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SYSTEMATIC REVIEW

Cardiovascular safety of febuxostat versus allopurinol among the Asian patients with or without gout: A systematic review and meta-analysis

Jian-hao Deng[1] | **Peng-hui Lai**[1] | **Li-shan Xie**[1] | **Shu-sheng Qiu**[1] | **De-sheng Qiu**[2] | **Jia-xing Zhang**[3]

[1]Pharmacy Department, Longyan Second Hospital, Longyan, China

[2]Neurology Department, Longyan Second Hospital, Longyan, China

[3]Pharmacy Department, Guizhou Provincial People's Hospital, Guiyang, China

Correspondence
De-sheng Qiu, Neurology Department, Longyan Second Hospital, Longyan 364000, China.
Email: qiudesheng69@163.com

Jia-Xing Zhang, Pharmacy Department, Guizhou Provincial People's Hospital, Guiyang 550002, China.
Email: zjx19870619@126.com

Abstract

The cardiovascular (CV) safety of febuxostat compared to allopurinol for the treatment of hyperuricemia among Asian patients is uncertain. In this study, we conducted a systematic review and meta-analysis to compare the CV safety profiles of febuxostat with allopurinol in Asian patients with hyperuricemia. A total of 13 studies were included. On the basis of the pooled results of cohort studies, febuxostat users were at a significantly higher risk for acute coronary syndrome (ACS; hazard ratio [HR]: 1.06, 95% confidence interval [CI]: 1.03–1.09, $p < 0.01$), atrial fibrillation (HR: 1.19, 95% CI: 1.05–1.35, $p < 0.01$) than allopurinol users, whereas no significant difference between febuxostat and allopurinol existed for urgent coronary revascularization (HR: 1.07, 95% CI: 0.98–1.16, $p = 0.13$), and stroke (HR: 0.96, 95% CI: 0.91–1.01, $p = 0.13$). Nevertheless, that difference in results of acute decompensated heart failure (ADHF; HR: 0.73, 95% CI: 0.35–1.53, $p = 0.40$) and all-cause death (HR = 0.86, 95% CI: 0.49–1.51, $p = 0.60$) was not significant based on randomized controlled trials. In the Chinese subgroup, febuxostat could increase the risk of ADHF (HR: 1.22, 95% CI: 1.01–1.48, $p < 0.05$), CV death (HR: 1.25, 95% CI: 1.03–1.50, $p < 0.05$), and all-cause mortality (HR: 1.07, 95% CI: 1.01–1.14, $p < 0.05$) compared to allopurinol. In conclusion, the use of febuxostat, compared with allopurinol among Asian patients, was associated with a significantly increased risk of adverse CV events.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Hyperuricemia is a prevalent metabolic disorder that is typically managed through the administration of xanthine oxidase inhibitors, including allopurinol and febuxostat. Nevertheless, the cardiovascular (CV) implications of these medications in the context of Asian patients remain inconclusive.

WHAT QUESTION DID THIS STUDY ADDRESS?

This systematic review aimed to compare the CV safety profiles of febuxostat with allopurinol in Asian patients with hyperuricemia.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Among Asian patients, the use of febuxostat, compared with allopurinol, was associated with a significantly increased risk of adverse CV events.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

It is imperative that future investigations encompassing larger sample sizes, multiple medical centers, extended durations, randomized participant selection, and double-blind methodologies be conducted within the Asian population.

INTRODUCTION

Gout, a prevalent rheumatic metabolic disease, exhibits varying prevalence rates across different regions, countries, and races.[1–3] In the United Kingdom, the estimated prevalence of gout is 0.03%, whereas in Taiwan Province it is 10.42%.[4] The incidence of gout is on the rise and is found in younger patients according to an epidemiologic study.[5] An acute gout attack is characterized by the presence of swelling, redness, and warmth in one or more joints, which can have a significant impact on work productivity and overall quality of life.[6,7]

The 2016 updated European League Against Rheumatism evidence-based recommendations for the management of gout and 2020 American College of Rheumatology guideline for the management of gout suggest the use of xanthine oxidase inhibitors (XOIs), such as allopurinol and febuxostat, as the preferred initial urate-lowering therapy.[8,9] Probenecid and benzbromarone can be used as second-line agent.[5,10]

In 2009, the US Food and Drug Administration (FDA) granted approval to Febuxostat as a novel non-purine highly selective XOI for the treatment of hyperuricemia. This medication demonstrated prominent efficacy and longer lasting hypouricemic activity in comparison to allopurinol. Subsequently, the Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities trial was conducted between 2010 and 2017 to assess whether Febuxostat was noninferior to allopurinol in terms of major cardiovascular (CV) events among patients with gout and cardiovascular disease (CVD).[11] A total of 6190 patients were enrolled in this study. The findings revealed that both all-cause mortality and CV mortality were higher in the febuxostat group compared to the allopurinol group.

In 2017 and 2019, the FDA issued a safety alert concerning the association between febuxostat and CV mortality, based on the aforementioned study.[12,13] To further evaluate the long-term CV safety of febuxostat in patients with gout with high CV risk, the Febuxostat vs. Allopurinol Streamlined Trial was conducted between 2011 and 2018.[14] This trial involved the enrollment of 6128 patients, and its findings indicated that febuxostat does not pose a higher risk of mortality or serious adverse events when compared to allopurinol. The inconsistency between these trial outcomes presents a perplexing situation. It is important to note that the populations included in both trials were predominantly composed of White patients, with Asian patients representing 3.0% (92/3098) and 0.4% (11/3063) of the total gout patient population, thus limiting the generalizability of the results to Asian populations.

The prevalence of the HLA–B*5801 allele is significantly higher in the Asian population, specifically among Han Chinese (12.5%) and Koreans (12.5%), compared to Europeans (1.6%).[15] Considering the potential reduction in the incidence of allopurinol hypersensitivity syndrome in the Asian population, using febuxostat as a first-line urate-lowering therapy may be beneficial.

The CV safety of febuxostat in Asian populations, in comparison to allopurinol, remains uncertain. To bridge this knowledge gap, a meta-analysis was performed, encompassing randomized controlled trials (RCTs) and observational studies, with the objective of exploring the CV safety of febuxostat versus allopurinol in Asian patients.

MATERIALS AND METHODS

Protocol and registration

This systematic review abides by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (Table S1). The study was registered at the PROSPERO (ID CRD 42023408900) in March 2023.

Search strategies

An article search was carried out in the following databases from its establishment to March 2023, including PubMed, Embase, China National Knowledge Infrastructure (http://www.cnki.net/), Chinese Scientific and Technological Journals Database (www.cqvip.com), Chinese Biomedical Literature Database (http://www.imicams.ac.cn/cbm/index.asp), and Wanfang Data Knowledge Service Platform (www.wanfangdata.com). The language was restricted to Chinese and English. In these databases, "febuxostat," "allopurinol," "hyperuricemia," and "gout" were used as the subject words.

The combination of MeSH keywords and free words were used for the search. We also searched the conference abstracts, dissertations, and other gray papers. Manual retrieval of all references was summarized in the review. Specific retrieval strategy was presented in Table S2.

Study selection

The eligibility criteria for studies were as follows. (a) Participants: adult patients (>18 years) among Asian populations with a diagnosis of hyperuricemia with or without gout. (b) Interventions/Comparisons: febuxostat or allopurinol. (c) Outcomes: Urgent coronary revascularization, acute coronary syndrome (ACS), acute decompensated heart failure (ADHF), stroke, atrial fibrillation (AF), all-cause mortality, and CV death. (d) Study design: prospective or retrospective cohort studies, cross-sectional studies, and case–control studies or RCTs.

The exclusion criteria were as follows. (a) Acute gout or secondary gout. (b) Animal experiments. (c) Unavailable full texts or abstract-only papers. (d) Studies published in a language other than Chinese or English. (e) Duplicate studies.

Data extraction

Two authors independently performed data extraction using standardized data extraction forms. Then, our results were cross-checked. Any disagreements were resolved by a third party. We extracted the following data: study characteristics, including design, number of patients fulfilling the predefined inclusion criteria. Participants characteristics, including gender, age, diagnosis, comorbidity, and country. Interventions, including dosage and duration of therapy. Outcome measures (as described above). When the studies reported both the crude hazard ratios (HRs) and the adjusted HRs, the adjusted figures were extracted.

Quality assessment

The risk of bias of the selected studies was independently assessed by two researchers, and disagreements were resolved by another researcher. Cochrane risk of bias tool, version 2.0[16] will be used to assess the risk of bias of RCTs. Study quality was evaluated based on seven aspects, including (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective reporting, and (7) other bias. Each indicator was scored as low risk of bias, unclear risk of bias, or high risk of bias. The Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of the included observational studies.[17] As part of this scale, up to 4 points can be assigned for low risk of bias in the domains of selection of patients and comparators, 2 points for comparability, and 3 points can be assigned for low risk of bias in the determination of exposure. A study is therefore assigned between 0 and 9 points, with higher scores indicating a lower bias risk. The evaluation results were divided into low risk of bias (NOS score ≥ 7 points), medium risk of bias (NOS score between 4 and 6 points), and high risk of bias (NOS score ≤ 3 points).

Statistical analysis

Review Manager 5.4.1 was used for data meta-analysis. We expressed time-to-event data as HR with 95% confidence interval (CI). The Q test and statistic I^2 were used to measure statistical heterogeneity. The $p > 0.1$ and $I^2 < 50\%$ indicated the heterogeneity across studies was considered relatively small. The $p < 0.1$ or $I^2 > 50\%$ was considered existing significant heterogeneity and we will explore the possible sources of heterogeneity by subgroup analyses according to different countries. In order to analyze CV risks of febuxostat on specific populations further, another meta-analysis was conducted among the experimental populations with high risks of CVD or diagnosed with CVD based on the participants' medical history included in the study. To minimize methodological heterogeneity, separate meta-analyses will be conducted based on different study designs. A random-effects model was used for the data synthesis, and a fixed-effects model was used for sensitivity analysis. Our meta-analysis included an additional sensitivity analysis to evaluate the impact of follow-up duration by calculating risk ratio (RR). If more than 10

trials were included, publication bias would be evaluated by a funnel plot.

RESULTS

Included studies characteristics

A comprehensive search strategy yielded a total of 1950 studies, which were subsequently reduced to 1399 after eliminating duplicates. Further screening based on titles and abstracts resulted in the exclusion of 1056 articles. After reviewing the full text of the remaining studies, an additional 331 were excluded. Ultimately, a total of 13 studies (4 RCTs[18–21] and 9 retrospective cohort studies[22–30]) were considered suitable for inclusion in the meta-analysis (Figure 1). The RCTs exclusively focused on the Japanese population, whereas the cohort studies encompassed Chinese[14,22,24,25,26] ($n = 5$), Korean[23,28,29] ($n = 3$), and Japanese populations[30] ($n = 1$).

The studies encompassed three RCTs[19–21] that focused on a population with chronic heart failure or diagnosed with CVD, whereas three cohort studies conducted subgroup analyses on individuals at high risk of CVD and one cohort study focused on a population diagnosed with CVD. We combined data on populations (hereafter called patients with CVD) with high risks of CVD and those diagnosed with CVD in the meta-analysis, due to insufficient data. The patients were monitored for a duration ranging from 23 weeks to 4 years. Table 1 provides an overview of the fundamental characteristics of these selected studies.

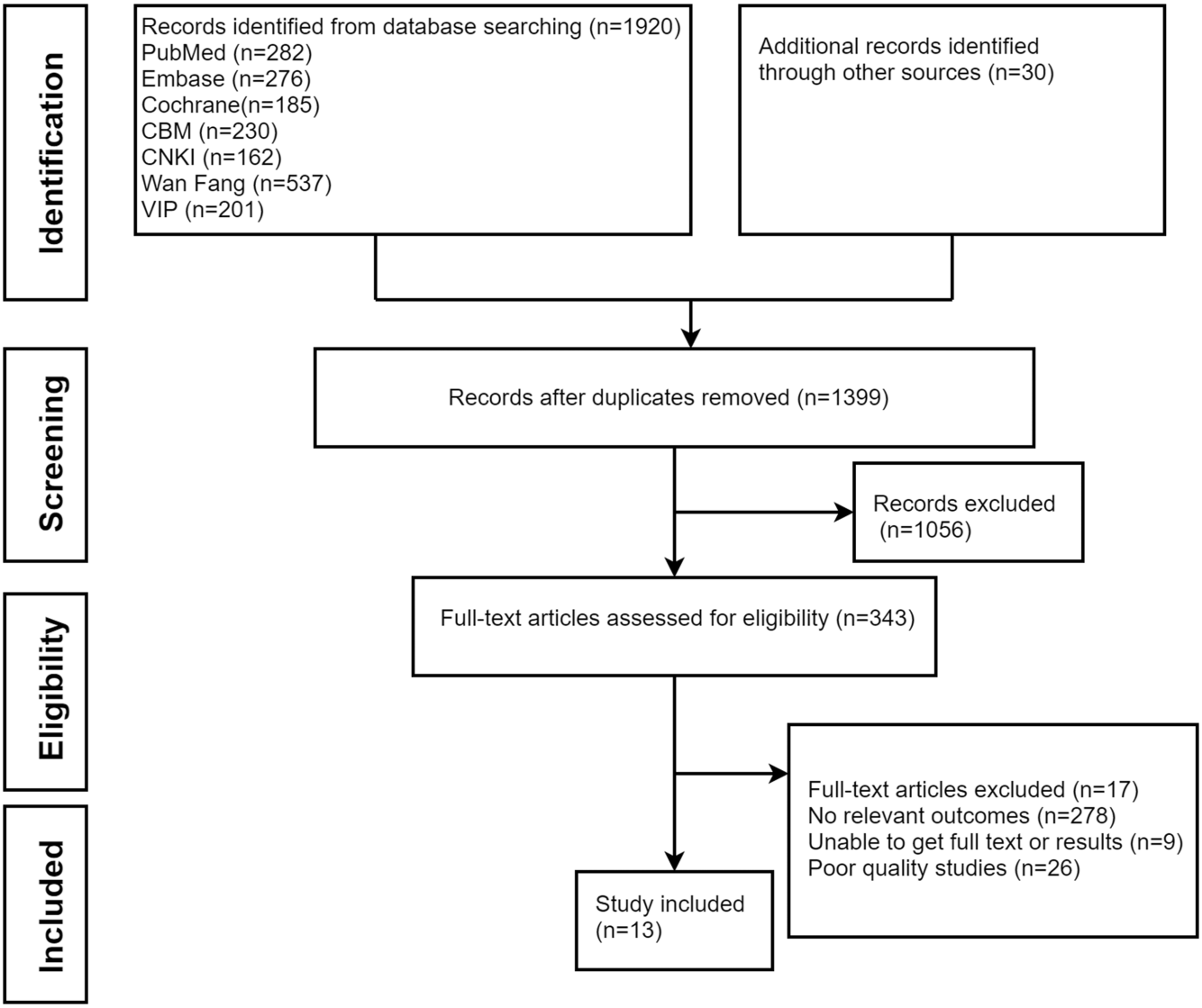

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram shows study selection. CBM, Chinese Biomedical Literature Database; CNKI, China National Knowledge Infrastructure; VIP, Chinese Scientific and Technological Journals Database.

TABLE 1 Basic characteristics of the 13 studies enrolled in the meta-analysis on cardiovascular safety of febuxostat and allopurinol among Asian population.

			Age, mean ± SD (year)		Male (*n* %)						Follow-up		
References	**Study design**	**Country**	**FBX**	**Allo**	**FBX**	**Allo**	**Patients**	**Sample size**	**FBX**	**Allo**	**FBX**	**Allo**	**Outcome**
Akihiro (2015)	RCT	Japanese	69.3 ± 10.0	71.8 ± 8.0	71	69	Hyperuricemia with chronic heart failure	120/135	80 mg	150 mg	12 months	12 months	②③④⑤⑦
Chen (2019)	Cohort study	Chinese Taiwan	65.5 ± 15.2	65.0 ± 15.1	72.8	73.5	Gout	5262/5257	≥40 mg/day	≥100 mg/day	4 years	4 years	②③⑥
Kang (2019)	Cohort study	Korean	59.4 ± 12.9	59.1 ± 12.5	78.3	78.9	Gout, subgroup analyses at high CV risk	9910/39,640	≥40 mg/day	≥100 mg/day	316 days	251 days	①②③⑦
Kojima (2019)	RCT	Japanese	75.4 ± 6.7	76.0 ± 6.5	69.1	69	Hyperuricemia	537/533	40 mg/day	100 mg/day	35.5 months	35.1 months	②③④⑦
Su (2019)	Cohort study	Chinese Taiwan	65.0 ± 15.7	64.1 ± 15.0	74.1	74.5	Hyperuricemia	44,111/44,111	≥40 mg/day	≥100 mg/day	200 days	160 days	②③④⑤⑥⑦
Ju (2020)	Cohort study	Chinese	70.4 ± 14.35	70.01 + 14.90	67.4	66.3	Hyperuricemia	276/828	≥40 mg/day	≥100 mg/day	1.5 years	1.96 years	②③④⑦
Suzuki (2021)	RCT	Japanese	71.0 ± 13.2	71.0 ± 13.2	70.3	63	Hyperuricemia with chronic heart failure	128/135	>10 mg/day	>200 mg/day	3 years	3 years	④⑥
Shin (2022)	Cohort study	Korean	59.3 ± 13.2	59.3 ± 13.0	79.6	79.6	Gout, subgroup analyses at high CV risk	160,930/160,930	>20 mg/day	≥100 mg/day	290 days	209 days	①②③④⑦
Konishi (2022)	RCT	Japanese	75.4 ± 6.7	77 ± 6.4	68.7	76.5	Hyperuricemia with cardiovascular disease	115/119	NA	NA	36 months	36 months	⑦
Cheng (2022)	Cohort study	Chinese Taiwan	66.8 ± 13.6	66.7 ± 14.4	68.3	69	Gout, subgroup analyses at high CV risk	76,084/76,084	NA	NA	1.1 years	1.1 years	④⑥⑦
Liu (2022)	Cohort study	Chinese Taiwan	68.2 ± 13.5	64.1 ± 14.1	83	89	Gout	430/63	NA	NA	47.2 months	62.2 months	⑤
Sawada (2023)	Cohort study	Japanese	NA	NA	80.6	81.4	Gout	1,357,671/1,273,211	≥40 mg/day	≥100 mg/day	245 days	213 days	②③⑤
Jeong (2023)	Cohort study	Korean	46.2 ± 15.4	45.7 ± 15.1	91.2	92	Gout, subgroup analyses at cardiovascular disease	27,761/27,761	NA	NA	321 days	524 days	① ②③④⑥

Note: Outcomes: ①Urgent coronary revascularization; ②acute coronary syndrome (ACS); ③acute decompensated heart failure (ADHF); ④stroke; ⑤atrial fibrillation (AF); ⑥cardiovascular death; ⑦ all-cause mortality.
Abbreviations: Allo, allopurinol; CV, cardiovascular; FBX, febuxostat; NA, not available; RCT, randomized controlled trial.

Included studies quality evaluation

The Cochrane risk of bias tool, version 2.0, was used to evaluate the methodological quality of four RCTs. In total, two RCTs (66.67%) were classified as having a low risk of bias, one RCT (33.33%) had a high risk of bias, whereas the remaining RCT was deemed unclear in terms of bias (Figures 2 and 3).

According to the NOS, six cohort studies (66.67%) were classified as high quality, and the remaining three cohort studies (33.33%) were categorized as moderate quality (Table 2).

Meta-analysis results

Urgent coronary revascularization

Three cohort studies reported urgent coronary revascularization. The Q test ($I^2=0\%$, $p=0.49$) indicated no significant heterogeneity among the studies, and the meta-analysis results revealed no statistically significant difference between the two groups (HR: 1.07, 95% CI: 0.98–1.16, $p=0.13$; shown in Table 3, Figure S1). Similarly, in patients with CVD, no significant difference was observed (HR: 1.05, 95% CI: 0.88–1.26, $p=0.58$; shown in Table 3, Figure S2).

Acute coronary syndrome

A comprehensive analysis of seven cohort studies was conducted to investigate the association between ACS and febuxostat. The Q test ($I^2=0\%$, $p=0.95$) revealed no significant heterogeneity among the included studies and the findings of the meta-analysis indicated a significant difference between the two groups (HR: 1.06, 95% CI: 1.03–1.09, $p<0.01$; shown in Table 3, Figure S3). This finding suggests that the allopurinol group exhibited superior outcomes compared to the febuxostat group. However, in the patients with CVD, no significant difference was observed (HR: 1.02, 95% CI: 0.86–1.20, $p=0.84$; shown in Table 3, Figure S4).

Stroke

A comprehensive analysis of stroke was conducted, incorporating a total of seven cohort studies. The Q test ($I^2=35\%$, $p=0.16$) indicated no significant heterogeneity among the studies and the outcomes of the meta-analysis revealed no discernible distinction between the two groups (HR: 0.96, 95% CI: 0.91–1.01, $p=0.13$; shown in Table 3, Figure S5). Similarly, in the patients with CVD, no significant distinction was observed (HR: 0.94, 95% CI: 0.86–1.03, $p=0.20$; shown in Table 3, Figure S6).

Acute decompensated heart failure

A comprehensive analysis of ADHF was conducted, incorporating a total of five cohort studies and two RCT studies. The Q test ($I^2=82\%$, $p<0.01$) revealed significant heterogeneity among the cohort studies. To explore the possible sources of heterogeneity, we performed subgroup analyses according to the different countries. In the subgroup

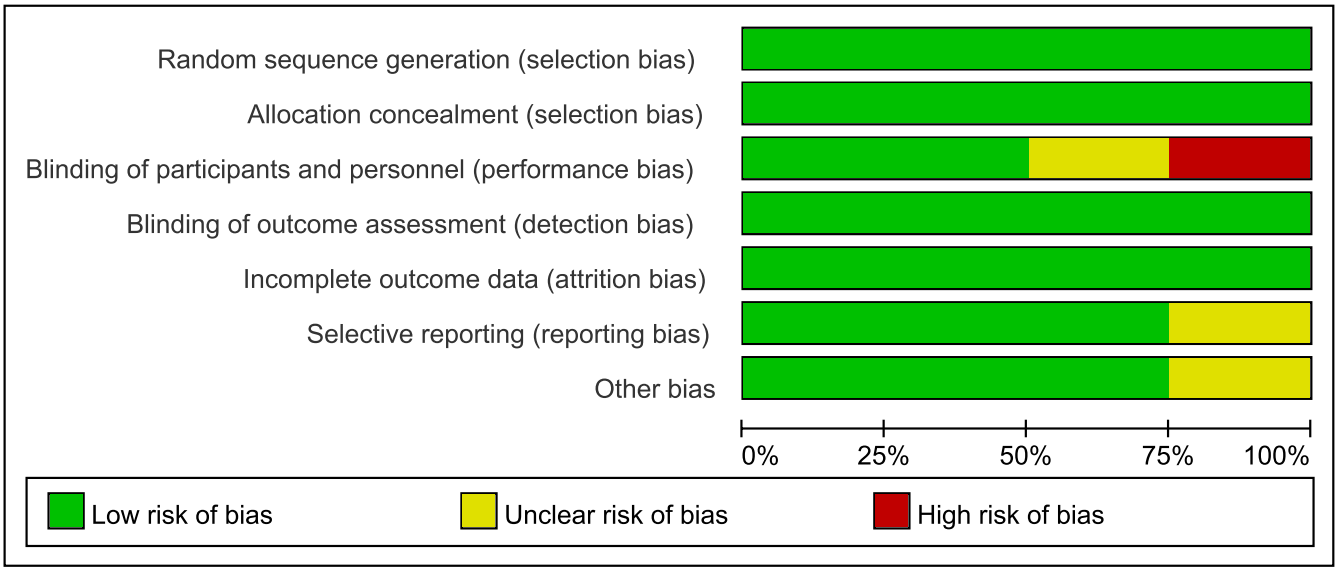

FIGURE 2 Risk assessment of bias.

analysis focusing on Chinese and Korean patients, the heterogeneity of each subgroup decreased in varying degrees (Chinese: $I^2=81\%$, $p<0.01$; Korean: $I^2=0\%$, $p=0.80$). However, the heterogeneity in Chinese patients was still high. The outcomes showed that febuxostat was significantly associated with a higher risk of ADHF versus allopurinol in both Chinese (HR: 1.22, 95% CI: 1.01–1.48, $p<0.05$; shown in Table 3, Figure S7) and Korean patients (HR: 1.07, 95% CI: 1.00–1.15, $p<0.01$; Table 3, Figure S7). However, in the patients with CVD, no significant distinction was observed (HR: 1. 14, 95% CI: 0.95–1.39, $p=0.17$; shown in Table 3, Figure S8).

In the meta-analysis of RCTs, no significant difference was observed (HR: 0.73, 95% CI: 0.35–1.53, $p=0.13$; shown in Table 3, Figure S9).

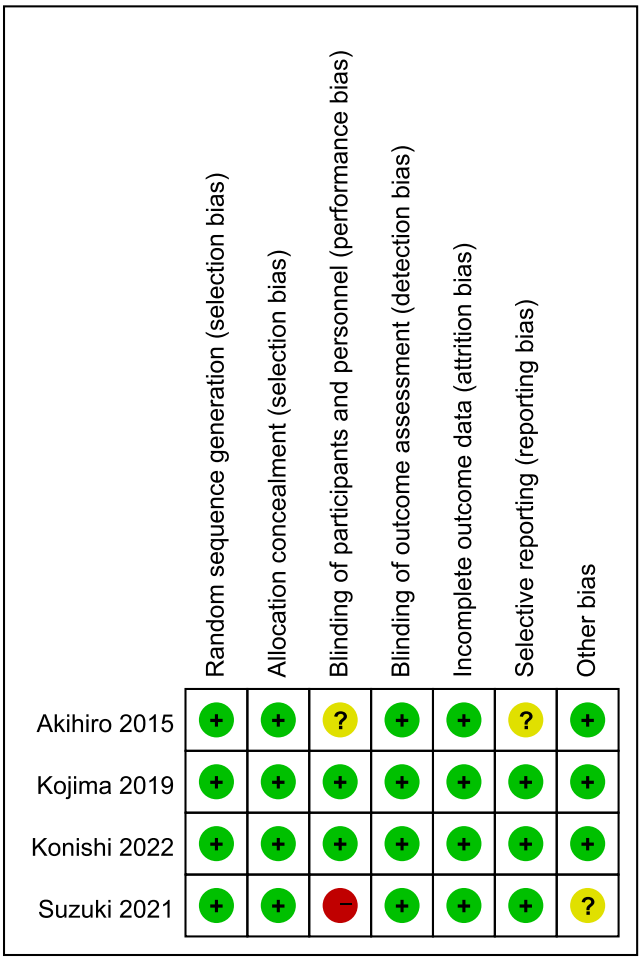

FIGURE 3 Risk of bias graph of included trials.

Atrial fibrillation

A comprehensive analysis of AF was conducted, incorporating a total of two cohort studies. The Q test ($I^2=0\%$, $p=0.99$) indicated no significant heterogeneity among the studies and the outcomes of the meta-analysis revealed significant distinction between the two groups (HR: 1.19, 95% CI: 1.05–1.35, $p<0.01$; shown in Table 3, Figure S10). Based on these results, allopurinol demonstrated superior outcomes compared to febuxostat.

Cardiovascular death

The analysis of CV death included a total of four cohort studies. The Q test ($I^2=84\%$, $p<0.01$) indicated the presence of significant heterogeneity among the studies. To explore the possible sources of heterogeneity, we performed subgroup analyses according to the different countries. In the subgroup analysis focusing on Chinese patients, heterogeneity test revealed low heterogeneity ($I^2=19\%$, $p=0.29$) and the outcomes showed febuxostat was significantly associated with a higher risk of CV death versus allopurinol in both Chinese patients (HR: 1.25, 95% CI: 1.03–1.50, $p<0.01$; shown in Table 3, Figure S11). Only one Japanese study was included in the analysis and

TABLE 2 Methodological quality assessment of cohort studies treating hyperuricemia.

		Selection				Comparability	Outcome assessment			
Authors	**Year**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Score**
Chen, C.H.	2019	*	*	*		**	*	*	*	8
Kang E.H.	2019	*	*	*		**	*			6
Su, C.Y.	2019	*	*	*		**	*			6
Ju C	2020		*	*		**	*	*	*	7
Shin	2022	*	*	*		**	*			6
Cheng	2022	*	*	*		**	*	*	*	8
Liu C.H.	2022	*	*	*		**	*	*	*	8
Sawada	2023	*	*	*		**	*	*	*	8
Jeong	2023	*	*	*		**	*	*	*	8

TABLE 3 Meta-analysis on the cardiovascular safety between febuxostat and allopurinol among Asian population.

Outcome	Study design	Patients	No. of studies	Sample size	HR (95% CI)			
					Random effects	I^2	Fixed effect	I^2
Urgent coronary revascularization	Cohort study	All patients	3	426,932	1.07 [0.98, 1.16]	0	1.07 [0.98, 1.16]	0
		CVD patients	3	125,678	1.05 [0.88, 1.26]	0	1.05 [0.88, 1.26]	0
ACS	Cohort study	All patients	7	3,157,659	**1.06 [1.03, 1.09]**	0	**1.06 [1.03, 1.09]**	0
		CVD patients	3	125,678	1.02 [0.86, 1.20]	0	1.02 [0.86, 1.20]	0
Stroke	Cohort study	All patients	7	3,157,659	0.96 [0.91, 1.01]	35	**0.93 [0.91, 0.96]**	35
		CVD patients	3	125,678	0.94 [0.86, 1.03]	13	0.94 [0.87, 1.02]	13
ADHF	Cohort study	All patients	5	618,876	**1.15 [1.02, 1.31]**	82	**1.18 [1.12, 1.23]**	82
		Chinese	3	241,494	**1.22 [1.01, 1.48]**	81	**1.27 [1.19, 1.35]**	81
		Korean	2	377,382	**1.07 [1.00, 1.15]**	0	**1.07 [1.00, 1.15]**	0
		CVD patients	3	135,638	1.14 [0.95, 1.39]	88	**1.15 [1.07, 1.22]**	88
	RCT	All patients	2	1333	0.73 [0.35, 1.53]	0	0.73 [0.35, 1.53]	0
AF	Cohort study	All patients	2	44,604	**1.19 [1.05, 1.35]**	0	**1.19 [1.05, 1.35]**	0
Cardiovascular death	Cohort study	All patients	4	2,881,791	1.13 [0.87, 1.46]	84	0.96 [0.90, 1.02]	84
		Chinese	3	250,909	**1.25 [1.03, 1.50]**	19	**1.22 [1.07, 1.39]**	19
		Japanese	1	2,630,882	**0.90 [0.84, 0.96]**	/	**0.90 [0.84, 0.96]**	/
All-cause mortality	Cohort study	All patients	6	668,426	1.01 [0.93, 1.09]	57	0.98 [0.95, 1.02]	57
		Chinese	3	241,494	**1.07 [1.01, 1.14]**	0	**1.07 [1.01, 1.14]**	0
		Korean	3	426,932	**0.94 [0.90, 0.98]**	0	**0.94 [0.90, 0.98]**	0
	RCT	All patients	1	1070	0.86 [0.49, 1.51]	/	0.86 [0.49, 1.51]	/
		CVD patients	1	234	**0.16 [0.05, 0.54]**	/	**0.16 [0.05, 0.54]**	/

Abbreviations: ACS, acute coronary syndrome; ADHF, acute decompensated heart failure; AF, atrial fibrillation; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; RCT, Randomized controlled trial.

Bold values denote statistically significant $p < .05$.

the outcomes showed allopurinol was significantly associated with a higher risk of CV death versus febuxostat in Japanese patients (HR: 0.90, 95% CI: 0.84–0.96, $p < 0.01$; shown in Table 3, Figure S11).

All-cause death

The analysis of all-cause mortality comprised six cohort studies and one RCT. The heterogeneity test ($I^2 = 57\%$, $p = 0.04$) revealed significant heterogeneity among the cohort studies. To explore the possible sources of heterogeneity, we performed subgroup analyses according to the different countries. In the subgroup analysis focusing on Chinese and Korean patients, the heterogeneity test revealed low heterogeneity (Chinese: $I^2 = 0\%$, $p = 0.86$; and Korean: $I^2 = 0\%$, $p = 0.97$). The outcomes showed febuxostat had a significantly higher risk of all-cause death versus allopurinol in both Chinese patients (HR: 1.07, 95% CI: 1.01–1.14, $p < 0.01$; shown in Table 3, Figure S12) and lower risk in Korean patients (HR: 0.94, 95% CI: 0.90–0.98, $p < 0.01$; shown in Table 3, Figure S12). In the patients with CVD in Korea, no significant distinction was observed (HR: 0.87, 95% CI: 0.74–1.01, $p = 0.07$; shown in Table 3, Figure S13).

In the meta-analysis of RCTs, which included only one study, no significant difference in all patients was observed (HR: 0.86, 95% CI: 0.49–1.51, $p = 0.60$; shown in Table 3, Figure S14). However, in another meta-analysis focusing on the patients with CVD, significant distinction was observed (HR: 0.16, 95% CI: 0.05–0.54, $p < 0.01$; shown in Table 3, Figure S15).

Sensitivity analyses

This sensitivity analysis compared a random-effects model (default analysis) with a fixed-effects model to test whether the results were robust. There was a change in statistical significance only, not in the direction of the effect. The results of the following analyses changed from non-statistically significant to statistically significant: stroke in cohort studies for all patients (HR: 0.96, 95% CI: 0.91–1.01, $p = 0.13$ vs. HR: 0.93, 95% CI: 0.91–0.96,

$p < 0.01$) and ADHF in cohort studies for the patients with CVD (HR: 1. 14, 95% CI: 0.95–1.39, $p = 0.17$ vs. HR: 1.15, 95% CI: 1.07–1.22, $p < 0.01$; shown in Table 4). An additional study[21] was included in the estimation of the RR for all-cause mortality in sensitivity analyses. There were some changes in the evidence on sensitivity analysis using RR: ACS in cohort studies for all patients (HR: 1.06, 95% CI: 1.03–1.09, $p < 0.01$ vs. RR: 1.04, 95% CI: 0.91–1.18, $p = 0.55$), ADHF in cohort studies for all patients (HR: 1. 15, 95% CI: 1.02–1.31, $p = 0.03$ vs. RR: 1.14, 95% CI: 0.87–1.49, $p = 0.34$), and AF in cohort studies for all patients (HR: 1.19, 95% CI: 1.05–1.35, $p < 0.01$ vs. RR: 1.31, 95% CI: 0.87–1.99, $p = 0.20$; shown in Table 4).

DISCUSSION

In our investigation, we conducted a meta-analysis encompassing RCTs and cohort studies among the Asian population with hyperuricemia. Our preliminary findings suggest a significant increase in the risk of ACS, ADHF, AF, CV death, and all-cause death when comparing febuxostat to allopurinol among the Asian population based on cohort studies. Meanwhile, that difference in results of ADHF, CV death, and all-cause mortality was found in the Chinese subgroup. The use of febuxostat was also associated with a higher risk of urgent coronary revascularization, ACS, and ADHF in patients with CVD, but the difference was not statistically significant. However, that difference in results of ADHF and all-cause death was not found among the Asian population based on RCTs. In our opinion, there are several main reasons for these contradictory findings between cohort studies and RCTs. First, in the RCTs, only 2403 patients were enrolled, whereas in the cohort studies 10,955,947 patients were enrolled; thus, there were 4559 times as many in the cohort studies. Considering the low incidence of CV events by allopurinol or febuxostat,[11] the sample size of the RCTs was underpowered. Second, study population in RCTs was all derived from Japan and having age greater than 70 years may confer some selection bias.

In order to find out whether our results were robust or not, we conducted sensitivity analyses using a fixed-effect approach and found that they were similar. Additionally, our meta-analysis incorporated an additional sensitivity analysis involving the calculation of RR, which yielded

TABLE 4 The estimation of the RR in sensitivity analyses.

Outcome	Study design	Patients	No. of studies	Sample size	RR (95% CI) Random effects	I^2
Urgent coronary revascularization	Cohort study	All patients	3	426,932	0.79 [0.55, 1.14]	85
		CVD patients	3	125,678	0.88 [0.55, 1.41]	86
ACS	Cohort study	All patients	7	3,157,659	1.04 [0.91, 1.18]	69
		CVD patients	3	125,678	1.05 [0.81, 1.37]	58
Stroke	Cohort study	All patients	7	3,157,659	0.93 [0.85, 1.03]	82
		CVD patients	3	125,678	0.98 [0.80, 1.20]	86
ADHF	Cohort study	All patients	5	618,876	1.14 [0.87, 1.49]	97
		Chinese	3	241,494	**1.41 [1.13, 1.75]**	89
		Korean	2	377,382	0.99 [0.84, 1.18]	98
		CVD patients	3	135,638	1.26 [0.86, 1.83]	98
	RCT	All patients	2	1333	0.68 [0.41, 1.12]	0
AF	Cohort study	All patients	2	44,604	1.31 [0.87, 1.99]	31
Cardiovascular death	Cohort study	All patients	4	2,881,791	1.28 [0.88, 1.86]	94
		Chinese	3	250,909	**1.44 [1.28, 1.63]**	0
		Japanese	1	2,630,882	**0.89 [0.84, 0.96]**	/
All-cause mortality	Cohort study	All patients	6	668,426	1.05 [0.88, 1.25]	94
		Chinese	3	241,494	1.16 [0.98, 1.38]	87
		Korean	3	426,932	**0.95 [0.91, 1.00]**	0
	RCT	All patients	2	1131	0.79 [0.46, 1.37]	0
		CVD patients	2	295	**0.20 [0.07, 0.55]**	0

Abbreviations: ACS, acute coronary syndrome; ADHF, acute decompensated heart failure; AF, atrial fibrillation; CI, confidence interval; CVD, cardiovascular disease; RCT, randomized controlled trial; RR, risk ratio.

Bold values denote statistically significant $p < .05$.

significantly different results. However, we find the analysis based on HR to be more plausible for several reasons. First, the duration of treatment varied between different arms within the study, potentially affecting the HR instead of RR over time. Second, the use of adjusted HRs, as opposed to crude HRs, helped mitigate selection bias and confounding bias in comparison to the analysis based on RR.

This study represents the examination of the CV safety of febuxostat in the Asian population with hyperuricemia. In Western countries, studies have indicated the potential benefit of using febuxostat in certain populations, our findings suggest that febuxostat treatment may offer disadvantages over the allopurinol treatment strategy in the context of secondary prevention for Asian population. Consequently, febuxostat may be not considered as a viable therapeutic option for managing hyperuricemia in the Asian population.

The underlying mechanism of febuxostat-related adverse CV outcomes remains undetermined. Hyperuricemia is linked to a heightened susceptibility to hypertension, diabetes, ischemic heart disease, and heart failure.[31–33] Furthermore, an escalated level of serum uric acid (UA) is significantly correlated with an augmented risk of unfavorable outcomes in individuals with CVD.[31,34] Multiple clinical investigations have demonstrated that febuxostat exhibits superior efficacy in reducing serum UA levels compared to allopurinol in patients with hyperuricemia.[35,36] One potential explanation for the cardioprotective effects of allopurinol, as opposed to febuxostat, may be attributed to the disparity in their respective mechanisms of action. Allopurinol functions as a purine analogue that can undergo metabolic processes involving various enzymes implicated in purine and pyrimidine synthesis metabolism.[37] In contrast, febuxostat acts solely as a non-purine analogue inhibitor of xanthine oxidase (XO).[38] The enzymes inhibited by allopurinol and its metabolites encompass XO, purine nucleoside phosphorylase in purine metabolism, and orotidine-5′-monophosphate decarboxylase in pyrimidine metabolism.[37] The potential benefit of allopurinol in preventing CVD may be attributed to its inhibition of enzymes involved in the generation of oxidative stress. Allopurinol acts by inhibiting XO, thereby reducing superoxide generation. Additionally, it facilitates the utilization of hypoxanthine in the synthesis of purine nucleotides, leading to the production of adenosine monophosphate, adenosine diphosphate, and ultimately adenosine triphosphate.[39] Furthermore, allopurinol directly scavenges free radicals.[40] Consequently, by mitigating oxidative stress, a crucial mechanism in the pathophysiology of CVD, allopurinol has the potential to lower the risk of developing CVD.[41]

Likewise, several systematic reviews[42,43] have investigated the association between febuxostat and CV safety among the Asian population by conducting explorative subgroup analyses. Liu et al.[43] found that febuxostat was associated with comparable CV mortality among the Asian population with hyperuricemia compared to allopurinol, which was consistent with ours. It is important to note, however, that the results of more recent RCTs and cohort studies have not yet been included. In another recent systematic review and meta-analysis performed by Gao et al., the results showed that febuxostat did not significantly increase the risk of CVD compared to allopurinol among the Asian population, which was inconsistent with ours.[42] The possible reasons can be concluded as follows. First, our meta-analyses were performed using HR instead of odds ratio to reduce bias from varied lengths of follow-up. Second, this meta-analysis included additional studies[19,20,22,26,28,29,30] compared to previous studies. Third, we performed meta-analysis for RCT and cohort studies separately. It is commonly observed that observational studies are more prone to selection bias, which may undermine the robustness of their findings.[44] Therefore, the utilization of both RCTs and cohort studies in the meta-analysis is deemed unsuitable due to variations in study designs and comparison groups, resulting in a significant methodological heterogeneity.[45]

LIMITATIONS

The limitations of this study must be taken into consideration when interpreting the findings. First, there were more eligible retrospective observational studies than RCTs, which is susceptible to selection and confounding biases. Despite the high quality of the included cohort studies (with scores ranging from 7 to 8) and the extraction of adjusted figures, it is important to acknowledge the potential influence of unidentified confounders on the results. Additionally, a subgroup analysis based on the different countries was conducted to minimize heterogeneity. However, it is worth noting that significant within-group heterogeneity still persisted in some subgroup findings, necessitating caution when interpreting these outcomes. Third, it is noteworthy that the administered doses of allopurinol ranged from 100 to 600 mg/day, whereas the doses of febuxostat ranged from 40 to 120 mg/day. A potential correlation between XOIs and CV outcomes may be dose-dependent. The utilization of fixed doses of allopurinol in several studies may also have introduced bias, thus contributing to the perceived superiority of febuxostat. However, our analysis was hindered by the limited number of studies available for dosage subgroup analysis, as well as

the lack of detailed information. Therefore, it is advisable to conduct longer-term follow-up investigations to assess CV safety more comprehensively. Fourth, there exist variations in the definitions of CVD outcomes across studies. Whereas most studies used International Classification of Disease (ICD) codes to identify CVD outcomes, a single study utilized both ICD codes and treatment factors.[30] This approach may have introduced bias in the study results. Furthermore, all the included cohort studies are retrospective, making it challenging to completely mitigate the influence of bias. Fifth, the inadequate number of RCTs included in this study, all originating from Japan, raises concerns about the generalizability of our findings. In spite of this, our findings suggest that we need more real-world data and that we need to gain a better understanding of how XOIs fare in various settings.

CONCLUSION

Based on the findings of this study, febuxostat users were associated with a significantly increased risk of adverse CV events than allopurinol users among Asian patients. However, to substantiate this assertion, it is imperative that future investigations encompassing larger sample sizes, multiple medical centers, extended durations, randomized participant selection, and double-blind methodologies be conducted within the Asian population.

AUTHOR CONTRIBUTIONS

J.-h.D. wrote the manuscript. D.-s.Q. and J.X.Z. designed the research. J.-h.D. and L.-s.X. performed the research. P.-h.L. and S.-s.Q. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

ORCID

Jian-hao Deng https://orcid.org/0000-0002-3095-6383
Jia-xing Zhang https://orcid.org/0000-0002-0178-7007

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