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ORIGINAL ARTICLE

Efficacy and safety of Febuxostat Versus Allopurinol in Hyperuricemic patients with or without Gout: A meta-analysis

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Abstract

OBJECTIVES: We conducted a meta-analysis to compare the febuxostat and allopurinol in hyperuricemic patients diagnosed with or without Gout.

MATERIAL AND METHODS: We searched the Pubmed, Cochrane and Embase electronic databases to identify the studies concerning febuxostat versus allopurinol in treatment of hyperuricemic subjects and/or gout updated to May, 2020. After rigorous evaluation on quality, the data was extracted from included publications.

RESULTS: A total of 10 articles involving 6989 subjects were included, with 4841 receiving febuxostat and 2148 using allopurinol. The pooled analysis showed that the febuxostat group (40, 80, or 120 mg QD) was greater in reducing serum urate levels than the allopurinol group (200 or 300 mg) (RR=1.56, 95% CI=1.37-1.78, $P<0.00001$). In addition, daily dosing of febuxostat 80 mg had greater efficacy to that of febuxostat 40 mg (RR=1.47, 95% CI=1.34-1.60, $P<0.00001$), and febuxostat 120 mg/day was associated with lower serum urate levels versus febuxostat 80 mg/day (RR=1.08, 95% CI=1.02-1.13, $P=0.004$). In terms of the adverse events, the pooling overall adverse events data did achieve advantage in the febuxostat group (RR=0.96, 95% CI=0.92-1.00, $P=0.04$). While, liver function test abnormalitie , diarrhea, skin rashes, musculoskeletal and connective tissue disorders, gastrointestinal disorders, headaches, the statistical significance between the two groups fail to be achieved ($P\geq0.05$).

CONCLUSION: Febuxostat was superior in reducing the serum urate levels of hyperuricemic patients, while with an acceptable tolerability profile than allopurinol. Moreover, our result suggested that dose titration to febuxostat 120 mg daily was superior to other daily dosing with regard to urate-lowering efficacy.

Abbreviations:

SUA	- serum uric acid
ULT	- urate-lowering pharmacotherapy
XO	- xanthine oxidase
MeSH	- Medical Subject Heading

INTRODUCTION

The hyperuricemia is a common biochemical aberration defined as serum uric acid (SUA) levels exceeding 6.8 mg/dl in the extracellular fluid, and is often manifested clinically as the deposition disease with urate crystal, gout (Pillinger *et al.* 2007). Gout is an inflammatory arthritis, manifesting as the deposition of monosodium urate crystals in synovial fluid and around the joints (Ruoff and Edwards 2016). The gout patients may suffer painful and destructive arthropathy, which will lead to impaired quality of life (Zhu *et al.* 2011).

Prolonged hyperuricemia is not only associated with high risk of gout- related disability, but also progression to metabolic disorders (Chen *et al.* 2007; Neogi 2011; Johnson *et al.* 1999). The primary therapy of hyperuricemia needs long-term urate- lowering and maintaining serum urate concentration belowing 360 lmol/L (6.0 mg/dL), which leads to the elimination of gout flares and resolution of urate crystal deposition (Perez-Ruiz *et al.* 2002; Sarawate *et al.* 2006).

The urate-lowering pharmacotherapy (ULT) is used to treat hyperuricemia, involve lowering urate production using a xanthine oxidase (XO) inhibitor. Allopurinol, a XO inhibitor, has been widely used to treat gout since the 1960s (https://www.medicines.org.uk/emc/product/ 5693/smpc. Accessed 08 April 2020; Underwood 2006). It is usually used for the prophylaxis of flares with low-dose, daily colchicine (Pascart and Frédéric 2019), and commonly approved at 300 mg daily in clinical practice. However, allopurinol is associated with multiple adverse effects, including increased toxicity when the rate of glomerular filtration is reduced, which may lead to the depression of bone marrow, hepatotoxicity and a risk of hypersensitivity syndrome (Gois and Souza 2013).

Febuxostat, a selective inhibitor of XO, was recently approved to treat hyperuricemia in gout subjects (Uloric® Full Prescribing Information. Takeda Pharmaceuticals North America, Inc., Deerfield, IL; 2009). In contrast to allopurinol, febuxostat is a non-purine XO inhibitor (Tayar *et al.* 2012). Thus, febuxostat is distinct from purine-like XO inhibitors, in its structure, inhibits both reduced and oxidized forms of XO and has little influence on other purine- and pyrimidine-metabolizing enzymes (Grabowski *et al.* 2011).

Compared to allopurinol, febuxostat has the advantages of reducing urate-lowering and a similar tolerability profile in previous studies (Xu *et al.* 2015; Wang *et al.* 2013; Huang *et al.* 2014). However, at the doses tested, non- inferiority and superiority of febuxostat 40 mg daily compared with allopurinol 300 mg daily was not reached in previous study (Xu *et al.* 2015). Moreover, febuxostat appears to be associate with a significant high risk of cardiovascular disease than the allopurinol 300 mg daily group (White *et al.* 2018).

It is, thus, suggests that effective managements are warranted. Our study performed a meta-analysis aiming to compare the efficacy and safety of febuxostat versus allopurinol in patients with hyperuricemic with or without Gout.

MATERIALS AND METHODS

Search strategy

Two authors take a systematic screening process of the electronic databases, such as Pubmed, Embase, Cochrane library up to May 2020 independently. The process was based on the Medical Subject Heading (MeSH) terms and the keywords: "hyperuricemic" AND "febuxostat" AND "allopurinol" AND "gout". We also hand-searched the reference materials for additional relevant studies.

Tab. 1. Presented a brief description of these eligible studies

Study year	Country	No. of patients		Treatment regimen		Study design
		Febuxostat	Allopurinol	Febuxostat (mg/d)	Allopurinol (mg/d)	
Beeker 2005	America, Canada	507	253	80, 120	300	with gout
Beeker 2009	America, Canada	883	139	80, 120	300	with gout
Beeker 2010	America, Canada	1513	756	40, 80	200, 300	with gout
Schumacher 2008	America	670	268	80, 120, 240	300	with gout
Kamatani P2 2011	Japan	19	19	40, 60	300	with/without gout
Kamatani P3 2011	Japan	122	121	40	200	with/without gout
Huang 2014	China	344	172	40, 80	300	with gout
Xu 2015	China	336	168	40, 80	300	with gout
Yu 2016	China	54	55	80	300	with gout
Zhang 2019	China	393	197	40, 80	300	with/without gout

Inclusion Criteria

Articles that meet the following criteria should be cited: (1) patients were underwent using febuxostat versus allopurinol; (2) patients were clinical diagnosis of hyperuricemic (SUA exceeding 6.8 mg/dL) with or without gout; (3) the interested outcomes were efficacy and toxicity.

Risk-of-Bias Assessments

The risk of bias was assessed by two investigators, separately. Article quality was rated using Newcastle-Ottawa Quality Assessment Scale. Publication bias was assessed using funnel plot.

Data selection

Contents were extracted by two researchers independently, and the third author help check for accuracy and resolve the disagreement. From each of the eligible researches, the main information based on the following: name of the first author, publication year, patient number, treatment regimen, study design, number and outcomes measures.

Statistical analysis

The Review Manager version 5.3 software conducted for statistical analysis. Between-study heterogeneity was examined using I2 statistic (Higgins and Thompson 2002). Articles with an I2 value larger than 50% were considered to have high heterogeneity, and the random-effects model was conducted. On the contrary, the fixed-effects model was used (Higgins *et al.* 2003). $P<0.05$ was identified as statistically significant difference.

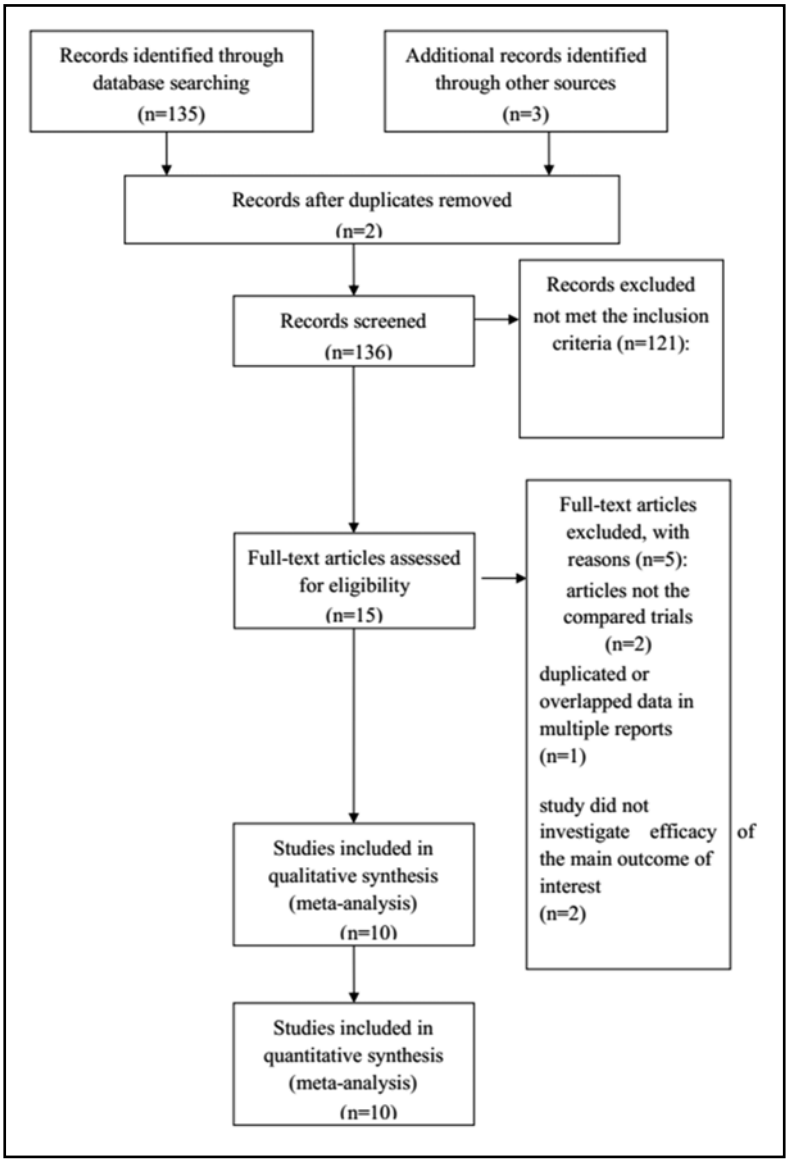

Fig. 1. PRISMA flow chart of selection process to identify studies eligible for pooling.

RESULTS

Characteristics of included studies

Totally, 136 articles were retrieved initially for evaluation. Relying on the criteria described in the methods, 15 studies were further evaluated, while some did not provide enough detail of results of two groups. Therefore, 10 articles (Xu *et al.* 2015; Huang *et al.* 2014; Becker *et al.* 2005; Becker *et al.* 2009; Becker *et al.* 2010; Schumacher *et al.* 2008; Kamatani *et al.* 2011; Kamatani *et al.* 2011; Yu *et al.* 2016; Zhang *et al.* 2019) were included. Figure 1 presented the search process. Table 1 presented a brief description of these eligible studies.

Outcomes and synthesis of results

Pooled analysis of urate-lowering efficacy comparing febuxostat with allopurinol.

As shown in Figure 2-3, there is significant statistical difference of urate-lowering efficacy when comparing the two approaches (RR=1.56, 95% CI=1.37-1.78, $P<0.00001$). Subgroup analysis by the daily dose of febuxostat, superiority of febuxostat 40 mg/day (RR=1.12, 95% CI=1.03-1.22, $P=0.01$) versus allopurinol was demonstrated. The same comparison was conducted comparing febuxostat 80 mg/day (RR=1.73, 95% CI=1.59-1.89, $P<0.00001$) or 120 mg/day (RR=2.04, 95% CI=1.84-2.26, $P<0.00001$) versus allopurinol.

Subgroup analysis of urate-lowering efficacy by dose-titration

The pooled data showed that urate-lowering efficacy in subjects was superior with febuxostat 80 mg/day than febuxostat 40 mg/day (RR=1.47, 95% CI=1.34-1.60, $P<0.00001$) (Figure 4-5). While, febuxostat 120 mg daily

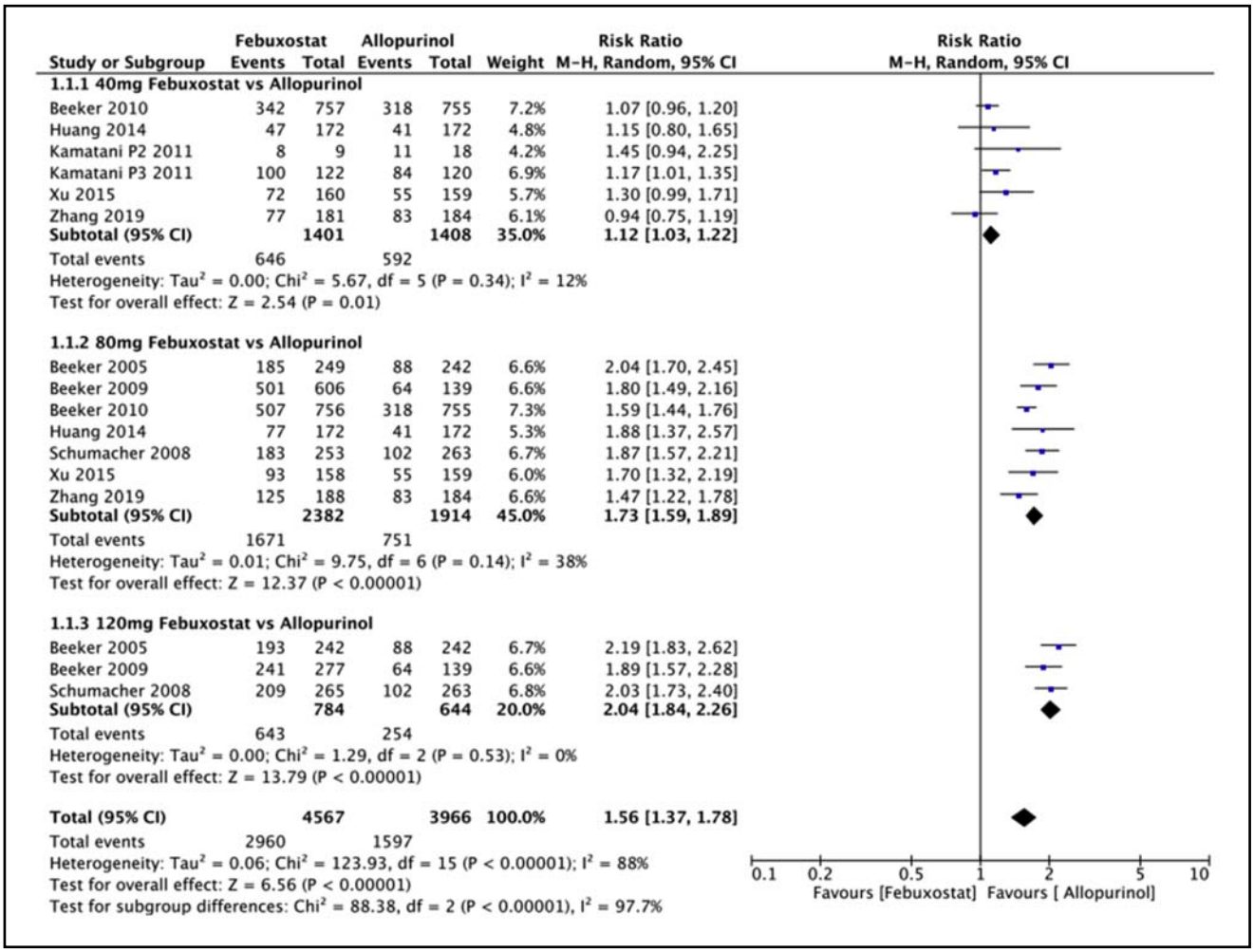

Fig. 2. Pooled analysis of urate-lowering efficacy comparing febuxostat with allopurinol.

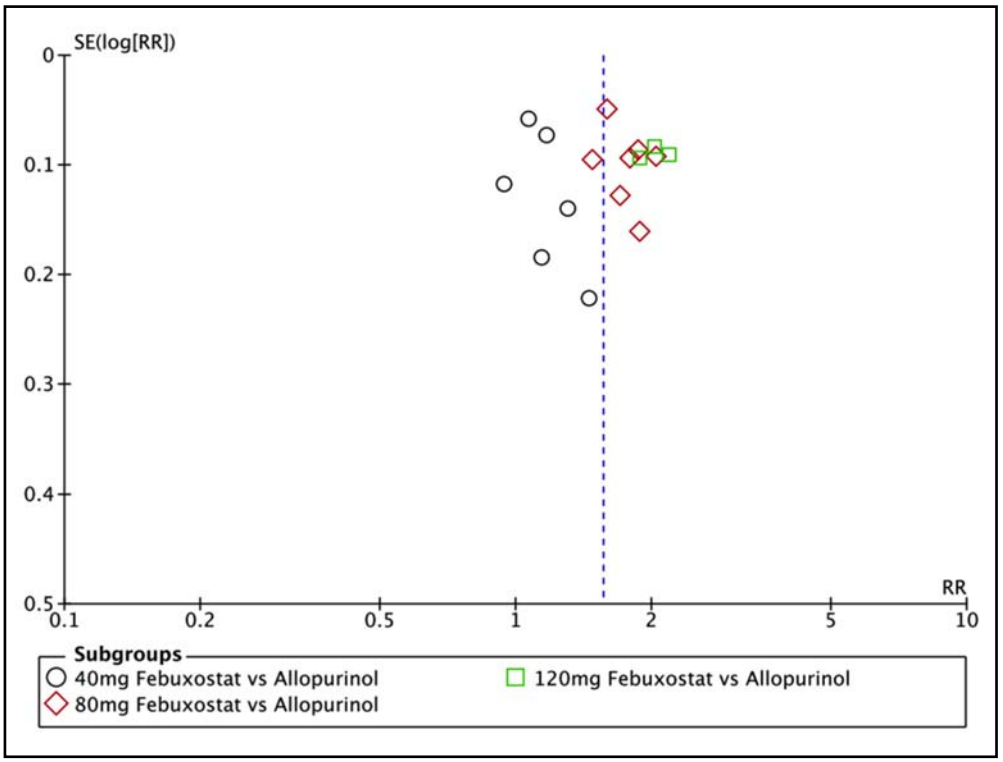

Fig. 3. Funnel plot of urate-lowering efficacy comparing febuxostat with allopurinol.

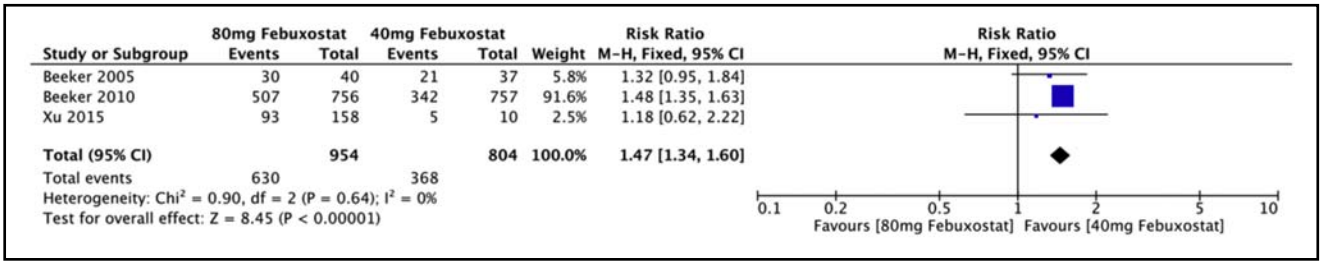

Fig. 4. Pooled analysis of urate-lowering efficacy comparing febuxostat 80 mg/day with febuxostat 40 mg/day.

had superior urate-lowering efficacy to that of febuxostat 80 mg daily (RR=1.08, 95% CI=1.02-1.13, *P*=0.004) (Figure 6-7).

Pooled analysis of AEs comparing febuxostat with allopurinol

Systematic analysis of overall AEs data were shown in the Figure 8-9. There is statistical difference when comparing two approaches (RR=0.96, 95% CI=0.92-1.00, *P*=0.04). While, liver function test abnormalitie, diarrhea, skin rashes, musculoskeletal and connective tissue disorders, gastrointestinal disorders, headaches, the difference between the two approaches had no statistical significance (P≥0.05) (Figure 10-11).

DISCUSSION

Allopurinol has been approved as the first-line medication to treat hyperuricemia (Gois and Souza 2013). Allopurinol along with its natural metabolite oxypurinol are purine base analogues that inhibit production of XO and urate. Febuxostat, a developed nonpurine selective inhibitor of XO, is a newly adopted urate-lowering agent accepted to treat hyperuricemia with or without gout (https://www.medicines.org.uk/emc/product/ 487/smpc. Accessed 26 July 2019).

In contrast to allopurinol, febuxostat inhibits both reduced and oxidized forms of XO and has little influence on other purine- and pyrimidine-metabolizing enzymes (Grabowski *et al.* 2011; Schumacher *et al.* 2008). On this basis, we launched a meta-analysis to evaluate the efficacy and toxicity using of febuxostat versus allopurinol to treat hyperuricemia patients with or without gout.

Several studies have assessed the efficacy and safety of febuxostat versus allopurinol. For example, Becker et al (2005) evaluated the effect of febuxostat versus allopurinol in 762 gout patients, and found that superior urate-lowering efficacy for febuxostat (80 or 120 mg QD) than allopurinol (300 mg QD). Kamatani *et al.* (2011) showed that febuxostat (40 mg QD) demonstrated superior urate-lowering than allopurinol (200 mg QD). Becker (2010) reported that the urate-lowering efficacy of febuxostat 40 mg was statistically

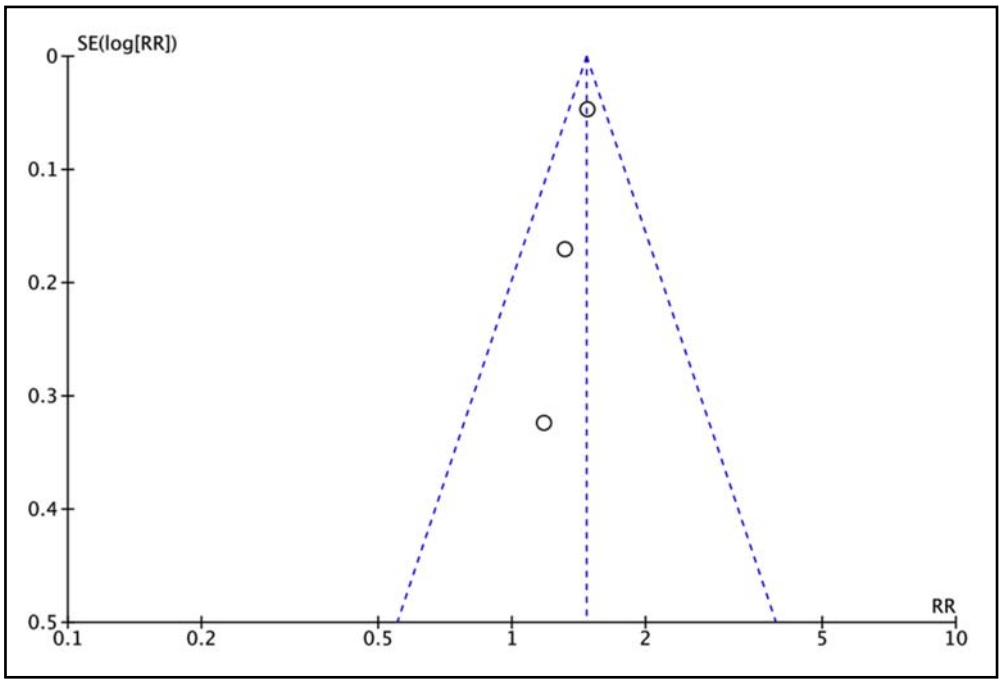

Fig. 5. Funnel plot of urate-lowering efficacy comparing febuxostat 80 mg/day with febuxostat 40 mg/day.

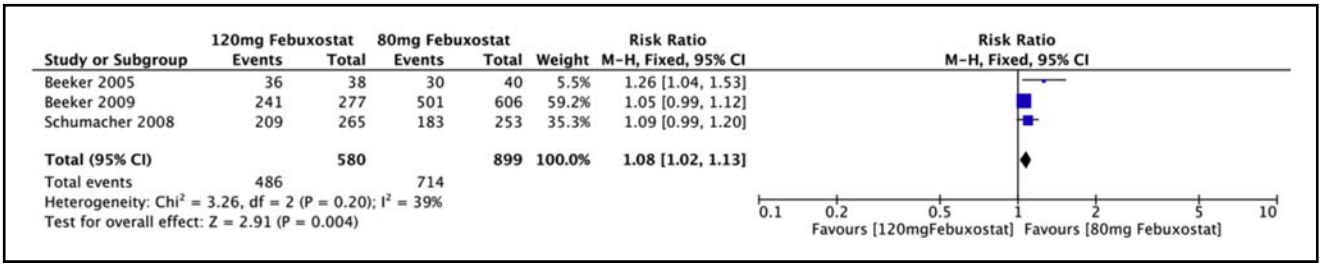

Fig. 6. Pooled analysis of urate-lowering efficacy comparing febuxostat 120 mg/day with febuxostat 80 mg/day.

non-inferior to that of allopurinol, while febuxostat 80 mg was superior versus allopurinol. While, in a randomized, double-blind, non-inferiority study by Zhang (2019), the primary endpoint of non-inferiority of febuxostat 40 mg/day was not achieved than the allopurinol (300 mg/day), which was contrasts with previous articles in China (Ye *et al.* 2013; Roddy and Doherty 2010) and North America (Schumacher *et al.* 2008; Kamatani *et al.* 2011).

The pooled results of our study indicated that the febuxostat at ascending doses of 40, 80, and 120 mg/day was superior to allopurinol with regard to safety and efficacy. The result suggests that therapy with either dose of febuxostat is superior in UL efficacy compared with is allopurinol treatment.

In addition, our study has demonstrated that febuxostat at doses of 80 mg/day is more likely to achieve sUA <6.0 mg/dL than febuxostat 40 mg/day, as well as the result comparing febuxostat 120 mg daily versus febuxostat 80 mg daily. It is possible that the dose titration of febuxostat could contribute to the final responses.

In Xu's (2015) study, it reported that febuxostat 80 mg/day had higher urate-lowering efficacy than febuxostat 40 mg/day and allopurinol 300 mg/day. The evidence from the study seems to indicate that febuxostat had urate- lowering efficacy depend on the dose. Moreover, considering that they only included subjects are Chinese subjects, which indicates that generic febuxostat products might have effect on the differences to some extent. Further studies should be conducted to access the differences between Chinese populations and European people.

Furthermore, as with all pharmacological therapies, potential treatment-related adverse events and drug–drug interactions may be taken into consideration. Our results do indicate that the safety profiles were similar between the two drugs. While, the pooling occurrence of overall treatment-related adverse events data did achieve advantage in the febuxostat group. This suggests that febuxostat represents an alternative therapy for hyperuricaemia with or without gout, especially for patients who cannot tolerate allopurinol.

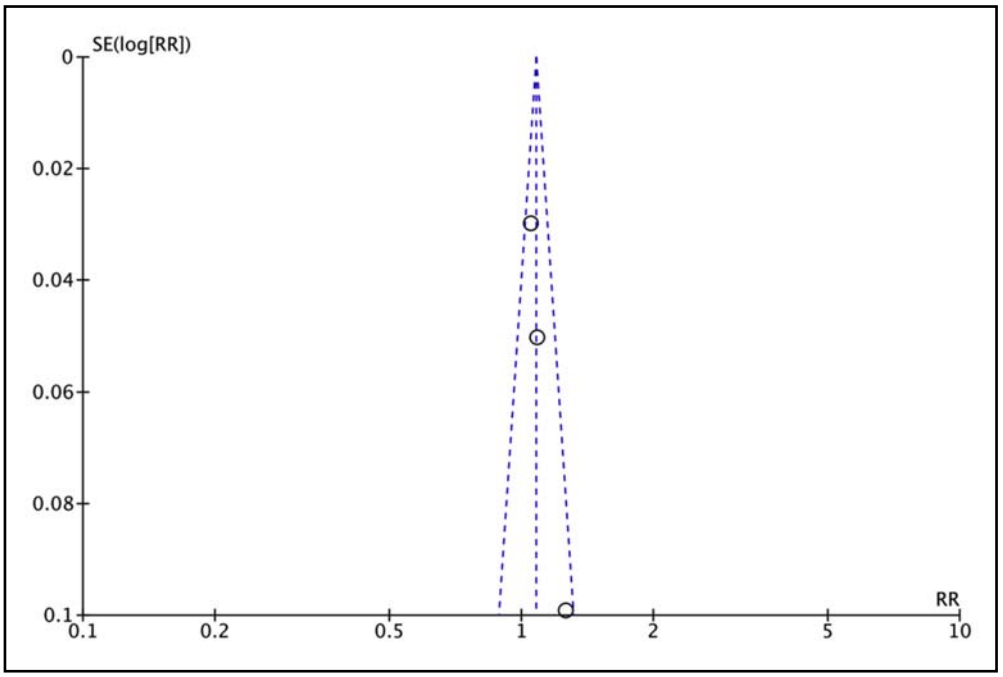

Fig. 7. Funnel plot of urate-lowering efficacy comparing febuxostat 120 mg/day with febuxostat 80 mg/day.

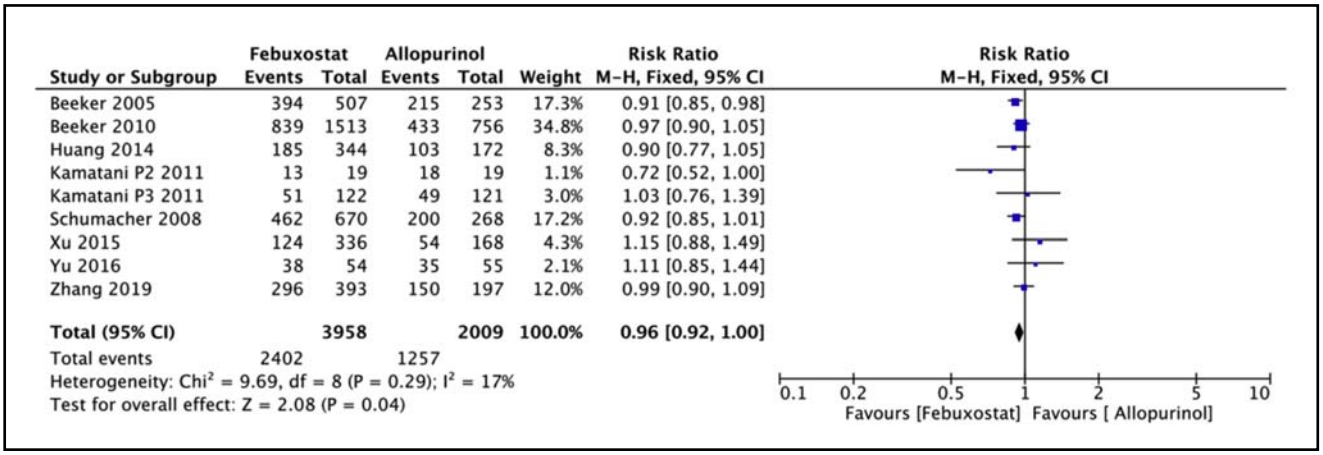

Fig. 8. Pooled analysis of total AEs comparing febuxostat with allopurinol.

Our study was based on well-maintained and updated databases. However, we must acknowledge that potential bias exists by the intrinsic different study design, clinical heterogeneity among studies. Such as different renal function and populations, which may have influence on the comparison of interested results. Thus, further studies should aim to identify subgroup patients, to refine patients who are more likely to achieve clinical benefit from the febuxostat group.

In conclusion, our meta-analysis revealed that febuxostat demonstrated superior effective in lowering serum urate with increasing dose (40, 80 or 120 mg QD) than allopurinol, and that dose titration to febuxostat 120 mg daily was superior to other daily dosing with regard to urate-lowering efficacy. In terms of the safety profiles, our results do indicate that the safety profiles were similar between the two drugs. This indicates that febuxostat is a safe and effective alternative to allopurinol, and that febuxostat may be particularly suitable for patients who cannot tolerate allopurinol.

DECLARATIONS

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

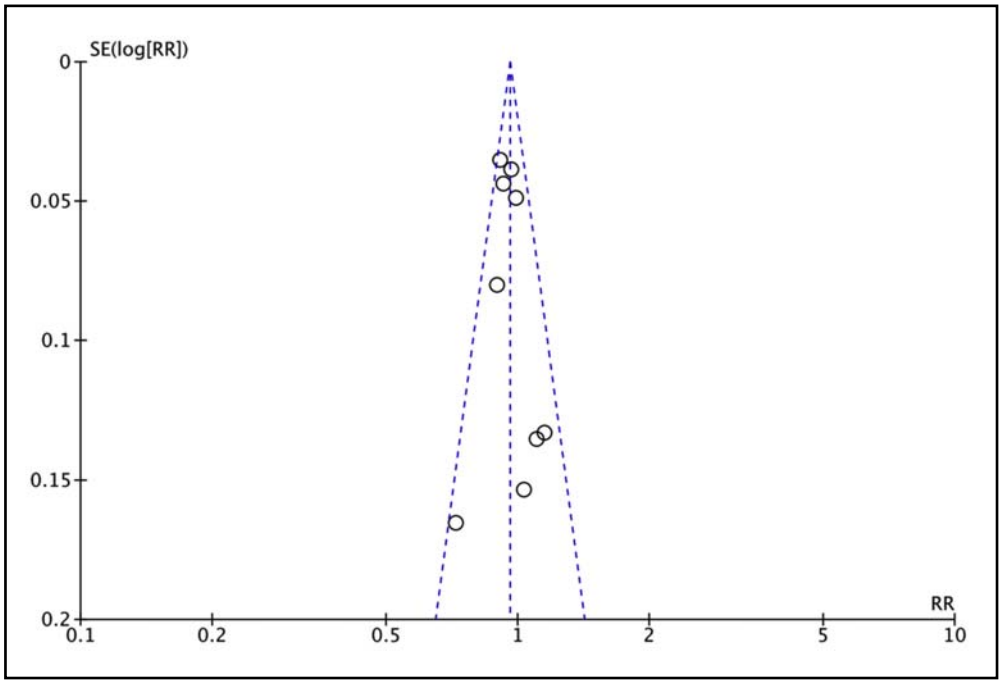

Fig. 9. Funnel plot of total AEs comparing febuxostat with allopurinol.

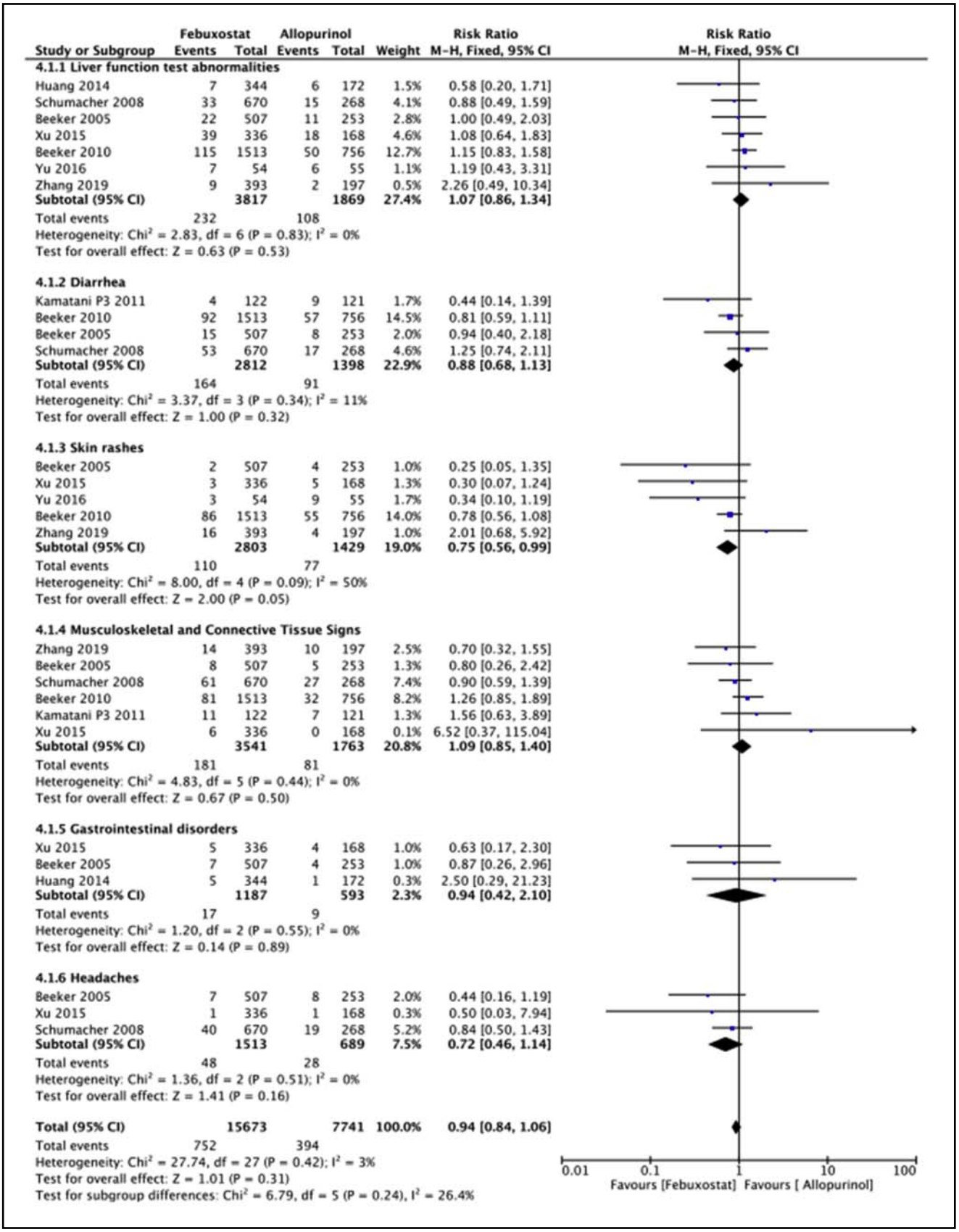

Fig. 10. Pooled analysis of AEs comparing febuxostat with allopurinol.

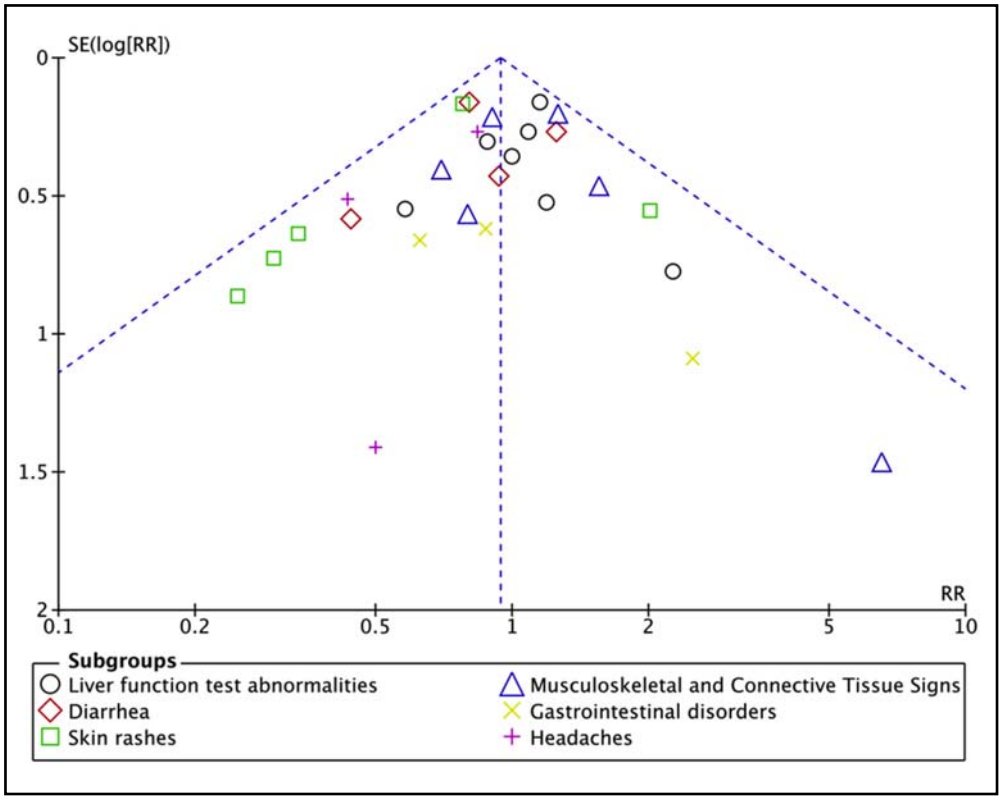

Fig. 11. Funnel plot of AEs comparing febuxostat with allopurinol.

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None.

Competing interests

There are no potential conflicts of interest to disclose.

Author Contributions

Bin Fan is resposible for the literature research, clinical studies, experimental studies, data acquisition & analysis, manuscript preparation; Ping Zhang is resposible for the manuscript editing & review; Xiaoyu Li is resposible for the guarantor of integrity of the entire study, study concepts & design; definition of intellectual content. All authors read and approved the final manuscript.

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