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Febuxostat Use and Risks of Cardiovascular Disease Events, Cardiac Death, and All-cause Mortality: Metaanalysis of Randomized Controlled Trials

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ABSTRACT. ***Objective.*** To assess whether febuxostat use increases the risk of developing cardiovascular (CV) events, cardiac death, and all-cause mortalities.

Methods. The relevant literature was searched in several databases including MEDLINE (PubMed, January 1, 1966–February 29, 2020), Web of Science, EMBASE (January 1, 1974–February 29, 2020), ClinicalTrials.gov, and Cochrane Central Register of Controlled Trials. Manual searches for references cited in the original studies and relevant review articles were also performed. All studies included in this metaanalysis were published in English.

Results. In the end, 20 studies that met our inclusion criteria were included in our metaanalysis. Use of febuxostat was found not to be associated with an increased risk of all-cause mortality (RR 0.87, 95% CI 0.57–1.32, $P = 0.51$). Also, there was no association between febuxostat use and mortalities arising from CV diseases (CVD; RR 0.84, 95% CI 0.49–1.45, $P = 0.53$). The RR also revealed that febuxostat use was not associated with CVD events (RR 0.98, 95% CI 0.83–1.16, $P = 0.83$). Further, the likelihood of occurrence of CVD events was found not to be dependent on febuxostat dose (RR 1.04, 95% CI 0.84–1.30, $P = 0.72$).

Conclusion. Febuxostat use is not associated with increased risks of all-cause mortality, death from CVD, or CVD events. Accordingly, it is a safe drug for the treatment of gout.

Keyword Indexing Terms: all-cause mortality, cardiovascular disease, febuxostat, metaanalysis

The association between hyperuricemia and cardiovascular disease (CVD) has been well established. Urate-lowering therapy has become a major consideration in the treatment of gout[1,2,3,4,5,6,7]. In 2009, the US Food and Drug Administration (FDA) approved the use of febuxostat, a xanthine oxidase inhibitor, for the treatment of hyperuricemia in patients with gout[8]. In effect, the drug has been widely used to reduce the serum urate (sUA) concentration in patients with gout. Several studies have validated the efficacy of febuxostat in reducing sUA compared with allopurinol, an older drug designed for the same function[9,10,11,12,13].

A previous multicenter China Ageing REspiratory infections Study (CARES) study at a phase III clinical trial assessing the safety of both febuxostat and allopurinol in patients with gout and cardiovascular (CV) comorbidities with regard to CV events showed that CV death and all-cause death were higher in febuxostat use compared with allopurinol[14]. As a result, on November 15, 2017, the FDA issued a public warning that febuxostat could be associated with an increased risk of heart-related mortalities[15]. More recently, on February 21, 2019, the FDA issued another caution that febuxostat use was associated with more CV deaths compared to allopurinol[16]. However, a systematic review and metaanalysis[17] encompassing 10 trials found that febuxostat use was not associated with an increased or reduced risk of CVD, but increases the risk of death from CV causes, consistent with findings reported in the CARES trial[14].

Considering the controversy surrounding the FDA alert, the metaanalyses of a few trials, and several findings in published (and some unpublished) studies at ClinicalTrials.gov on the association between febuxostat use and both heart-related disorders and CV mortality[9,10,12,13,14,18–33], we conducted our metaanalysis to validate the safety of the drug with regard to the risk of CVD and CV mortality.

METHODS

We developed and followed a standard protocol based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Our study is registered with PROSPERO (number CRD42019131872).

Search strategy and study selection. The relevant literature was searched

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The authors report no conflicts of interest.

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in several databases including MEDLINE (PubMed, January 1, 1966–February 29, 2020), Web of Science, EMBASE (January 1, 1966–February 29, 2020), ClinicalTrials.gov, and the Cochrane Central Register of Controlled Trials. The key search words were as follows: ([febuxostat] OR [xanthine oxidase inhibitor]) AND ([all-cause death OR all-cause mortality OR mortality] OR [cardiovascular disease]). Relevant articles identified in original studies were also searched and evaluated. All studies included in our metaanalysis were published in English. The detailed steps involved in retrieving and analyzing relevant studies are presented in Figure 1.

Inclusion and exclusion criteria. To be included in our analysis, the relevant studies must have met the following criteria: (1) must be a randomized controlled trial (RCT); (2) the research must have lasted for more than 1 month; (3) must have assessed the safety of febuxostat in comparison with a control group (placebo or allopurinol); and (4) should have reported on 1 or more of several outcomes (i.e., mortality, CVD events, or CVD death). Studies were excluded from the analysis when (1) the safety comparative outcome between febuxostat and control group was not reported; (2) there was no report on all-cause mortality, CVD events, or CVD death; and (3) the studies were duplicates.

The definition of "CVD events" was based on the International Classification of Diseases, 9th Revision, Clinical Modification diagnosis codes. CVD events were defined as the occurrence of coronary heart disease (e.g., myocardial infarction, angina, and other coronary heart disease), heart failure, and cerebrovascular disease (e.g., stroke, transient cerebral ischemia attack, cerebrovascular accident, and other cerebrovascular disease)[34,35].

Data collection. Data searches and extraction were performed by 2 independent reviewers (BLZ and HD). The key elements captured were the first authors' surnames, year of publication, study design, sample size, incidences of follow-up, and eventual outcomes. Any disagreement in data extraction was resolved through a discussion between these 2 reviewers but in consultation with the other authors (HMJ, XHY, and JDT).

Assessment of heterogeneity. Heterogeneity was evaluated using the Cochran Q and I^2 statistics. The study was considered to be heterogeneous if $P < 0.1$ (Cochran Q). Studies with I^2 value < 50% were considered to be nonheterogeneous, and thus a fixed effects model was used in their analysis. Studies with $I^2 > 50\%$ were considered to be heterogeneous; hence, they were analyzed using a random effects model.

Quality assessment. The quality of methodologies employed by individual studies included in our metaanalysis was assessed independently by 2 researchers (XHY and BLZ) using the risk of bias tool. Several variables were assessed: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete data assessment (attrition bias), selective reporting (reporting bias), and other bias. The methodologies were henceforth classified into "high risk," "unclear risk," and "low risk" categories. A third reviewer (HMJ) arbitrated any disagreement arising from this classification.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (gdt.gradepro.org/app) was used for evaluating the quality of the evidence. The evaluation included study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations. Four quality levels were developed: very low, low, moderate, and high.

Summary measures and synthesis of results. The risk ratios (RR) for the association between febuxostat and all-cause mortality, CVD events, and CVD death were either calculated or extracted from individual studies. Subgroup analysis of different febuxostat doses was used to assess the effect of different doses of the drug on the relative risk of a CVD event. In addition, several baseline characteristics for all included studies, such as the sample size, age, BMI, baseline serum uric acid concentration, study type, phase, intervention group, comparison group, outcomes, mean follow-up time, nationality, and population structure, were also captured. To assess potential for publication bias, we constructed funnel plots for each outcome in which the log RR were plotted against corresponding standard errors. Sensitivity analyses were also performed to evaluate the effect of the study on the overall estimate.

Statistical analyses. Data were analyzed using STATA version 14.0 (StataCorp). The risks of all-cause mortality, CVD events, and CVD death outcomes associated with febuxostat were assessed based on RR. Subgroup analyses were also performed to evaluate the association of different febuxostat doses with all-cause mortality, CVD events, and CVD death. The Egger and Begg tests were used to examine the presence of publication bias. The Review Manager 5.3 (RevMan 5.3) was used to assess the risk of bias. Statistical significance for all the analyses was set at $P < 0.05$.

RESULTS

Study flow and study characteristics. The conditions to be satisfied before a study was included in our metaanalyses are shown in Figure 1. In total, 20 studies encompassing a combined 19,986 participants were assessed. Table 1 shows the characteristics of the 20 studies on febuxostat. Of these, 16 studies reported on CVD events, 11 were on all-cause mortality, and 9 reported on CVD death.

Association between febuxostat and all-cause mortality, CVD death and CVD events. All-cause mortality, CVD death, and CVD events reported in individual studies are summarized in

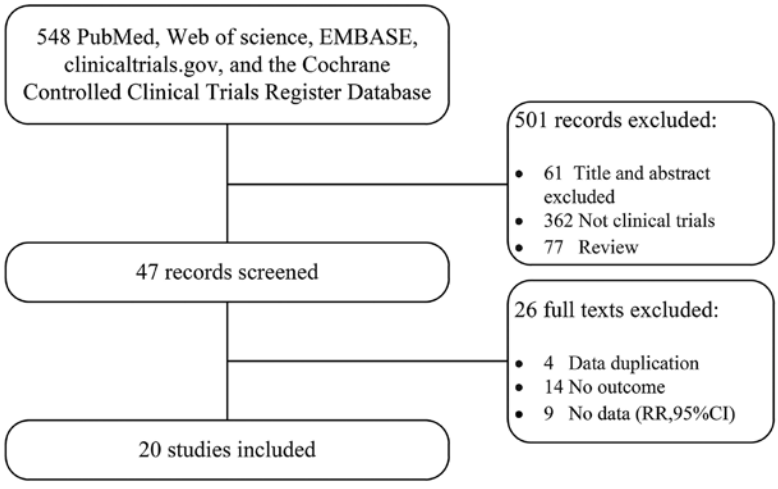

Figure 1. Study selection process.

Table 1. Characteristics of 20 studies associated with CVD events, all-cause mortality, and CVD mortality in hyperuricemia population (N = 19,986).

First Author, Yr	Patients, n	Age, Yrs, mean ± SD	BMI, kg/m^2, mean ± SD	Baseline sUA Concentration, mean ± SD	Study Type	Trial Phase	Intervention Group, mg	Comparison Group	Outcome	Follow-up, Weeks	Nation	Population
Becker, 2005[10]	760	51.8 ± 11.6	N/A	9.84 ± 1.25	RCT	3	FBX 80, 120	ALLO	AD, CVDD	52	USA	Gout
Schumacher, 2008[9]	1072	52.0 ± 12.0	33.0 ± 6.7	N/A	RCT	3	FBX 80, 120, 240	ALLO/ placebo	CVD	28	USA	Gout
Becker, 2009[12]	1466	51.4 ± 11.9	32.7 (21–65)[a]	9.80 ± 1.25	RCT	3	FBX 80, 120	ALLO	CVD, AD, CVDD	52	USA	Gout
Becker, 2010[13]	2269	52.8 ± 11.7	32.8 ± 6.3	9.6 ± 1.17	RCT	N/A	FBX 40, 80	ALLO	CVD, AD, CVDD	52	USA	Gout
Kamatani, 2011[33]	202	52.7 ± 12.8	26.5 ± 4.1	8.8 ± 1.0	RCT	2	FBX 20, 40, 60, 80	Placebo	CVD	16	JPN	Gout
Wells, 2012[29]	2091	53.0 ± 11.7	32.8 ± 6.1	9.5 ± 1.2	RCT	N/A	FBX 40, 80	ALLO	CVD	28	USA	Gout
Huang, 2014[28]	516	46.6 ± 11.2	25.4 ± 2.6	9.9 ± 1.4	RCT	N/A	FBX 40, 80	ALLO	CVD, AD	28	CHN	Gout
Nakagomi, 2015[26]	61	70.6 ± 9	23.4 ± 2.8	N/A	RCT	N/A	FBX 40	ALLO	CVDD	52	JPN	Chronic HF
Saag, 2016[30]	96	65.7 ± 10.6	33.4 ± 6.7	10.5 ± 1.7	RCT	N/A	FBX 40, 60, 80	Placebo	CVD, AD, CVDD	52	USA	Gout with CKD
Dalbeth, 2017[32]	314	50.8 ± 12.1	32.8 ± 6.3	8.8 ± 1.4	RCT	2	FBX 40, 80	Placebo	CVD, AD, CVDD	104	USA	Gout
Gunawardhana, 2017[27]	121	53.6 ± 10.6	32.8 ± 5.6	N/A	RCT	2	FBX 80	Placebo	CVD	6	USA	Hyperuricemia
Kimura, 2018[18]	441	65.4 ± 12.1	24.8 ± 4.0	7.8 ± 0.9	RCT	N/A	FBX < 40	Placebo	CVD, AD	108	JPN	Hyperuricemia with CKD 3
Mukri, 2018[19]	93	N/A	N/A	N/A	RCT	N/A	FBX 40	No treatment	CVD	28	MY	Hyperuricemia with DKD
White, 2018[14]	6190	64.0 ± 6.5	33.5 ±7.0	8.7 ± 1.7	RCT	3	FBX 40, 80	ALLO	CVD, AD, CVDD	138	USA	Gout
Saag, 2019[31]	1783	55.0 ± 11.7	34.3 ± 7.8	N/A	RCT	3	FBX 40, 80	Placebo	AD	52	USA	Gout
Cicero, 2019[20]	255	77.0 ± 7.6	26.0 ± 2.1	7.7 ± 1.9	RCT	N/A	FBX 80	ALLO	AD, CVDD	12	ITA	Chronic HF
Kojima, 2019[21]	1070	75.7 ± 6.6	24.7 ± 3.9	7.5 ± 1.1	RCT	N/A	FBX 40	Non-FBX	CVD, AD, CVDD	154	JPN	Hyperuricemia, n > 65 yrs
Beddhu, 2016[25]	80	68.0 ± 10.0	N/A	7.2 ± 1.4	RCT	N/A	FBX 80	Placebo	CVD	24	USA	Hyperuricemia with T2DM and CKD
Spina, 2015[24]	346	58.4 ± 13.8	N/A	N/A	RCT	3	FBX	ALLO	CVD	N/A	USA	TLS
Chohan, 2012[23]	760	51.2 ± 12.1	N/A	N/A	RCT	3	FBX 80, 120	ALLO	CVD	52	USA	Gout

[a] Median (IQR). AD: all death; ALLO: allopurinol; BP: blood pressure; CAD: coronary artery disease; CHN: China; CKD: chronic kidney disease; CVD: cardiovascular disease; CVDD: cardiovascular disease–related death; DKD: diabetic kidney disease; FBX: febuxostat; HF: heart failure; ITA: Italy; JPN: Japan; MY: Malaysia; N/A: not applicable; RCT: randomized controlled trial; SBP: systolic blood pressure; SCR: serum creatinine; sUA: serum urate acid; T2DM: type 2 diabetes mellitus; TLS: tumor lysis syndrome.

Supplementary Table 1 (available from the authors on request). As shown in Figure 2, the metaanalysis on the association between febuxostat and all-cause death was inconclusive because there was no clear association between the drug and increased or reduced risk of all-cause mortality from pooled results (RR 0.87, 95% CI 0.57–1.32, P = 0.51). Further, compared with allopurinol or placebo, there was also no significant association between febuxostat and the incidence of all-cause mortality (RR 0.79, 95% CI 0.35–1.78 and RR 0.79, 95% CI 0.39–1.61, respectively).

Likewise, there was no association between febuxostat use and incidences of CVD death from pooled results, as shown in Figure 3 (RR 0.84, 95% CI 0.49–1.45, P = 0.53). Compared with allopurinol or placebo, febuxostat was also not associated with CVD death (RR 0.75, 95% CI 0.32–1.73 and RR 0.89, 95% CI 0.34–2.35, respectively).

Association between febuxostat and CVD events. Of the 20 studies, 18 focused on CVD events in participants. As shown in Figure 4, the RR estimates revealed that febuxostat was not associated with CVD events from pooled results (RR 0.98, 95% CI 0.83–1.16, P = 0.83). Similarly, compared with allopurinol or placebo, febuxostat was also found not to be associated with CVD events. This relationship is shown in Figure 4 (RR 1.01, 95% CI 0.82–1.23 and RR 0.89, 95% CI 0.59–1.36, respectively).

Subgroup analysis on the relative risk of CVD events under different febuxostat doses. As shown in Figure 5, pooled results from 14 studies revealed that increased risk of CVD events was not dependent on febuxostat dosage (RR 1.04, 95% CI 0.84–1.30, P = 0.72).

Sensitivity analysis and publication bias. The sensitivity analysis revealed that exclusion of any individual study from the meta-analysis did not alter the overall conclusions. Publication bias was assessed by visually examining a funnel plot. Asymmetry was empirically assessed using the Egger and Begg tests. Consequently, no publication bias in the pooled studies was found (all-cause death: P = 0.56; CVD death: P = 0.15; CVD events: P = 0.36).

Risk of bias assessment. The risk assessment for any bias is presented in Supplementary Figure 1 (available from the authors on request). All studies that employed randomization and random sequence generation (selection bias) were rated as low risk for bias. For the allocation concealment (selection bias), 7 studies[9,19,20,25,29,30,32] were classified as unclear risk of bias with no mention of the random method. Most studies employed double-blindness and were accordingly rated as low risk for bias. In assessing the risk of incomplete outcome data, 6 studies[14,20,21,28,29,32] were rated high risk for bias because numerous data were missing and more than 10% of their participants had been lost to follow-up. Eight studies[10,13,14,19,20,26,28,33] had no mention of National Clinical Trial numbers and were thus classified under the unclear risk of bias category for selective reporting. Other bias was unclear in most studies.

Quality of evidence assessment. The GRADE system was used to assess the quality of the evidence. The eventual evaluation is shown in Supplementary Figure 2 (available from the authors on request). Ultimately, the quality of evidence for all-cause death and CVD events was rated as high, while CVD death was rated as moderate.

DISCUSSION

In our review and metaanalysis, we found that when compared with allopurinol or placebo, febuxostat is not associated with increased risk of developing CV events when used for controlling hyperuricemia in patients with gout. Further, compared with

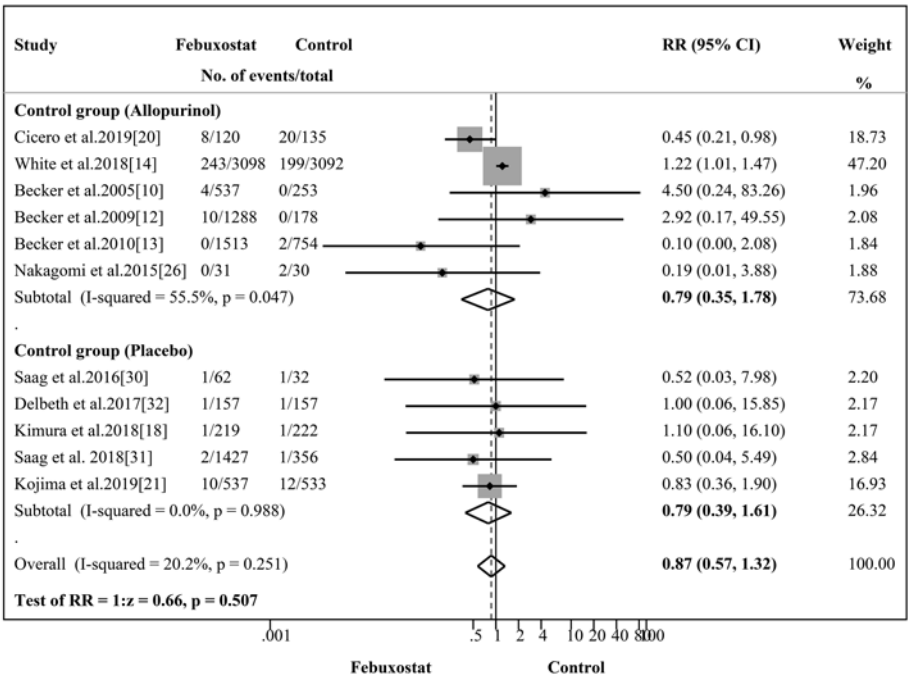

Figure 2. Risk ratios (RR) for all-cause death events associated with febuxostat from pooled studies.

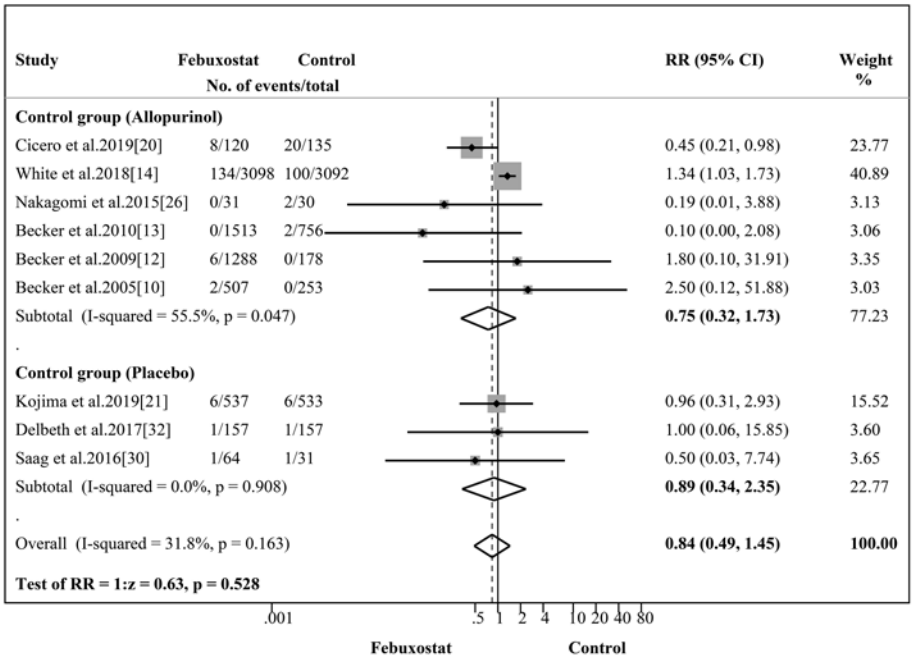

Figure 3. Risk ratios (RR) for CVD death associated with febuxostat use from pooled studies.

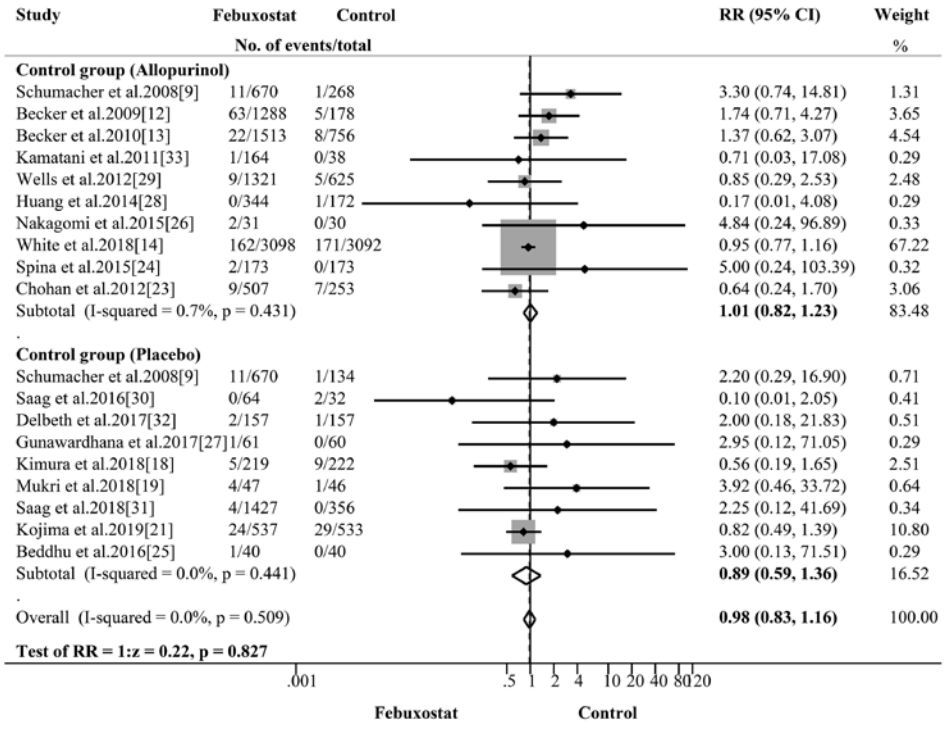

Figure 4. Risk ratios (RR) for CVD events associated with febuxostat use from pooled studies.

allopurinol or placebo, no association was found between the use of febuxostat and increased risk of CV death or all-cause death.

Gout is not only the most common type of inflammatory arthritis but also the most mismanaged and misdiagnosed inflammatory complication. Interestingly, it is the only inflammatory arthritis that is curable with appropriate therapy. Lowering urea is the fundamental basis for any gout therapeutic approach. Febuxostat has been widely used in patients with gout who have underlying hyperuricemia since its approval in 2009 by the FDA. The FDA recommends a dose of 40 or 80 mg once daily (FDA.gov). The initial recommended dose was 40 mg/day, but because this dosage did not reduce the sUA by < 6 mg/dL

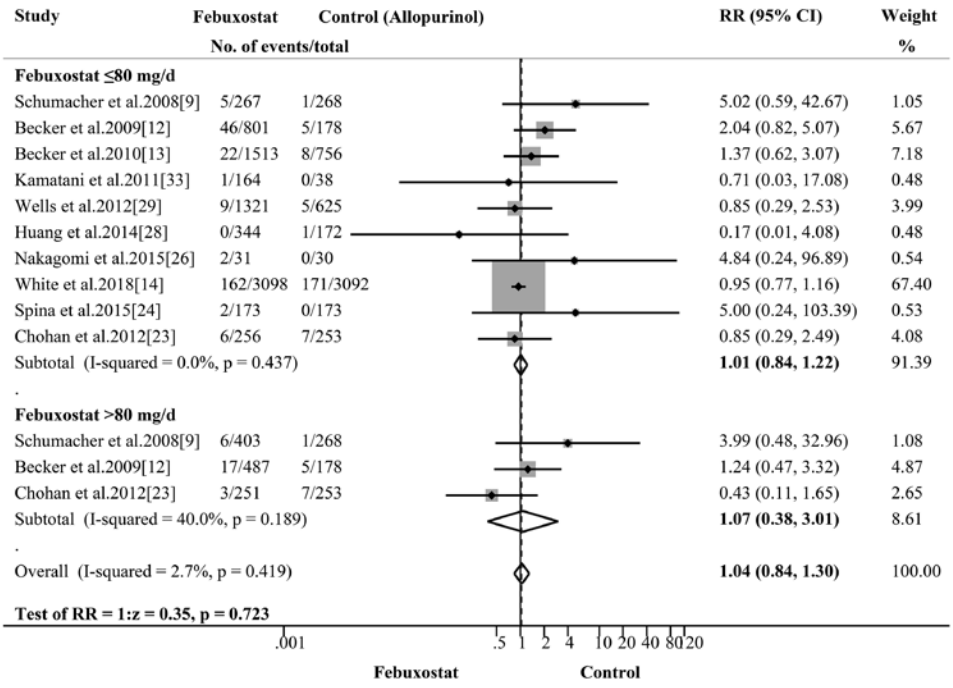

Figure 5. Risk ratios (RR) for CVD events associated with different doses of febuxostat from pooled studies.

within a period of 2 weeks, 80 mg/day of febuxostat was effectively recommended[8]. A separate study found that febuxostat dose of up to 300 mg/day for 7 days did not result in apparent dose-related toxicities in healthy volunteers[8].

Several studies have found that febuxostat is more effective than allopurinol in lowering sUA levels[9,10,11,12,13]. In a CONFIRM trial, the urate-lowering efficacy of 40 mg of febuxostat once daily was equivalent to that of commonly used doses of allopurinol (200/300 mg/d)[13], and the urate-lowering capacity of febuxostat 80 mg once daily was more robust than febuxostat 40 mg/day[13]. In addition, in an allopurinol and placebo-controlled study on the efficacy of febuxostat (APEX trial), febuxostat 80 mg, 120 mg, or 240 mg were all found to be superior to the urate-lowering efficacy of 200/300 mg of allopurinol[9]. In a study comparing febuxostat and allopurinol, the proportion of patients with serum urate levels < 6 mg/dL within 2 weeks after receiving 80 mg or 120 mg of febuxostat was significantly greater than that of patients receiving 300 mg of allopurinol[10].

However, the safety of febuxostat has been of particular concern to researchers, especially regarding the risks of developing CV events and associated deaths linked to the use of the drug. In 2009, the FDA issued warnings and precautions on the use of the drug[8,15,16]. In a CARES trial, however, it was found that there was no difference in the incidence of major heart-related events between individuals put on febuxostat or allopurinol. Nevertheless, compared with allopurinol, 1 study found that febuxostat use is associated with more CV mortality and all-cause death[14]. In other studies, there was no clear evidence on the association between febuxostat and increased risk of CV mortality[9,10,11,12,13,18–33].

In our metaanalysis, subgroup analysis was performed to assess whether increased risk of CVD death was related to the febuxostat dosage. It was found that there was no significance difference between febuxostat > 80 mg/day and ≤ 80mg/day, implying that the risks of heart-related death are not dose-dependent.

In some studies, it was observed that the concentration and activity of circulating xanthine oxidase (the critical source of reactive oxygen species [ROS] during myocardial ischemia–reperfusion injury) can increase dramatically in response to inflammatory stimulus, thus inducing oxidative damage to organs. Because it can bind and act on vascular endothelium of various organs, xanthine oxidase is associated with the development of free radicals and oxidative stress, both of which play a pathogenic role in many cardiovascular diseases[36,37,38].

Both *in vivo* and *in vitro* studies show that febuxostat reverses antioxidant variables[39], and more effectively inhibits endothelium-bound xanthine oxidase. This in turn prevents vascular inflammation[11]. In animal experiments, researchers observed that febuxostat reduces oxidative stress and apoptosis by suppressing the expression of proapoptotic proteins (BAX and caspase-3), reducing TUNEL-positive cells and increasing the level of antiapoptotic proteins (Bcl-2). Additionally, febuxostat could reduce secretion of inflammatory cytokines, such as tumor necrosis factor-α, interleukin 6, and nuclear factor-κB[40]. Febuxostat also protects against ischemia-reperfusion injury by suppressing inflammation and apoptosis mediated by the MAPK/NF-κBp65/TNF-α pathway[40]. Febuxostat protects the mitochondrial function after myocardial ischemia–reperfusion, inhibits hypoxia/reoxygenation–induced ROS generation, stabilizes the mitochondrial transmembrane potential, alleviates

cytosolic translocation of mitochondrial cytochrome c, inhibits activation of caspase-3 and -9, upregulates antiapoptotic proteins, and downregulates several proapoptotic proteins[37]. Further, febuxostat has been found to decrease creatine kinase and lactate dehydrogenase serum levels and to improve cardiac function[37]. Based on animal experiments, febuxostat can prevent the development of cardiac events, owing to its antioxidant, anti-inflammatory, and antiapoptotic properties[37,38,39,40,41].

A previous systematic review and metaanalysis on the association between febuxostat and CVD by Cuenca, *et al* had several limitations[17]. First, it only included 10 published articles and failed to include clinical studies from ClinicalTrials.gov. Second, many newly published studies were not included in their meta-analysis. There was also greater emphasis on CARES trials; thus, their results were subject to variability if any of the incorporated studies were excluded. Interestingly, our metaanalysis arrived at a contradicting conclusion to those reported in CARES trials regarding the association between febuxostat and CV mortality. One likely reason is that in our study, the primary endpoint was the development of a cardiovascular event, while in the CARES trials most patients already had underlying CV diseases. Additionally, longer follow-up times in CARES trials might have increased the probability of CV mortality[14]. However, at least to date, our metaanalysis did not find any association between febuxostat and increased risk of CV death or all-cause mortality.

Our metaanalysis suffered several limitations, particularly involving the limited number of published articles and data on studies in the registry of clinical trials. Second, about half of the published articles and all clinical trials in the registry did not capture data on death from all-cause and CV mortality. Third, several of the studies included in our metaanalyses were short-term or evaluated few participants, and reported on few adverse CV events, death from all causes, and CVD-associated mortality. The CI for the OR for CV events, death from all causes, and CV mortality were also large, casting uncertainty on the findings. Additionally, not all studies refer to the coexisting CV diseases or high heart-related risks (ex., obesity, BMI, etc.). Finally, most of the studies included in our analysis failed to report on other drugs used in combination with the drugs of interest, which could possibly contribute to the occurrence of heart-related events.

Our metaanalysis is consistent with experts' opinions[42], which suggest that patients with gout have an inherently disproportionate risk of developing CVD, and that this risk is not exacerbated by febuxostat use. Febuxostat use was thus concluded to be safe, and is a very effective urate-lowering therapeutic agent. The "black box" warning on the product monograph, together with the caution issued by the FDA, might have perturbed its benefits and appropriate use[16].

Despite these limitations, our review and metaanalysis show that the use of febuxostat is not associated with increased risk of CVD events, heart-related death, and all-cause mortality. In spite of this, patients and doctors should carefully consider the potential CV risks associated with febuxostat use in the treatment of patients with gout and underlying hyperuricemia. In future, more RCT should be performed to validate the findings of our metaanalysis.

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