Cardiovascular safety of febuxostat compared to allopurinol for the treatment of gout: A systematic and meta-analysis

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Abstract
The cardiovascular safety of febuxostat compared to allopurinol for the treatment of gout remains equivocal. Febuxostat had a better safety outcome compared with allopurinol. In this systematic review and meta-analysis, we searched MEDLINE and Embase for articles published between March 1, 2000 and April 4, 2021, without any language restrictions. We did a systematic review and meta-analysis of included clinical trials to evaluate the cardiovascular safety of febuxostat compared to allopurinol for treatment of chronic gout. Two reviewers independently selected studies, assessed study quality, and extracted data. Risk ratios were calculated with random effects and were reported with corresponding 95% confidence intervals (CI). From 240 potentially relevant citations, 224 papers were excluded; 16 studies were ultimately included in the analysis. Febuxostat had a better safety outcome compared with allopurinol, which was the composite of urgent coronary revascularization (OR: 0.84, 95% CI: 0.77–0.90, p < .0001) and stroke (OR: 0.87, 95% CI: 0.79–0.97, p = .009). However, that difference was not found in nonfatal myocardial infarction (OR: 0.99, 95% CI: 0.80–1.22, p = .91), cardiovascular related mortality (OR: 0.98, 95% CI: 0.69–1.38, p = .89) and all-cause mortality (OR: 0.93, 95% CI: 0.75–1.15, p = .52). No significant differences in cardiovascular related mortality and all-cause mortality were observed across any subgroup. This meta-analysis adds new evidence regarding the cardiovascular safety of febuxostat in patients. Initiation of febuxostat in patients was not associated with an increased risk of death or serious cardiovascular related adverse events compared with allopurinol.

KEYWORDS
allopurinol, cardiovascular safety, febuxostat

1 | INTRODUCTION

Gout is a common clinical metabolic system disease and may contribute to many adverse health events. Evidence shows that the risk of hyperuricemia increased with advanced age in both sexes.¹² At present, drugs are the first choice for the treatment of gout in clinical practice. Studies have found that the treatment of gout with xanthine oxidase inhibition (allopurinol, febuxostat) can increase uric acid excretion via the kidneys and achieve better results. Recent studies have shown that febuxostat, a novel non-purine selective inhibitor of xanthine oxidase (XO), is more effective than allopurinol in lowering the uric acid levels in patients with hyperuricemia and gout.³⁴ It is particularly useful in patients who are refractory or intolerant to allopurinol, and requires no dose limitation in stages 1–3 chronic kidney disease.⁵ However, the

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food and drug administration (FDA) issued a public safety alert, responding to results of cardiovascular safety of febuxostat and allopurinol in patients with gout and cardiovascular morbidities (CARES) trail. The FDA public safety alert highlights the discussion of CV safety of febuxostat. By contrast, the European Medicines Agency (EMA)-required febuxostat versus allopurinol streamlined trial, a prospective, randomized, open-label, blinded-endpoint, non-inferiority trial of febuxostat (80–120 mg/day) versus allopurinol, does not support the finding of an increased cardiovascular risk of febuxostat. 

The evidence for a causal relationship between xanthine oxidase inhibitors and cardiovascular diseases (CVD) remains equivocal. Therefore, this study intends to conduct a systematic review of the relevant clinical trials published in recent years to analyze the adverse cardiovascular events and death risks of febuxostat compared with allopurinol in patients.

2 | METHODS

2.1 | Search strategy and selection criteria

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in this systematic review and meta-analysis. We systematically searched clinical trials of febuxostat and allopurinol treatment of gout in the elderly in PubMed, EMBASE, the Cochrane Library database and reviews of relevant articles from January 2000 to April 4, 2021. The following terms were used: “Gout” “Febuxostat” “Allopurinol” OR “Clinical Trial” “adverse events.” Language of publication did not influence article selection. Titles and abstracts were screened to exclude ineligible studies.

Studies were included if they met the following criteria: (i) clinical trials; (ii) treatment status as treated with febuxostat and allopurinol; (iii) long-term follow up of patients.

Exclusion criteria: (i) Documents in languages other than Chinese and English. (ii) There are no statistics on cardiovascular and death-related adverse events for the outcome indicators, and the data is incomplete. (iii) Patients with severe liver and kidney dysfunction, unstable vital signs, long-term alcoholism, and other conditions that will affect the resolution of indicators (iv) Patients with secondary gout.

Gao LG and Bin Wang screened titles, abstracts, and full text of papers identified in our search and assessed for risk of bias. The titles of the primary 240 publications identified were reviewed and 224 were discarded although they were identified by our search terms. The studies were also discarded because the enrolled patients with acute hyperuricemia or secondary hyperuricemia (e.g., end-stage renal disease). Finally, 14 publications were chosen for the meta-analysis.

2.2 | Study groups and clinical evaluation

The study population in the present meta-analysis consisted of 257 851 patients. Patients were categorized by treatment status as treated with febuxostat or allopurinol. The details in the pharmacologic intervention were listed in Table 1. All patients underwent complete clinical evaluations and fulfilled the diagnostic criteria. Outcomes of major events from each trial were selected, which were consisted of cardiovascular related mortality, major vascular events (including myocardial infarction or other acute coronary syndrome, coronary revascularization, or stroke, etc.) and all-cause mortality.

2.3 | Data extraction

Two authors (L.G. and B.W.) independently assessed and abstracted relevant trials that met the standardized, predefined criteria. Disagreements were identified computationally. Each was checked independently. If data could not be extracted or calculated from the article with confidence, no data were entered. Any discrepancies between the two reviewers were resolved through discussion. A data extraction form was used to collect the following information: (i) authors, study location, dates of study; (ii) number and age of participants; (iii) study design; (iv) comorbidities; (v) details of administration; (vi) follow-up time; (vii) outcomes. L.G. and B.W. extracted the data for patients using a standardized data form.

2.4 | Statistical analysis

The heterogeneity of the included studies was examined by Cochran chisquare tests ($p < .1$). The $I^2$ statistic was also examined, and we considered $I^2 > 50\%$ to indicate significant heterogeneity between the trials. Publication bias was evaluated using both the Begg’s funnel plot and the Egger plot. The Mantel–Haenszel fixed-effect model or the random-effects model was chosen for meta-analysis of the comparison of efficacy and cardiovascular safety of and endpoint events between febuxostat -treated group and allopurinol -treated group. Statistical analyses were carried out with Review Manager 5.0. $p$ values that were <.05 were considered statistically significant. All statistical tests were two-sided.

To examine the cardiovascular safety and identify the possible source of heterogeneity within these studies, previously defined subgroup analyses were performed (age, population and study design).

3 | RESULTS

3.1 | Results of the literature search

Initially, 240 articles were identified from the databases PubMed, EMBASE, and the Cochrane Library. Based on the predefined selection criteria, 224 papers were excluded for different reasons (Figure 1). As a result, 16 clinical trials with 257 851 subjects met all the inclusion criteria and were included in the meta-analysis (Figure 1). Demographic data for the patients was shown in Table 1. Among febuxostat users, the median age was from 45.5 to
| Study          | Comparison                  | Year of publication | Study design | No. of patients | Median age | Population | Male sex — no. (%) | Hypertension | Hyperlipidemia |
|---------------|-----------------------------|---------------------|--------------|----------------|------------|------------|-------------------|--------------|----------------|
| Ju et al.     | Febuxostat                  | 2020                | Retrospective cohort study | 276           | 70.41 (14.35) | Chinese     | 186 (67.4)         | -            | 123 (44.6)     |
| Ju et al.     | Allopurinol                | 2020                | Retrospective cohort study | 828           | 70.01 (14.90) | Chinese     | 549 (66.3)         | -            | 374 (45.2)     |
| Becker et al. | Febuxostat (80 mg)         | 2005                | P; R; O      | 256           | 51.8 ± 11.7 | White Race | 243 (95)          | 106 (41)     | 90 (35)        |
| Becker et al. | Febuxostat (120 mg)        | 2005                | P; R; O      | 251           | 52.0 ± 12.1 | White Race | 243 (97)          | 113 (45)     | 79 (31)        |
| Becker et al. | Allopurinol (300 mg)       | 2005                | P; R; O      | 253           | 51.6 ± 12.6 | White Race | 243 (96)          | 112 (44)     | 86 (34)        |
| Becker et al. | Febuxostat (80 mg)         | 2009                | P; R; O      | 649           | 51.4 ± 11.95 | White Race | >90%              | 295 (45.5)   | 229 (35.3)     |
| Becker et al. | Febuxostat (120 mg)        | 2009                | P; R; O      | 292           | 50.9 ± 11.57 | White Race | >90%              | 115 (39.4)   | 89 (30.5)      |
| Becker et al. | Allopurinol (300 mg)       | 2009                | P; R; O      | 145           | 51.0 ± 11.30 | White Race | >90%              | 73 (50.3)    | 47 (32.4)      |
| Becker et al. | Febuxostat (40 mg)         | 2010                | Double-blind RCT | 757           | 52.5 ± 11.68 | White Race | 722 (95.4)        | -            | 299 (39.5)     |
| Becker et al. | Febuxostat (80 mg)         | 2010                | Double-blind RCT | 756           | 53.0 ± 11.79 | White Race | 710 (93.9)        | -            | 308 (40.7)     |
| Becker et al. | Allopurinol (200/300 mg)   | 2010                | Double-blind RCT | 756           | 52.9 ± 11.73 | White Race | 709 (93.8)        | -            | 335 (44.3)     |
| Kamatani et al.| Febuxostat (40 mg)         | 2011                | P; R; O      | 122           | 51.6 ± 13.1  | Japanese   | 118 (96.7)        | 49 (40.2)    | 51 (41.8)      |
| Kamatani et al.| Allopurinol (200 mg)       | 2011                | P; R; O      | 121           | 52.6 ± 14    | Japanese   | 119 (98.3)        | 32 (26.4)    | 44 (36.4)      |
| Huang et al.  | Febuxostat (40 mg)         | 2014                | Double-blind RCT | 172           | 46.42 ± 10.90 | Chinese   | 167 (97.1)        | 54 (31.40)   | 6 (3.49)       |
| Huang et al.  | Febuxostat (80 mg)         | 2014                | Double-blind RCT | 172           | 47.40 ± 11.18 | Chinese   | 169 (98.2)        | 45 (26.16)   | 5 (2.91)       |
| Huang et al.  | Allopurinol (300 mg)       | 2014                | Double-blind RCT | 172           | 46.17 ± 11.56 | Chinese   | 168 (97.7)        | 44 (25.58)   | 2 (1.16)       |
| Xu et al.     | Febuxostat (80 mg)         | 2015                | Double-blind RCT | 168           | 48.2 ± 12.0  | Chinese   | 146 (92.4)        | 32 (20.3)    | 13 (8.2)       |
| Xu et al.     | Febuxostat (40 mg)         | 2015                | Double-blind RCT | 168           | 45.5 ± 11.9  | Chinese   | 158 (98.8)        | 20 (12.5)    | 15 (9.4)       |
| Xu et al.     | Allopurinol (300 mg)       | 2015                | Double-blind RCT | 168           | 46.6 ± 10.7  | Chinese   | 149 (93.7)        | 22 (13.8)    | 11 (6.9)       |
| Tanaka et al. | Febuxostat (40 mg)         | 2015                | P; R; O      | 21            | 70.1 ± 9.5   | Japanese | 19 (90.5)         | 11 (52)      | -              |
| Tanaka et al. | Allopurinol (300 mg)       | 2015                | P; R; O      | 19            | 66.1 ± 7.0   | Japanese | 16 (84.2)         | 6 (32)       | -              |
| Nakagomi et al.| Febuxostat                | 2015                | P; R; O      | 31            | 69.3 ± 10.0  | Japanese | 22 (71)           | 27 (87.1)    | 30 (96.8)      |
| Nakagomi et al.| Allopurinol               | 2015                | P; R; O      | 30            | 71.8 ± 8.0   | Japanese | 18 (69)           | 30 (100)     | 29 (96.7)      |
| Yu et al.     | Febuxostat (80 mg)         | 2016                | P; R; O      | 54            | 46.0 ± 11.0  | Taiwan    | 53 (98.1)         | -            | -              |
| Yu et al.     | Allopurinol (300 mg)       | 2016                | P; R; O      | 55            | 45.2 ± 12.0  | Taiwan    | 53 (96.4)         | -            | -              |
| Study          | Comparison | Year of publication | Study design     | No. of patients | Median age   | Population Male sex – no. (%) | Hypertension | Hyperlipidemia |
|---------------|------------|---------------------|------------------|----------------|--------------|--------------------------------|--------------|----------------|
| White et al.  | Febuxostat | 2018                | Double-blind RCT | 3098           | 64.0 (58–71) | White race (69.7%)              | 2604 (84.1) | 2864 (92.4)   |
| White et al.  | Allopurinol| 2018                | Double-blind RCT | 3092           | 65.0 (58–71) | White race (69.2%)              | 2592 (83.8) | 2851 (92.2)   |
| Su et al.     | Febuxostat | 2019                | Cohort study     | 44             | 65.0 + 15.7  | Taiwan                          | 32 694 (74.1)| 30 433 (69.0) |
| Su et al.     | Allopurinol| 2019                | Cohort study     | 39             | 59.1 (12.5)  | Korean                          | 78.3         | 55.4          |
| Kang          | Febuxostat | 2019                | Cohort study     | 537            | 75.4 ± 6.7   | Japanese                        | 371 (69)    | 506 (94.2)    |
| Kang          | Allopurinol| 2019                | Cohort study     | 533            | 76.0 ± 6.5   | Japanese                        | 368 (69)    | 501 (94.0)    |
| Kojima et al. | Febuxostat | 2019                | Observational trial | 120          | 75.9 ± 8.9   | Italy                           | 79 (65.8)    | 114 (95.0)    |
| Kojima et al. | Allopurinol| 2019                | Observational trial | 135          | 78.1 ± 6.3   | Italy                           | 81 (60)      | 122 (90.4)    |
| Mackenzie et al. | Febuxostat | 2020                | P; R; O          | 3063           | 71.0 (6.4)   | 99.1% White race                 | 2619 (85.5%) | 2345 (76.6%)  |
| Mackenzie et al. | Allopurinol| 2020                | P; R; O          | 3065           | 70.9 (6.5)   | 99.1% White race                 | 2606 (85.0%) | 2439 (79.6%)  |
| Zhang et al.  | Febuxostat | 2020                | Cohort study     | 24             | 76 (70–82)   | 76.4% White race                | 52.3         | 95.4          |
| Zhang et al.  | Allopurinol| 2020                | Cohort study     | 74             | 76 (71–82)   | 76.2% White race                | 52.3         | 95.4          |

| Study          | Coronary heart disease | Diabetes (%) | BMI | Follow-up period | Urgent Coronary revascularisation n (%) | Nonfatal myocardial infarction N OR CAD (%) | Cardiovascular death | Nonfatal stroke OR Cerebrovascular disease | Death from any cause |
|---------------|------------------------|--------------|-----|------------------|----------------------------------------|---------------------------------------------|----------------------|------------------------------------------|---------------------|
| Ju et al.     | -                      | 59 (21.4)    | -   | -                | -                                      | 0                                           | 6                    | 52                                       |                     |
| Ju et al.     | -                      | 185 (22.3)   | -   | -                | -                                      | 19                                          | 0                    | 25                                       | 204                 |
| Becker et al. | 23 (9)                 | 17 (7)       | 32.7 ± 6.1 | 52 weeks        | 0                                      | 0                                           | 1                    | 0                                        | 2                   |
| Becker et al. | 28 (11)                | 17 (7)       | 32.3 ± 5.7 | 52 weeks        | 0                                      | 0                                           | 1                    | 0                                        | 2                   |
| Becker et al. | 23 (9)                 | 19 (8)       | 32.6 ± 6.1 | 52 weeks        | 0                                      | -                                           | 0*                   | 0*                                      | 0*                  |
| Becker et al. | 71 (10.9)              | 46 (7.1)     | 32.3 ± 5.78 | 172 weeks      | -                                      | -                                           | 6                    | -                                        | 7                   |
| Becker et al. | 33 (11.3)              | 15 (5.1)     | 33.2 ± 6.17 | 172 weeks      | -                                      | -                                           | -                    | -                                        | 3                   |
| Becker et al. | 14 (9.7)               | 12 (8.3)     | 33.8 ± 6.79 | 172 weeks      | -                                      | -                                           | 0                    | -                                        | 0                   |
| Becker et al. | 421 (55.6)             | 89 (11.8)    | -   | 28 weeks        | -                                      | 0*                                          | 0*                   | 0*                                      | 1                   |
| Becker et al. | 440 (58.2)             | 113 (14.9)   | -   | 28 weeks        | -                                      | 1                                           | 0                    | 2                                        | 1                   |
| Becker et al. | 436 (57.7)             | 110 (14.6)   | -   | 28 weeks        | -                                      | 1                                           | 2                    | 0                                        | 3                   |
## TABLE 1 (Continued)

| Study            | Coronary heart disease | Diabetes (%) | BMI   | Follow-up period | Urgent Coronary revascularisation n (%) | Nonfatal myocardial infarction N OR CAD (%) | Cardiovascular death | Nonfatal stroke OR Cerebrovascular disease | Death from any cause |
|------------------|------------------------|--------------|-------|------------------|----------------------------------------|---------------------------------------------|----------------------|--------------------------------------------|----------------------|
| Kamatani et al.  | 12 (9.8)               | -            | 8 weeks | 0               | 0                                      | 0                                           | 0                   | 0                                          | 0                   |
| Kamatani et al.  | 12 (9.9)               | -            | 8 weeks | 0               | 0                                      | 0                                           | 0                   | 0                                          | 0                   |
| Huang et al.     | 57 (33.14)             | 14 (8.14)    | 25.63 ± 2.80 | 28 weeks | 0                                      | 0                                           | 0                   | 0                                          | 0                   |
| Huang et al.     | 47 (27.33)             | 9 (5.23)     | 25.25 ± 2.64 | 28 weeks | 0                                      | 0                                           | 0                   | 0                                          | 0                   |
| Huang et al.     | 45 (26.16)             | 10 (5.81)    | 25.44 ± 2.53 | 28 weeks | 0                                      | 0                                           | 0                   | 0                                          | 0                   |
| Xu et al.        | 2 (1.3)                | 5 (3.2)      | 25.1 ± 2.6  | 24 weeks | 0                                      | 0                                           | 0                   | 0                                          | 0                   |
| Xu et al.        | 4 (2.5)                | 10 (6.3)     | 25.3 ± 2.7  | 24 weeks | 0                                      | 0                                           | 0                   | 0                                          | 0                   |
| Xu et al.        | 4 (2.5)                | 9 (5.7)      | 25.4 ± 3.3  | 24 weeks | 0                                      | 0                                           | 0                   | 0                                          | 0                   |
| Tanaka et al.    | -                      | -            | 24.1 ± 3.8  | 12 weeks | 0                                      | 0                                           | 0                   | 0                                          | 0                   |
| Tanaka et al.    | -                      | -            | 26.1 ± 2.9  | 12 weeks | 0                                      | 0                                           | 0                   | 0                                          | 0                   |
| Nakagomi et al.  | -                      | 9 (29.0)     | 23.6 ± 2.4  | 23 (13–47) | -                                     | -                                           | -                   | 2 (2/31)                                   | -                   |
| Nakagomi et al.  | -                      | 12 (40.0)    | 23.1 ± 3.1  | 23 (13–47) | -                                     | -                                           | -                   | 5 (1/6)                                    | -                   |
| Yu et al.        | -                      | -            | 26.8 ± 3.7  | 12 weeks | 0                                      | 0                                           | 0                   | -                                          | 0                   |
| Yu et al.        | -                      | -            | 27.8 ± 4.2  | 12 weeks | 0                                      | 0                                           | 0                   | -                                          | 0                   |
| White et al.     | 1197 (38.6)            | 1193 (38.5)  | 33.6 ± 7.0  | 72 months | 49 (1.6)                              | 111 (3.6)                                   | 134 (4.3)           | 71 (2.3)                                   | 243 (7.8)           |
| White et al.     | 1231 (39.8)            | 1213 (39.2)  | 33.4 ± 6.9  | 72 months | 56 (1.8)                              | 118 (3.8)                                   | 100 (3.2)           | 70 (2.3)                                   | 199 (6.4)           |
| Su et al.        | 9390 (21.3)            | 16 875 (38.3)| -          | 28.5 weeks | -                                     | 272 (0.6)                                   | 468 (1.06)          | 344 (0.8)                                  | 1630 (3.7)          |
| Su et al.        | 8582 (19.5)            | 15 480 (35.1)| -          | 22.5 weeks | -                                     | 193 (0.4)                                   | 334 (0.75)          | 298 (0.7)                                  | 1301 (2.9)          |
| Kang             | 1.6                    | 29.5         | -          | 43.2 weeks | 44 (0.4)                              | 20                                          | -                   | 78                                         | 135                 |
| Kang             | 1.6                    | 28.6         | -          | 35.9 weeks | 267 (0.64)                           | 88                                           | -                   | 382                                        | 545                 |
| Kojima et al.    | 45 (8.4)               | 197 (36.7)   | 24.74 ± 3.71| 152 weeks | 2                                      | 4                                           | -                   | 9                                          | 10                  |
| Kojima et al.    | 45 (8.4)               | 199 (37.3)   | 24.61 ± 3.65| 150 weeks | 3                                      | 7                                           | -                   | 7                                          | 12                  |
| Cicero et al.    | 67 (55.8)              | 32 (26.7)    | 25.9 ± 2.9  | 6 years   | -                                     | -                                           | -                   | -                                          | -                   |

(Continues)
76.0 years and 52.3%–98.8% were male in the included studies. Among allopurinol users, the median age was from 65.0 to 76.0 years and 52.3%–98.3% were male. In both groups, 1.3%–58.2% had history of coronary heart disease at baseline. Hypertension (12.5%–100%), hyperlipidemia (2.9%–96.8%), and diabetes (3.2%–55.2%) were common comorbidities in both groups.

3.2 | Effect of febuxostat versus allopurinol treatment on clinical events

Compared with allopurinol treatment group, the febuxostat group had a better safety outcome, which was the composite of urgent coronary revascularization (OR: 0.84, 95% CI: 0.77–0.90, p < .0001 Figure 2(A)) and stroke (Figure 2(B)) (OR: 0.87, 95% CI: 0.79–0.97, p = .009). However, that difference was not found in nonfatal myocardial infarction (Figure 2(C)) (OR: 0.98 95% CI: 0.80–1.22, p = .91), cardiovascular related mortality (Figure 2(D)) (OR: 0.98, 95% CI: 0.69–1.38, p = .89) and all-cause mortality (Figure 2(E)) (OR: 0.93, 95% CI: 0.75–1.15, p = .52).

Begg's funnel plot indicated that there are no strong evidences of publication selection bias.

3.3 | Results of subgroup analyses

To clarify the heterogeneity, subgroup analyses were performed to investigate the source of heterogeneity (Table 2). Compared with allopurinol treatment group, subgroup analyses according to age, population and study design showed that the febuxostat treatment could significantly reduce the occurrence of stroke in age ≥ 65 years group (OR: 0.88, 95% CI: 0.79–0.99, p = .03), white race (≥70%) group (OR:
0.88, 95% CI: 0.79–0.99, p = .04) and cohort study group (OR: 0.87, 95% CI: 0.78–0.98, p = .04). Subgroup analyses according to population showed that the febuxostat treatment could significantly reduce the incidence of nonfatal myocardial infarction in white race participants (OR: 0.87, 95% CI: 0.79–0.96, p = .007). No significant differences in cardiovascular related mortality and all-cause mortality were observed across any subgroup.

### DISCUSSION

The present study suggests compared with allopurinol, the use of febuxostat results in significantly decreased risks of urgent coronary revascularization and stroke. Initiation of febuxostat did not increase the risk of nonfatal myocardial infarction, the cardiovascular related mortality and all-cause mortality. Subgroup analyses according to age,
population and study design showed that the febuxostat treatment could significantly increase the occurrence of stroke in patients with age ≥65 years and white race (≥70%).

**TABLE 2** Subgroup and sensitivity analyses of adverse events stratified by previously defined study characteristics

| Variables           | Nonfatal myocardial infarction | Stroke | Cardiovascular related mortality | All-cause mortality |
|---------------------|---------------------------------|--------|----------------------------------|--------------------|
|                     | No. of trials OR (95% CI)        | No. of trials OR (95% CI) | No. of trials OR (95% CI) | No. of trials OR (95% CI) |
| Subgroup analysis   | p for heterogeneity              | p for heterogeneity | Heterogeneity: Not applicable | p for heterogeneity |
| Age                 |                                 |                    |                                 |                     |
| <65 years           | 3 0.89 (0.56, 1.43) .83          | 1 0.82 (0.64, 1.04) |                                 | 5 0.99 (0.25, 3.89) .46 |
| ≥65 years           | 6 0.98 (0.77, 1.24) .0006        | 5 0.88 (0.79, 0.99) | .59                              | 6 0.97 (0.66, 1.40) .0004 |
| Study design        |                                 |                    |                                 |                     |
| RCT                 | 5 0.92 (0.76, 1.11) .91          | 3 0.88 (0.69, 1.10) | .28                              | 8 0.95 (0.59, 1.52) .08 |
| Cohort study        | 4 1.00 (0.70, 1.44) .0001        | 3 0.87 (0.78, 0.98) | .74                              | 3 0.82 (0.25, 2.71) .006 |
| Population          |                                 |                    |                                 |                     |
| White Race (≥50%)   | 4 0.87 (0.79, 0.96) .88          | 3 0.88 (0.79, 0.99) | .36                              | 8 0.86 (0.52, 1.41) .03 |
| Asian               | 5 1.01 (0.74, 1.39) .03          | 3 0.83 (0.66, 1.04) | .65                              | 3 0.92 (0.26, 3.25) .11 |
|                     |                                 |                    |                                 | 4 0.99 (0.75, 1.29) .001 |

In conclusion, our meta-analysis suggested that febuxostat users did not significantly increase the risk of cardiovascular events or all-cause mortality compared with allopurinol users. Further research is needed to clarify the safety and efficacy of febuxostat in specific populations.
cause mortality compared with allopurinol users. However, more
high-quality, double-blinded, large, randomized studies are needed to
elucidate this issue.

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CONFLICT OF INTEREST
The authors declares no conflicts of interest.

DATA AVAILABILITY STATEMENT
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