; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; Cr: Creatinine; eGFR: Estimated glomerular filtration rate; NR: Not Reported; TC: Cholesterol; TG: Triglyceride; UA: Uric acid.

of patients with primary gout is caused by relatively inadequate UA excretion. Therefore, benzbromarone seems to be more effective in reducing UA in patients with gout[21]. Yan et al[14] showed that the percentage of participants with serum UA levels < 6 mg/dl in the benzbromarone group during treatment was significantly higher than that in the febuxostat group, which supports our results.

During febuxostat metabolism, up to 40% of the drugs are directly metabolized by diphosphate-uridine diphosphate glucosyl transferase (UGT), including UGT1A1, UGT1A8 and UGT1A9, to form acyl glucuronides. Approximately 35% of febuxostat is oxidized by cytochrome P450 (CYP) 1A1, CYP1A2, CYP2C8 and CYP2C9[22]. Compared with febuxostat, benzbromarone did not significantly increase ALT and AST, suggesting that long-term administration of febuxostat caused more serious damage to hepatocytes. Zhou et al[10] showed that abnormal liver function was

more common in the febuxostat group, which is consistent with our results. Yan et al[14] results showed that the percentage of participants with increased AST in the benzbromarone group was significantly lower than that in the febuxostat group, which deviated from our results. However, the difference reported in the results of Liang et al[6] study was not statistically significant. Therefore, the hepatotoxicity of the two drugs needs to be evaluated by larger sample-size studies.

Implications

Our study has some implications for the choice of drugs for the clinical treatment of gout patients in the future. The mechanisms of the two drugs are different in the treatment of gout. Febuxostat is more suitable for patients with excessive urate secretion, while benzbromarone is more suitable for patients with insufficient urate excretion[6]. For patients with excessive urate secretion and insufficient urate excretion, the use of febuxostat and benzbromarone will achieve a better UA reduction effect[6]. The two drugs are metabolized through the liver, which may lead to a certain degree of hepatotoxicity. Liver function and enzymes should be actively monitored during the use of these two drugs[9]. In patients with liver dysfunction, they should be used with caution. As an XO inhibitor, febuxostat can prevent kidney stones by antioxidation and reducing UA excretion, and it should be given priority in gout patients with renal insufficiency or kidney stones[13]. Clinicians should choose drugs reasonably and target them according to the occurrence mechanism of gout and the conditions of patients. At the same time, monitoring the liver function of patients in real-time should be conducted to avoid serious consequences of hepatotoxicity.

Strengths and Limitations

The advantage of this study was the comprehensive evaluation of the efficacy of febuxostat and benzbromarone in the treatment of gout using the eight outcome indicators of renal function (UA, Cr, eGFR, BUN), liver function (ALT, AST) and blood lipids (TC, TG). In addition, this study formulated and adopted a retrieval strategy that was not limited by time or language. Subject words and free words were used to conduct a comprehensive search in the PubMed, Embase, and Cochrane Library databases and to find potentially relevant studies as much as possible to avoid the impact of publication bias on the results. We followed the Preferred Reporting Items of the Meta-Analysis (PRISMA) guidelines and the NOS scale to analyze the results of this study[17,19]. Finally, to minimize the impact of medication time on the outcome, we counted and combined the baseline, short-term, mid-term, and long-term data of all outcomes. We also analyzed the heterogeneity and publication bias of the data in each period by means of forest plots, funnel plots, Egger's test, sensitivity analysis, and so on.

This meta-analysis also has some limitations. First, a total of 1,271 patients were reported in 7 studies, and the sample size of the total population was small. Second, all the included studies were from China, and the subjects were geographically limited and ethnically unitary, which may be because benzbromarone has been discontinued in most European countries since 2003 because of its possible severe hepatotoxicity. In addition, when using UA to evaluate renal function in patients with gout, a study had a significant impact on outcomes, which was corrected by sensitivity analysis. In addition, there are differences in baseline data between the two groups, which may be related to clinicians' medication choices. In the future, more well-documented and higher-level evidence studies are needed to analyze the differences between the two drugs in the treatment of gout.

Conclusions

Meta-analysis showed that febuxostat had a significant effect on increasing eGFR and reducing Cr and BUN, while benzbromarone had a better effect on reducing UA. Benzbromarone was not as significant as febuxostat in increasing ALT and AST, which may indicate lower hepatotoxicity with the use of benzbromarone. There was no significant difference in the efficacy of the two drugs in reducing blood lipids. However, the efficacy of the two drugs in the treatment of gout needs to be further confirmed in large, well-designed studies.

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Authors' Contributions
Conception and design: ML, ZX; Acquisition of data: All authors; Analysis and interpretation of data: CL, CY, CS, SX and ZL.; Drafting the manuscript: CL, CY; Critical revision of the manuscript: All authors; Statistical analysis: CL, CS, SX and ZL; Study supervision: ML, ZX.

Conflict of Interest
The authors declare no potential conflicts of interest.

Ethics Approval and Informed Consent
Because of the nature of the study, informed consent and Institutional Review Board approval are not required.

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Data Availability
The authors declare that the data collected was gathered from publicly available databases and is available upon request.

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