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Febuxostat use and risks of CVD events, death from cardiac-cause and all-cause mortality: meta-analysis of randomized controlled trials

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Running title: Febuxostat and risk of death

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ABSTRACT

Objective: To assess whether febuxostat use increases the risk of developing cardiovascular events, death from cardiac-cause and all-cause mortalities.

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

Results: In the end, 20 studies that met our inclusion criteria were included in this meta-analysis. 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* =0.507). Also, there was no association between febuxostat use and mortalities arising from cardiovascular diseases (CVD) (RR = 0.84, 95% CI 0.49–1.45, *P*=0.528). The RR also revealed that febuxostat use was not associated with CVD events (RR = 0.98, 95% CI 0.83–1.16, *P* =0.827). Furthermore, 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* =0.723).

Conclusions: 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.

Systematic review registration: PROSPERO CRD42019131872

Keywords

meta−analysis; febuxostat; cardiovascular disease; all-cause mortality

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Introduction

The association between hyperuricemia and cardiovascular disease has been well-established. Urate-lowing therapy has become a major consideration in the treatment of gouts[1-7]. 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 gouts.[8] In effect, the drug has been widely used to reduce the serum urate (sUA) concentration in patients with gouts. Several studies have validated the efficacy of febuxostat in reducing sUA, compared with allopurinol, an old drug designed for the same function[9-13].

In a previous multi-central study at phase 3 clinical trial assessing the Safety of both Febuxostat and Allopurinol in patients with Gout and Cardiovascular Morbidities (CARES) with regard to cardiovascular events showed that cardiovascular death and all-cause death were higher in febuxostat use compared with allopurinol.[14] As a result, on 15th Nov. 2017, the FDA issued a public warning that perhaps febuxostat was associated with an increased risk of heart-related mortalities.[15] Recently on Feb. 21st 2019, the FDA issued another caution that febuxostat use was associated with more cardiovascular deaths compared with allopurinol.[16] One systematic review and meta-analysis[17] encompassing 10 trials however found that febuxostat use was not associated with an increased or reduced risk of cardiovascular disease (CVD), but increases the risk of death from cardiovascular causes, consistent with findings reported in CARES trial.[14]

Considering the controversy surrounding the FDA alert, the meta-analysis of few trials and several findings in published and some unpublished studies at clinical-trials.gov on the association between febuxostat use and both heart-related disorder and cardiovascular mortality,[9,10,12-14,18–33] we conducted this meta-analysis to validate the safety of the drug with regard to the risk of CVD and cardiovascular mortality.

Methods

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

Search strategy and Study selection

The relevant literature was searched in several databases including MEDLINE (PubMed, 1 Jan. 1966–29 Feb. 2020), Web of science, EMBASE (1 Jan. 1966–29 Feb. 2020), ClinicalTrials.gov and 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 this meta-analysis were published in English. The detailed steps in retrieving and analyzing relevant studies are presented in Fig. 1.

Inclusion and exclusion criteria

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

Appendix : The definition of CVD events was based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) Diagnosis Codes. CVD events have been defined as the occurrence of coronary heart disease (including myocardial infarction, angina and other coronary heart disease), heart failure and cerebrovascular disease (including stroke,

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transient cerebral ischemia attack, cerebrovascular accident and other cerebrovascular disease) [34-35].

Data collection

The searches and extraction were performed by two independent reviewers (Zhang BL and Deng H). The key elements captured were the author's surname, 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 two reviewers but in consultation with the other authors (Jin HM, Yang XH and Tong JD).

Assessment of heterogeneity

Heterogeneity was evaluated using the Cochran Q and I^2 statistics. The study was considered to be heterogeneic if the *P* value is < 0.1(Cochran Q). Studies with I^2 value less than 50% were considered to be non-heterogeneic, thus a fixed effects model was used in their analysis, whereas studies with $I^2 > 50\%$ were considered to be heterogeneic, hence they were analyzed using the random effects model.

Quality Assessment

The quality of methodologies employed by individual studies included in this meta-analysis was assessed independently by two researchers (Yang XL and Zhang BL) using the risk of bias tool. Several parameters 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 in to high risk, unclear risk and low risk. A third reviewer (Jin HM) arbitrated any arising disagreement regarding this classification.

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The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system (https://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 (RRs) for the association between febuxostat and all-cause mortality, CVD events or 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 CVD event. In addition, several baseline characteristics of all included studies such as the sample size of study, age, BMI and baseline serum uric acid (SUA) concentration of individuals included in the study, 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 RRs 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, TX, USA). The risks of all-cause mortality, CVD events and CVD death outcomes associated with febuxostat were assessed based on RRs. Subgroup analyses were also performed to evaluate the association of different febuxostat doses with all-cause mortality, CVD events and CVD death. The Egger's and Bgge's 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

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Study flow and study characteristics

The conditions to be satisfied before a study was included in our meta analyses are shown in Fig.1. In general, 20 studies encompassing a combined 19986 participants were assessed. Table 1 shows the characteristics of the 20 studies on febuxostat. Out of these, 18 studies reported on CVD events, 11 were on all-cause mortality whereas 9 reported on CVD death.

Association between febuxostat and all-cause mortality, CVD death and CVD events

All-cause mortalities, CVD death and CVD events reported in individual studies are summarized in Table S1. As shown in Fig.2, the meta-analysis 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* =0.507). Furthermore, 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; RR = 0.79, 95% CI 0.39–1.61; respectively).

Likewise, there was no association between febuxostat use and the incidences of CVD death from pooled results as shown in Fig.3 (RR = 0.84, 95% CI 0.49–1.45, *P*=0.528). Compared with allopurinol or placebo, febuxostat was also not associated with CVD death as shown in Fig.3 (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 of them focused on CVD events in the participants. As shown in Fig. 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* =0.827). Similarly, compared with allopurinol or placebo, febuxostat was also found not to be associated with CVD events. This relationship is shown in Fig.4 (RR = 1.01, 95% CI 0.82–1.23 and RR = 0.89, 95% CI 0.59–1.36; respectively).

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Subgroup analysis on the relative risk of CVD events under different febuxostat doses

As shown in Fig. 5, Pooled results of 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* =0.723).

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's and Begg's tests. Consequently, no publication bias in the pooled studies was found (all-cause death *P*=0.556, CVD death *P*=0.152, CVD events *P*=0.362).

Risk of bias assessment

The risk assessment for any bias is presented in Fig.S1. All studies that employed randomization and random sequence generation (selection bias) were rated as low risk for bias. As to the allocation concealment (selection bias), seven studies [9, 19, 20, 25, 29, 30, 32] were rated as unclear risk of bias for this item with no mention the random method. Most studies employed double-blindness, and were accordingly rated as low risk to bias. In assessing the risk of incomplete outcome data, six studies [14, 20, 21, 28, 29, 32] were rated high risk to bias because numerous data was missing and had lost to follow up more than 10% of their participants. Eight studies[10, 13, 14, 19, 20, 26, 28, 33] had no mention of NCT number and were thus classified under the unclear risk of bias 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 Fig.S2. In summary, the quality of evidence for all cause death and CVD events was rated as high, whereas that for CVD death was rated as moderate.

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Discussion

In this reviews and meta-analysis, it was found that when compared with allopurinol or placebo, febuxostat is not associated with increased risk of developing cardiovascular events when used for controlling hyperuricemia in patients with gouts. Furthermore, compared with allopurinol or placebo, no association was found between the use of febuxostat and increased risk of cardiovascular death and all-cause death.

Gout is not only the most common 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 gout patients with underlying hyperuricemia since its approval in 2009 by the FDA. FDA recommends a dose of 40 or 80 mg once daily (FDA.gov). The initial recommended dose was 40 mg per day, but because this dosage did not reduce the serum uric acid by less than 6 mg per deciliter within a period of 2 weeks, 80 mg per day of febuxostat was effectively recommended.[8] A separate study found that febuxostat dose of up to 300 mg per 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 serum urea levels.[9-13] In one CONFIRM trial, the urate-lowing efficacy of 40mg of febuxostat once daily was equivalent of that of commonly used doses of allopurinol (200/300mg per day)[13], and the urate-lowing capacity of febuxostat 80 mg once daily was more robust than febuxostat 40 mg per day.[13] In addition, in an Allopurinol and Placebo-Controlled study on the efficacy of Febuxostat (APEX), febuxostat 80mg, 120mg or 240 mg were found to be superior to the urate-lowing efficacy of 200/300 mg of allopurinol.[9] In a study comparing Febuxostat and Allopurinol, the proportions of patients with serum urate levels less than 6 mg per deciliter within 2 weeks after receiving 80

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mg or 120mg of febuxostat were significantly greater than those of patients receiving300 mg of allopurinol.[10]

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

In this meta-analysis, subgroup analysis was performed to assess whether increased risk of CVD death was related to the febuxostat dosage. It was found that there was not significance difference between febuxostat >80mg/d and <=80mg/d, implying that the risk of heart-related death are not dose dependent.

In some basic research, 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, which plays a pathogenic role in many cardiovascular diseases.[36-38]

Both in vivo and in vitro studies show that febuxostat reverses antioxidant parameters[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 pro-apoptotic proteins (Bax and caspase-3),

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reducing TUNEL-positive cells and increasing the level of anti-apoptotic proteins (Bcl-2) level. Additionally, febuxostat could reduce secretion of inflammatory cytokines such TNF-α, IL-6 and NF-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 (H/R) -induced ROS generation, stabilizes the mitochondrial trans-membrane potential, alleviates cytosolic translocation of mitochondrial cytochrome C, inhibits activation of caspase -3 and 9, up-regulates anti-apoptotic proteins and down-regulates several pro-apoptotic proteins.[37] Furthermore, febuxost has been found to decrease Creatine Kinase (CK) and lactate dehydrogenase (LDH) serum levels and improves cardiac function.[37] Based on animal experiments, febuxostat can prevent the development of cardiac events owing to its antioxidant, anti-inflammatory and anti-apoptotic properties.[37-41]

A recent systematic review and meta-analysis on the association between febuxostat and CVD by Cuenca et al suffered several limitations [17]. First it only included 10 published articles and failed to include clinical studies at clinical-trails.gov. Second many new published studies were also 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 is excluded. Interestingly, our meta-analysis arrived at contradicting conclusion with those reported in CARES trials regarding the association between febuxostat and cardiovascular mortality. One likely reason is that in this study, the primary endpoint was the development of a cardiovascular event, and in CARES trial, most patients already had underlying cardiovascular diseases. Additionally, longer follow-ups in CARES trials may have increased the probability of cardiovascular mortality.[14] However, at least to date, our meta-analysis did not find any association between febuxostat and increased risk of cardiovascular death and all-cause mortality.

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This meta-analysis suffered several limitations, particularly on the limited number of published articles and data on studies in the registry of clinical-trials. Second, about half of published articles and all clinical-trial in the registry did not capture the data on death from all-cause and cardiovascular mortality. Third, several of the studies included in our meta-analyses were short-term or evaluated few participants, reported on few adverse cardiovascular events and death from all-cause and CVD associated mortality. The confidence intervals (CI) for the odd ratios for cardiovascular event, death from all causes and cardiovascular mortality were also large, casting uncertainty on the findings. Also, not all studies refer the coexisted cardiovascular diseases or heart-related high risks (obesity, body mass index, etc.). Finally, most of the studies included in this analysis failed to report on other drugs used in combination with the drugs of interest, which could possibly contribute to the occurrence heart-related events.

Our meta-analysis is consistent with experts' opinion[42], it is suggested that patients with gout have an inherent 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 caution issued by FDA might have perturbed its beneficial and appropriate use.

Conclusion

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

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Figure legends

Fig. 1. Study selection process.

Fig. 2. Risk ratios (RRs) for all cause deaths events associated with febuxostat from pooled studies.

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

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

Fig. 5. Risk ratios (RRs) for CVD events associated with the dose of febuxostat from pooled studies.

Fig. S1. Risk of bias assessment. (A) Risk of bias summary. (B) Risk of bias graph.

Fig. S2. The Summary of findings (GRADE method).

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

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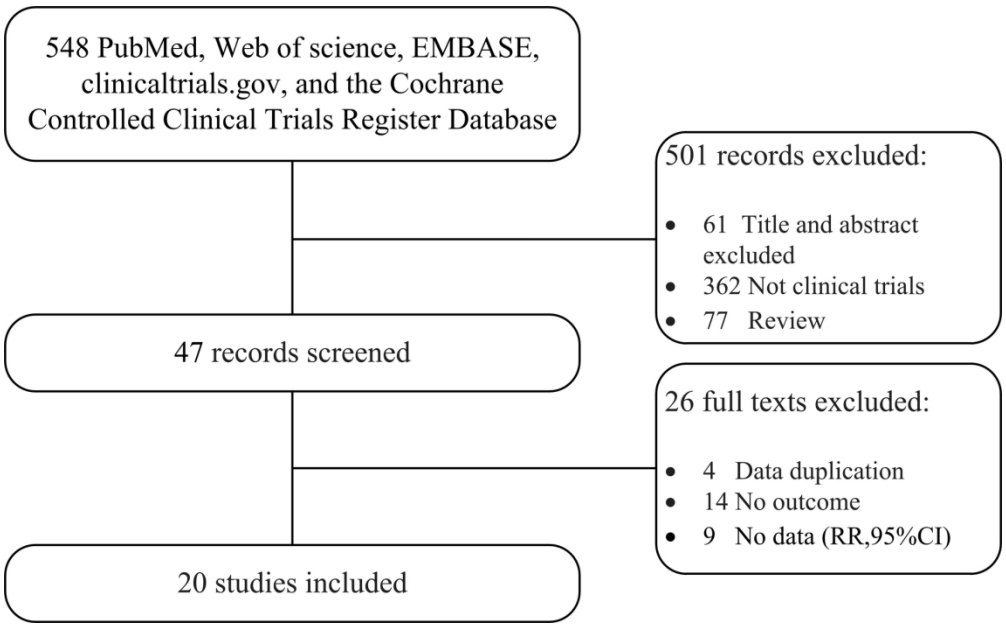

Fig. 1. Study selection process.

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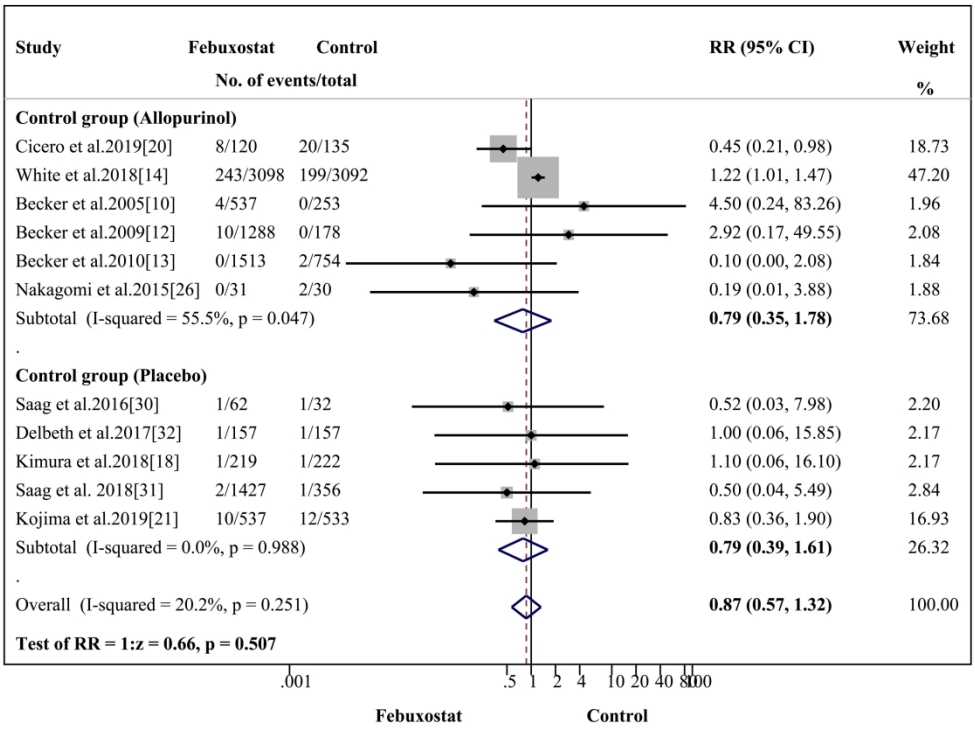

Fig. 2. Risk ratios (RRs) for all cause deaths events associated with febuxostat from pooled studies.

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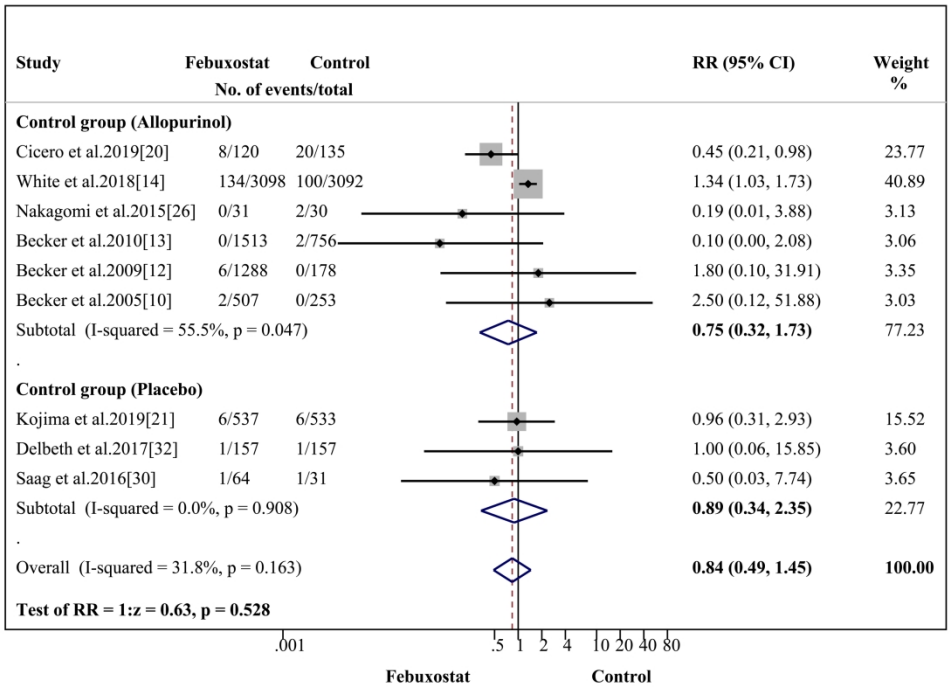

Fig. 3. Risk ratios (RRs) for CVD death associated with febuxostat use from pooled studies.

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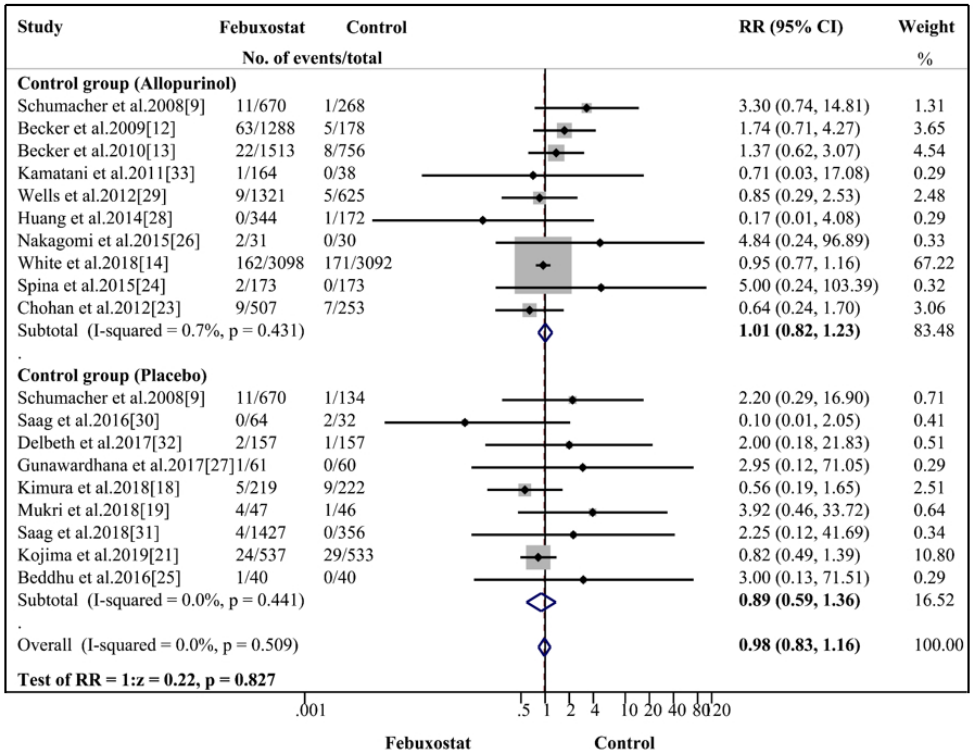

Fig. 4. Risk ratios (RRs) for CVD events associated with febuxostat use from pooled studies.

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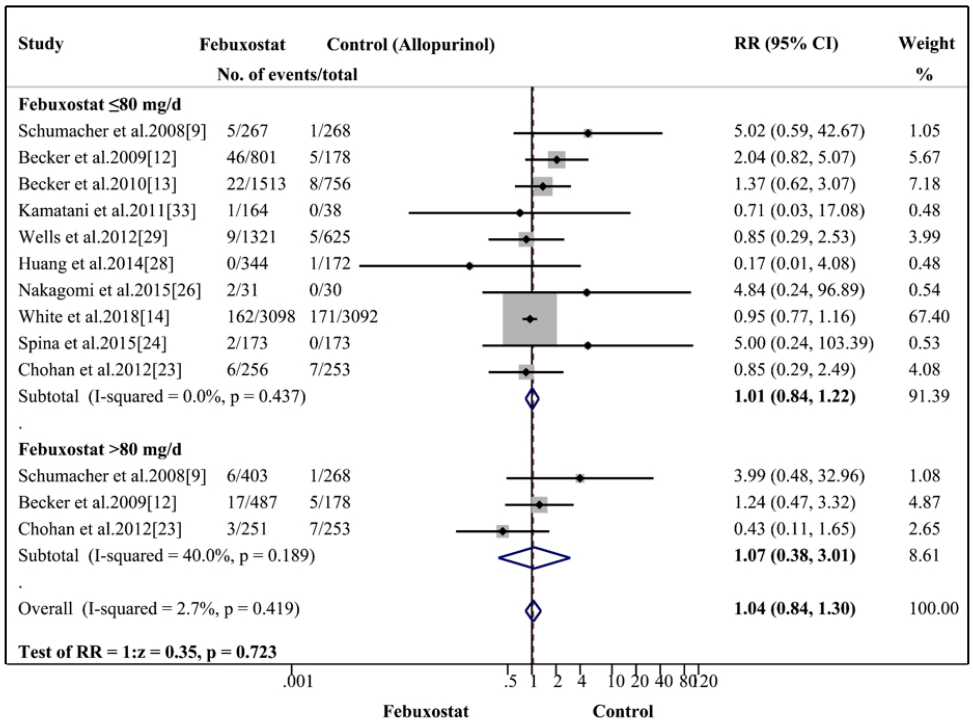

Fig. 5. Risk ratios (RRs) for CVD events associated with the dose of febuxostat from pooled studies.

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Table1. Characteristics of 20 studies associated with all/CVD mortality and CVD events in hyperuricemia population

Study	N	Age (years)	BMI (kg/m^2)	Baseline SUA concentration	Study type	Phase	Intervention group (mg)	Comparison group	Outcome	Follow up (weeks)	Nation	Population
Becker et al. 2005[10]	760	51.8±11.6	N/A	9.84±1.25	RCT	3	FBX80, 120	ALLO	All/CVD death	52	US	Gout
Schumacher et al.2008[9]	1072	52.0±12.0	33.0±6.7	N/A	RCT	3	FBX 80,120,240	ALLO/ Placebo	CVD	28	US	Gout
Becker et al. 2009[12]	1466	51.4±11.9	32.7 (21-65)	9.80±1.25	RCT	3	FBX 80,120	ALLO	CVD，All/CVD death	52	US	Gout
Becker et al. 2010[13]	2269	52.8±11.7	32.8±6.3	9.6±1.17	RCT	N/A	FBX40, 80	ALLO	CVD，All/CVD death	52	US	Gout
Kamatini et al. 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	Goat
Wells et al. 2012[29]	2091	53.0±11.7	32.8±6.1	9.5±1.2	RCT	N/A	FBX40, 80	ALLO	CVD	28	US	Gout
Huang et al. 2014[28]	516	46.6±11.2	25.4±2.6	9.9±1.4	RCT	N/A	FBX40, 80	ALLO	CVD，All death	28	CHN	Gout
Nakagomi et al.2015[26]	61	70.6±9	23.4±2.8	N/A	RCT	N/A	FBX 40	ALLO	CVD death	52	JPN	Chronic HF
Saag et al. 2016[30]	96	65.7±10.6	33.4±6.7	10.5±1.7	RCT	N/A	FBX40, 60,80	Placebo	CVD，All/CVD death	52	US	Gout with CKD
Delbeth et al. 2017[32]	314	50.8±12.1	32.8±6.3	8.8±1.4	RCT	2	FBX40, 80	Placebo	CVD，All/CVD death	104	US	Gout

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Gunawardhana et al. 2017[27]	121	53.6±10.6	32.8±5.6	N/A	RCT	2	FBX 80	Placebo	CVD	6	US	Hyperuricemia
Kimura et al. 2018[18]	441	65.4±12.1	24.8±4.0	7.8±0.9	RCT	N/A	FBX <40	Placebo	CVD，All death	108	JPN	Hyperuricemia with CKD 3
Mukri et al. 2018[19]	93	N/A	N/A	N/A	RCT	N/A	FBX 40	No treatment	CVD	28	MY	Hyperuricemia with DKD
Saag et al. 2018[31]	1783	55.0±11.7	34.3±7.8	N/A	RCT	3	FBX40, 80	Placebo	All death	52	US	Gout
White et al. 2018[14]	6190	64.0±6.5	33.5±7.0	8.7±1.7	RCT	3	FBX 40/80	ALLO	CVD，All/CVD death	138	US	Gout
Cicero et al. 2019[20]	255	77.0±7.6	26.0±2.1	7.7±1.9	RCT	N/A	FBX 80	ALLO	All/CV death	12	ITA	Chronic HF
Kojima et al. 2019[21]	1070	75.7±6.6	24.7±3.9	7.5±1.1	RCT	N/A	FBX 40	Non-FBX	CVD，All/CVD death	154	JPN	Hyperuricemia with aged>65
Beddhu et al. 2016[25]	80	68.0±10.0	N/A	7.2±1.4	RCT	N/A	FBX 80	Placebo	CVD	24	US	Hyperuricemia with T2DM and CKD
Spina et al.2015 [24]	346	58.4±13.8	N/A	N/A	RCT	3	FBX	ALLO	CVD	N/A	US	TLS
Chohan et al.2012 [23]	760	51.2±12.1	N/A	N/A	RCT	3	FBX80, 120	ALLO	CVD	52	US	Gout

N=19986

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N/A:not applicable; FBX:febuxostat; ALLO:Allopurinol; CVD:cardiovascular desease; BMI:body mass index; SUA: serum urate acid; BP:blood pressure; SBP:systolic blood pressure; SCR:serum creatinine; eGFR:estimated glomerular filtration rate; CKD:chronic kidney desease; DKD:diabetic kidney disease; CAD: coronary artery disease; HF:heart failure; T2DM:type 2 diabetes mellitus; US:Unite States; CHN:China; JPN:Japan; ITA:Italia; MY:malaysia; TLS: Tumor Lysis Syndrome

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