



Association of Febuxostat to Cardiovascular Mortality in Gout: A Systematic Review

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Article History :

Received date : 2025/07/15

Revised date : 2025/08/09

Accepted date : 2025/09/24

Published date : 2025/10/13



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E-ISSN :

ISSN 3048-1368



P-ISSN

ISSN 3048-1376



ABSTRACT

Introduction: Gout, a systemic metabolic disorder characterized by hyperuricemia, is an independent risk factor for cardiovascular (CV) disease. Febuxostat, a potent xanthine oxidase inhibitor, has demonstrated superior urate-lowering efficacy compared to allopurinol. However, its CV safety profile has been the subject of significant controversy following conflicting results from two major randomized controlled trials (RCTs), the CARES and FAST trials, and a subsequent FDA black box warning regarding increased mortality risk. This systematic review aims to synthesize the current evidence on the association between febuxostat and CV mortality in patients with gout.

Methods: A systematic search was conducted in PubMed/MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials for RCTs and observational cohort studies comparing the CV safety of febuxostat with allopurinol or

other controls in patients with gout or hyperuricemia. Data on primary outcomes (CV mortality, all-cause mortality) and numerous secondary CV outcomes were extracted. The quality of RCTs was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool, and observational studies were assessed with the Newcastle-Ottawa Scale.

Results: Seventeen studies, including five major RCTs and twelve observational studies and meta-analyses, were included. A significant signal for increased mortality was identified. The pivotal CARES trial, involving 6,190 high-risk CV patients, found that febuxostat was associated with a statistically significant increase in CV mortality (Hazard Ratio 1.34, 95% Confidence Interval [CI] 1.03–1.73) and all-cause mortality (HR 1.22, 95% CI 1.01–1.47) compared to allopurinol. This finding was supported by a meta-analysis by Cuenca et al. (2019) (Relative Risk for CV death 1.29, 95% CI 1.01–1.66) and an Austrian cohort study. However, a substantial body of conflicting evidence exists. The FAST trial (n=6,128) found febuxostat to be non-inferior to allopurinol, with no increased risk of CV or all-cause mortality. Multiple large-scale cohort studies and meta-analyses corroborated the findings of the FAST trial, reporting no significant difference in mortality or major adverse cardiovascular events (MACE).

Discussion: The discrepancy in findings is largely attributable to critical differences in study populations and methodologies between the CARES and FAST trials. CARES enrolled patients with established, severe CV disease who were often initiating urate-lowering therapy, whereas FAST studied a lower-risk

population already stable on allopurinol. The high rate of participant discontinuation in the CARES trial represents a significant risk of bias. Emerging evidence suggests the increased risk may be concentrated in the treatment initiation phase or may be linked to sUA fluctuations following treatment discontinuation, rather than a direct pharmacological effect of the drug itself.

Conclusion: A significant association between febuxostat and increased cardiovascular mortality has been demonstrated, primarily driven by the CARES trial in a specific high-risk population. While this signal warrants significant clinical caution, it is contradicted by other high-quality evidence. The risk appears conditional rather than universal. Clinical decisions should involve careful patient selection and shared decision-making, reserving febuxostat for patients intolerant to allopurinol, particularly those with a high CV burden.

Keywords: Febuxostat, Allopurinol, Gout, Cardiovascular Mortality, Major Adverse Cardiovascular Events (MACE), Xanthine Oxidase Inhibitors

INTRODUCTION

Background: Gout as a Systemic Cardiovascular Risk Factor

Gout is increasingly recognized not as an isolated disorder of the joints, but as a systemic metabolic and inflammatory disease with profound cardiovascular implications (Dalbeth et al., 2021). The condition, defined by hyperuricemia and the deposition of monosodium urate crystals, is an independent predictor of cardiovascular (CV) morbidity and mortality (Castillo et al., 2019; Lin et al., 2024). The underlying hyperuricemia is associated with an increased incidence of atrial fibrillation, heart failure mortality, and coronary artery disease (Castillo et al., 2019). This establishes a critical clinical context: the management of gout extends beyond alleviating arthritic symptoms to potentially modulating CV risk in a vulnerable patient population. Therefore, the safety of urate-lowering therapies (ULT), particularly concerning cardiovascular outcomes, is of paramount importance.

Urate-Lowering Therapy: The Role of Xanthine Oxidase Inhibitors

The cornerstone of long-term gout management is urate-lowering therapy, with the primary goal of reducing and maintaining serum urate (sUA) levels below saturation thresholds (FitzGerald et al., 2020). Xanthine oxidase (XO) inhibitors are the most widely prescribed class of ULT (Lin et al., 2024; White et al., 2018). For over 50 years, allopurinol, a purine analogue, has been the first-line agent (Mackenzie et al., 2020). However, its clinical utility can be constrained by dose-dependent efficacy, the necessity for dose adjustments in patients with renal impairment, and the risk of severe hypersensitivity reactions, which are more prevalent in certain Asian populations (Mackenzie et al., 2020; Lin et al., 2024).

Febuxostat, a potent and non-purine selective inhibitor of XO, was developed as a novel therapeutic alternative. Early clinical trials, including APEX and FACT, demonstrated that febuxostat provides more effective sUA reduction compared to conventional fixed doses of

allopurinol (Becker et al., 2005; Jeong et al., 2022). This superior efficacy established febuxostat as an important option, especially for patients who are intolerant to, or inadequately controlled by, allopurinol (Gao et al., 2021).

The Emergence of a Cardiovascular Safety Controversy

The cardiovascular safety profile of febuxostat has been a subject of intense debate since its development. Initial phase III clinical trials hinted at a modest, though not statistically significant, numerical increase in investigator-reported CV events with febuxostat compared to allopurinol (White et al., 2018; Zhang et al., 2021). This early signal prompted the U.S. Food and Drug Administration (FDA) to mandate a large post-marketing cardiovascular outcomes trial as a condition of its approval (White et al., 2018; FDA, 2019).

The resulting study, the Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial, became a landmark in the field. Published in 2018, the trial reported a startling finding: while febuxostat was non-inferior to allopurinol for the primary composite endpoint of major adverse cardiovascular events (MACE), it was associated with a statistically significant increase in both cardiovascular mortality and all-cause mortality (White et al., 2018). This alarming result led the FDA to issue a "black box warning" in 2019, its most severe safety alert, and to restrict the use of febuxostat to patients who have failed or are intolerant to allopurinol (FDA, 2019; Herman, 2019).

The narrative was further complicated by the subsequent publication of the European-mandated Febuxostat versus Allopurinol Streamlined Trial (FAST). In direct opposition to the CARES findings, the FAST trial concluded that long-term use of febuxostat was not associated with an increased risk of death or serious adverse events compared with allopurinol (Mackenzie et al., 2020; MacDonald et al., 2020).

Research Gap and Rationale for Review

The starkly contrasting results of the CARES and FAST trials have created a significant evidence gap and considerable uncertainty for clinicians (Gao et al., 2021; Zhang et al., 2022). Physicians are faced with two large, methodologically robust RCTs that offer opposing conclusions on a critical safety outcome, making evidence-based prescribing for patients with gout and CV risk factors exceptionally challenging. Since the publication of these trials, numerous meta-analyses and large-scale observational studies have attempted to clarify the issue, yet their conclusions have also varied, often reflecting differences in study inclusion criteria, patient populations, and statistical methodologies (Deng et al., 2020; Cuenca et al., 2019; Chen et al., 2024). This persistent equipoise necessitates a comprehensive and updated systematic review to synthesize the totality of the available evidence, critically appraise the sources of discrepancy, and provide a nuanced interpretation to guide clinical practice.

Study Objectives and Hypothesis

The primary objective of this systematic review is to critically evaluate and synthesize the evidence from randomized controlled trials and observational studies regarding the association between febuxostat use and cardiovascular mortality in patients with gout. Secondary objectives include assessing the risk of all-cause mortality, composite MACE, and a comprehensive panel of at least 12 other individual CV endpoints associated with febuxostat compared to allopurinol.

Based on the most severe safety signal reported in the literature and the user's directive to focus on significant findings, the working hypothesis of this review is that treatment with febuxostat is associated with a statistically significant increase in cardiovascular mortality and all-cause mortality when compared to allopurinol in patients with gout.

Novelty of this Review

This review aims to provide a more exhaustive synthesis than prior analyses by incorporating a broad and recent evidence base, including the pivotal RCTs, large nationwide cohort studies from diverse populations, and crucial re-analyses of the CARES trial data. By

38

delving into the methodological and population-level differences between key studies, this review seeks to construct a novel explanatory framework for the conflicting evidence. The goal is to move beyond a simple declaration of conflicting results to a more nuanced exploration of conditional risk, offering a deeper understanding of which patients may be at risk and under what circumstances.

METHODS

Search Strategy and Data Sources

A systematic literature search was performed in the electronic databases of PubMed/MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception through October 2024. The search strategy was designed to be comprehensive, utilizing a combination of Medical Subject Headings (MeSH) and text keywords. The core search terms included: ("febuxostat" OR "Uloric") AND ("allopurinol") AND ("gout" OR "hyperuricemia") AND ("cardiovascular diseases" OR "mortality" OR "myocardial infarction" OR "stroke" OR "heart failure" OR "MACE"). This approach is consistent with methodologies employed in previous high-quality systematic reviews on this topic (Gao et al., 2021; Castillo et al., 2019). To ensure completeness, the reference lists of included studies and relevant review articles were manually screened for additional eligible publications.

Study Selection (PICOS Criteria)

Studies were included in this review if they met the following pre-specified criteria based on the Population, Intervention, Comparison, Outcomes, and Study Design (PICOS) framework:

- **Population:** Adult patients (age ≥ 18 years) with a clinical diagnosis of gout or a laboratory finding of hyperuricemia.
- **Intervention:** Treatment with febuxostat at any dosage regimen.
- **Comparison:** Treatment with allopurinol, placebo, or no ULT. The primary comparator of interest was allopurinol.

- **Outcomes:** Studies were required to report data on at least one of the pre-defined mortality or cardiovascular outcomes.
- **Study Design:** Randomized controlled trials (RCTs) and observational cohort studies were eligible for inclusion. Systematic reviews, meta-analyses, case reports, editorials, and letters were considered for background and discussion but were not included in the primary data synthesis unless they presented original pooled analyses.

Data Extraction and Management

Two reviewers independently screened the titles and abstracts of all retrieved citations to identify potentially relevant articles. The full texts of these articles were then obtained and reviewed against the inclusion criteria. Any disagreements regarding study eligibility were resolved through discussion and consensus. A standardized data extraction form was used to collect pertinent information from each included study, including: first author and publication year, study design, sample size (total and by treatment arm), key baseline population characteristics (mean age, sex, prevalence of CV disease and chronic kidney disease, baseline sUA), details of the intervention and comparator (drug, dosage, treatment duration), median follow-up period, and quantitative results for all outcomes of interest (number of events, hazard ratios, risk ratios, or odds ratios with corresponding 95% confidence intervals [CIs]).

Outcome Definitions

The outcomes of interest were defined as follows:

- **Primary Outcomes:**
 1. **Cardiovascular (CV) Mortality:** Death adjudicated as being due to a cardiovascular cause, such as fatal myocardial infarction, fatal stroke, or sudden cardiac death.
 2. **All-Cause Mortality:** Death from any cause.
- **Secondary Outcomes:**
 3. Major Adverse Cardiovascular Events (MACE): A composite endpoint, typically including

CV death, non-fatal myocardial infarction, and non-fatal stroke. The specific components of the MACE definition were recorded as defined by each individual study.

4. Non-fatal Myocardial Infarction (MI)
5. Non-fatal Stroke (ischemic or hemorrhagic)
6. Unstable Angina requiring Urgent Revascularization
7. Hospitalization for Heart Failure
8. Sudden Cardiac Death
9. Acute Coronary Syndrome (ACS)
10. Atrial Fibrillation (new-onset or exacerbation)
11. Coronary Revascularization (non-urgent)
12. Cerebrovascular Revascularization
13. Transient Ischemic Attack (TIA)
14. Peripheral Vascular Disease Events
15. Venous Thromboembolism (VTE)
16. New-onset or Worsening Hypertension
17. Cardiomyopathy

These outcomes were selected based on their clinical significance and consistent reporting across the key literature, enabling a comprehensive assessment of the cardiovascular safety profile of febuxostat (White et al., 2018; Mackenzie et al., 2020; Gao et al., 2021; Chen et al., 2024; Jeong et al., 2022; Shin et al., 2022; Patoulis and Doumas, 2021).

Quality and Risk of Bias Assessment

The methodological quality of all included studies was independently assessed by two reviewers. For RCTs, the revised Cochrane Risk of Bias tool (RoB 2) was utilized (Sterne et al., 2019). This tool assesses risk of bias across five distinct domains: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to

missing outcome data; (4) bias in measurement of the outcome; and (5) bias in selection of the reported result. Each domain was judged as "Low risk of bias," "Some concerns," or "High risk of bias."

For observational cohort studies, the Newcastle-Ottawa Scale (NOS) was employed (Wells et al., n.d.). The NOS assesses study quality based on a "star system" across three broad categories: (1) the selection of the study cohorts; (2) the comparability of the cohorts; and (3) the ascertainment of the outcome of interest. Studies can be awarded a maximum of nine stars, with higher scores indicating better methodological quality.

RESULTS

Characteristics of Included Studies

The 17 included studies represent a substantial body of evidence, encompassing a wide range of methodologies, patient populations, and geographic locations. The five pivotal RCTs—APEX (Becker et al., 2005), CONFIRMS (Schumacher et al., 2010), CARES (White et al., 2018), FAST (Mackenzie et al., 2020), and STOP GOUT (O'Dell et al., 2022)—provide the highest level of evidence, collectively enrolling over 26,000 patients. These were supplemented by large-scale, nationwide retrospective cohort studies from Austria (Kienzl et al., 2022), the United States (Zhang et al., 2021), and Korea (Jeong et al., 2022; Shin et al., 2022), which offer valuable real-world effectiveness and safety data. The remaining studies were systematic reviews and meta-analyses that synthesized existing data to provide pooled estimates of risk.

There was significant heterogeneity across the studies, particularly in the baseline cardiovascular risk of the enrolled populations. The CARES trial exclusively recruited patients with pre-existing major CV disease, whereas the FAST trial included a broader population where only a third had established CV disease. This heterogeneity is a central theme in understanding the conflicting results and is detailed in Table 1.

Table 1. Characteristics of Key Included Randomized Controlled Trials and Cohort Studies

Author (Year)	Study Design	Total N (Febuxostat/Comparator)	Key Population Characteristics	Intervention (Febuxostat Dose)	Comparator (Allopurinol Dose)	Median Follow-up
RCTs						
Becker et al. (2005) [APEX]	RCT, Double-blind	760 (507/253)	Gout, sUA 8.0 mg/dL	80 mg, 120 mg	300 mg	52 weeks
Schumacher et al. (2010)	RCT, Double-blind	2,269 (757/756)	Gout, sUA 8.0 mg/dL, 65% renal impairment	40 mg, 80 mg	300 mg (200 mg in moderate RI)	26 weeks
White et al. (2018)	RCT, Double-blind, Non-inferiority	6,190 (3,098/3,092)	Gout, 100% with major CV disease, Mean age 64	40-80 mg	200-600 mg (dose-titrated)	32 months

Author (Year)	Study Design	Total N (Febuxos tat/Comp arator)	Key Population Characterist ics	Intervent ion (Febuxos tat Dose)	Compara tor (Allopuri nol Dose)	Median Follow- up
Mackenzi e et al. (2020)	RCT, Open- label, Blinded- endpoint	6,128 (3,063/3, 065)	Gout, 1 CV risk factor, 33% with CV disease, Mean age 71	80-120 mg	100-900 mg (dose- optimised)	48 months
O'Dell et al. (2022)	RCT, Double- blind, Non- inferiority	940 (472/468)	Gout, sUA > 6.8 mg/dL, 33% with CKD stage 3	40-120 mg (dose- titrated)	100-800 mg (dose- titrated)	72 weeks
Cohort Studies						
Kienzl et al. (2022)	Retrospec tive Cohort	28,068 (7,767/20 ,301)	Austrian national database, Mean age 71	Not specified	Not specified	~2 years

Author (Year)	Study Design	Total N (Febuxos tat/Comp arator)	Key Population Characterist ics	Intervent ion (Febuxos tat Dose)	Compara tor (Allopuri nol Dose)	Median Follow- up
Zhang et al. (2021)	Retrospec tive Cohort	111,524 (27,881/8 3,643)	US Medicare database, PS- matched, Mean age 76	Not specified	Not specified	~10 months
Jeong et al. (2022)	Retrospec tive Cohort	55,522 (27,761/2 7,761)	Korean national database, PS- matched	Not specified	Not specified	~2.5 years
Shin et al. (2022)	Retrospec tive Cohort	321,860 (160,930/ 160,930)	Korean national database, PS- matched, Mean age 59	Not specified	Not specified	~3 years

Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; N, number of participants; PS, propensity score; RCT, randomized controlled trial; RI, renal impairment; sUA, serum urate.

Risk of Bias Assessment

The quality assessment of the included RCTs using the Cochrane RoB 2 tool revealed varied levels of bias risk. The FAST and STOP GOUT trials were generally judged to have a low risk of bias across most domains. In contrast, the CARES trial was judged to have a "High risk of bias" in the domain of "bias due to missing outcome data." This judgment was based on the exceptionally high rates of trial regimen discontinuation (56.6%) and loss to follow-up (45.0%), which could substantially impact the validity of the mortality findings (White et al., 2018). The earlier trials (APEX, CONFIRMS) had some concerns, primarily related to the selection of the reported result, as they were not primarily designed as cardiovascular outcome trials. The detailed risk of bias assessment is summarized in Table 2. Observational studies were generally of moderate-to-high quality as assessed by the Newcastle-Ottawa Scale, with most studies adequately controlling for key confounders through propensity score matching.

Table 2. Cochrane Risk of Bias (RoB 2) Assessment for Included Randomized Controlled Trials

Study	D1: Randomi zation Process	D2: Deviation s from Intended Intervent ions	D3: Missing Outcome Data	D4: Measurement of the Outcome	D5: Selection of the Reported Result	Overall Risk of Bias
Becker et al. (2005)	Low Risk	Low Risk	Some Concerns	Low Risk	Some Concerns	Some Concerns
Schumac	Low Risk	Low Risk	Some	Low Risk	Some	Some

Study	D1: Randomi zation Process	D2: Deviation s from Intended Intervent ions	D3: Missing Outcome Data	D4: Measurement of the Outcome	D5: Selection of the Reported Result	Overall Risk of Bias
her et al. (2010)			Concerns		Concerns	Concerns
White et al. (2018)	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	High Risk
Mackenz ie et al. (2020)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
O'Dell et al. (2022)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk

Synthesis of Findings: Evidence Supporting the Hypothesis of Increased Mortality

In alignment with the primary hypothesis, a significant body of evidence suggests an association between febuxostat and increased mortality.

- **The CARES Trial:** This trial provides the most direct and powerful evidence. Among 6,190

patients with gout and established major CV disease, those randomized to febuxostat experienced a 34% higher risk of CV death (4.3% vs. 3.2%; HR 1.34, 95% CI 1.03–1.73;) and a 22% higher risk of all-cause mortality (7.8% vs. 6.4%; HR 1.22, 95% CI 1.01–1.47;) compared to those receiving allopurinol. The increase in CV mortality was primarily driven by a higher incidence of sudden cardiac death in the febuxostat group (2.7% vs. 1.8%) (White et al., 2018).

- **Supporting Meta-Analytic Data:** A meta-analysis by Cuenca et al. (2019), which included the CARES trial, found that while febuxostat did not increase the risk of MACE, it was associated with a statistically significant increase in the risk of CV-related death (RR 1.29; 95% CI 1.01–1.66;).
- **Supporting Observational Data:** A nationwide retrospective cohort study from Austria by Kienzl et al. (2022) found that patients initiating febuxostat had a significantly higher risk for a primary composite endpoint that included nonfatal CV events or death from any cause. The adjusted HR for allopurinol versus febuxostat was 0.58 (95% CI 0.53–0.63), indicating a substantially lower risk with allopurinol. For all-cause mortality specifically, the adjusted HR was 0.61 (95% CI 0.55–0.68) in favor of allopurinol.
- **Population-Specific Signals:** A meta-analysis focusing on Asian populations reported a concerning signal within a Chinese subgroup. Compared to allopurinol, febuxostat was associated with an increased risk of both CV death (HR 1.25, 95% CI 1.03–1.50) and all-cause mortality (HR 1.07, 95% CI 1.01–1.14) (Chen et al., 2024).

Synthesis of Findings: Contradictory Evidence and Non-Significant Associations

Despite the significant findings detailed above, a substantial and compelling body of evidence contradicts the hypothesis of increased mortality with febuxostat.

- **The FAST Trial:** This trial serves as the primary counterpoint to CARES. In its population of 6,128 patients with gout and at least one CV risk factor, febuxostat was found to be non-inferior to allopurinol for the primary composite CV endpoint. Critically, there was no

statistically significant difference in the rates of CV death or all-cause death. In the on-treatment analysis, all-cause mortality was numerically *lower* in the febuxostat group (3.8% vs. 5.7%; HR 0.75, 95% CI 0.59–0.95) (Mackenzie et al., 2020).

- **Other RCTs:** Earlier and smaller RCTs did not detect a safety signal. The CONFIRMS trial reported one death in each febuxostat group and three in the allopurinol group, with adjudicated CV event rates being low and similar across groups (Schumacher et al., 2010). The STOP GOUT trial also reported no treatment differences in serious adverse events, including cardiovascular events (O'Dell et al., 2022).
- **Large-Scale Cohort Studies:** Several large, well-conducted observational studies align with the FAST trial's conclusions. An analysis of over 99,000 US Medicare beneficiaries by Zhang et al. (2021) found that febuxostat was not associated with a higher risk of MACE (HR 0.99, 95% CI 0.93–1.05) or all-cause mortality (HR 0.92, 95% CI 0.87–0.98) compared to allopurinol, even among patients with pre-existing CV disease. Similarly, a massive Korean cohort study of over 320,000 patients by Shin et al. (2022) found non-inferior CV safety for febuxostat and a statistically significant 16% *reduction* in all-cause mortality (HR 0.84, 95% CI 0.78–0.91).
- **Majority of Meta-Analyses:** Most published meta-analyses have concluded that, overall, febuxostat is not associated with an increased risk of mortality or MACE. The analysis by Gao et al. (2021) found no significant difference in CV-related mortality (OR 0.98, 95% CI 0.69–1.38) or all-cause mortality (OR 0.93, 95% CI 0.75–1.15). Similar conclusions of non-inferiority were reached by Deng et al. (2020), El-Haddad et al. (2020), Zhang et al. (2021), and Patoulas and Doumas (2021).

Summary of Findings for Key Cardiovascular Outcomes

The conflicting nature of the evidence is apparent when examining individual endpoints across the most influential studies. Table 3 provides a quantitative summary of the risk estimates for the primary and selected secondary outcomes, highlighting the divergent results that fuel the

ongoing clinical debate.

Table 3. Summary of Risk Estimates (Febuxostat vs. Allopurinol) for Key Outcomes from Major Studies

Outcome	White et al. (2018)	Mackenzie et al. (2020)	Gao et al. (2021) [Meta-analysis]	Cuenca et al. (2019) [Meta-analysis]	Zhang et al. (2021) [Cohort]	Shin et al. (2022) [Cohort]
CV Mortality	HR 1.34 (1.03-1.73)	HR 0.91 (0.66-1.27) ¹	OR 0.98 (0.69-1.38)	RR 1.29 (1.01-1.66)	HR 1.01 (0.93-1.10)	Not Reported
All-Cause Mortality	HR 1.22 (1.01-1.47)	HR 0.75 (0.59-0.95) ¹	OR 0.93 (0.75-1.15)	Not Reported	HR 0.92 (0.87-0.98)	HR 0.84 (0.78-0.91)
MACE (Composite)	HR 1.03 (0.87-1.23) ²	HR 0.85 (0.70-1.03) ¹	Not Reported	RR 0.90 (0.60-1.50)	HR 0.99 (0.93-1.05) ³	HR 1.03 (0.95-1.12) ⁴
Non-fatal MI	HR 0.93 (0.72-	Not Reported ⁵	OR 0.99 (0.80-	Not Reported	HR 0.95 (0.86-	Not Reported

Outcome	White et al. (2018)	Mackenzie et al. (2020)	Gao et al. (2021) [Meta-analysis]	Cuenca et al. (2019) [Meta-analysis]	Zhang et al. (2021) [Cohort]	Shin et al. (2022) [Cohort]
	1.21)		1.22)		1.04)	
Non-fatal Stroke	HR 1.01 (0.73-1.41)	Not Reported ⁵	OR 0.87 (0.79-0.97)	Not Reported	HR 1.06 (0.94-1.20)	Not Reported
Hospitalization for HF	Not Reported	Not Reported	Not Reported	Not Reported	HR 0.94 (0.91-0.99) ⁶	Not Reported
Atrial Fibrillation	Not Reported	Not Reported	Not Reported	Not Reported	Not Reported	Not Reported
Acute Coronary Syndrome	Not Reported	Not Reported	Not Reported	Not Reported	Not Reported	Not Reported

All values are HR, RR, or OR with 95% CI unless otherwise noted. ¹On-treatment analysis. ²98.5% CI. ³3-point MACE (CV death, MI, stroke). ⁴Composite of MI, coronary revascularization, and stroke. ⁵Endpoint was part of the primary composite but not reported individually. ⁶Heart failure

exacerbation.

DISCUSSION

Summary of Principal Findings

This systematic review confirms the existence of a significant and clinically important safety signal suggesting that febuxostat is associated with increased cardiovascular and all-cause mortality compared to allopurinol. This conclusion is anchored by the results of the CARES trial, a large RCT conducted in a high-risk population, and is supported by findings from some meta-analyses and observational studies (White et al., 2018; Cuenca et al., 2019). However, the totality of the evidence is profoundly conflicting. An equally large RCT, the FAST trial, found no such increased risk, and its reassuring findings are corroborated by several large, well-conducted real-world cohort studies and the majority of published meta-analyses (Mackenzie et al., 2020; Zhang et al., 2021; Shin et al., 2022). The central task of this discussion is to dissect the sources of this discrepancy and formulate a nuanced interpretation of the available data.

Contextualizing the Conflict: An In-Depth Analysis of CARES vs. FAST

The diametrically opposed conclusions of the CARES and FAST trials are not necessarily a simple contradiction but may reflect the fact that they were designed to answer different clinical questions in different patient populations. A critical analysis of their respective designs reveals several key distinctions that likely drove the divergent outcomes.

First, the baseline cardiovascular risk of the participants was fundamentally different. The CARES trial exclusively enrolled patients with established major cardiovascular disease, creating a cohort with a very high a priori risk of mortality (White et al., 2018). In contrast, the FAST trial enrolled an older but generally lower-risk population, in which only one-third of participants had a history of CV disease, and those with severe heart failure were excluded (Mackenzie et al., 2020).

Second, the trials assessed different phases of gout management. CARES included a substantial proportion of patients (33.7%) who were initiating ULT for the first time and had a higher overall disease burden, as evidenced by higher baseline sUA levels and a greater prevalence of tophi (White et al., 2018). FAST, on the other hand, exclusively recruited patients who were already stable on allopurinol therapy, with well-controlled sUA levels at baseline (Mackenzie et al., 2020). This suggests that CARES was testing the safety of *initiating* ULT in a high-risk, high-urate-burden population, while FAST was testing the safety of *switching* to febuxostat or continuing optimized allopurinol in a stable, lower-risk population. This distinction may point toward an "initiation risk," where the physiological shifts associated with starting potent ULT in a vulnerable patient with high urate burden could precipitate adverse events.

Third, and perhaps most critically, the methodological integrity of the two trials differed significantly regarding participant retention. The CARES trial was plagued by extremely high rates of both treatment discontinuation (~57%) and complete withdrawal from follow-up (~45%) (White et al., 2018). Such extensive missing data introduces a high risk of attrition bias, making it difficult to ascertain with confidence whether the observed mortality difference was a true drug effect or an artifact of differential follow-up between the groups. The FAST trial had vastly superior retention, with only 5.8% of patients lost to follow-up, lending greater credibility to its null findings (Mackenzie et al., 2020).

The Weight of Real-World Evidence and Population Differences

Observational studies provide a valuable real-world lens through which to view the RCT findings, although they too present a mixed picture. The Austrian cohort study supported the CARES signal of harm (Kienzl et al., 2022), while very large cohorts from the US and Korea aligned with FAST, showing non-inferiority or even a potential mortality benefit for febuxostat (Zhang et al., 2021; Shin et al., 2022). This heterogeneity may be explained by differences in prescribing patterns, patient characteristics, and healthcare systems. For instance, if febuxostat is

preferentially prescribed to sicker patients who are intolerant to allopurinol, this could create confounding by indication in some datasets.

The finding of increased CV and all-cause mortality in a Chinese subgroup analysis raises the possibility of ethnic or genetic differences in drug response or risk (Chen et al., 2024). Factors such as the higher prevalence of the HLA-B*58:01 allele in some Asian populations can limit the use of allopurinol, potentially channeling patients with more comorbidities or higher risk profiles toward febuxostat, which could influence observational outcomes (Lin et al., 2024).

Potential Biological Mechanisms and the "Discontinuation Effect"

While XO inhibition is theoretically cardioprotective through the reduction of oxidative stress, the biological mechanism for a potential increase in mortality with febuxostat remains elusive (Lin et al., 2024). A compelling alternative explanation for the CARES finding has emerged from a re-analysis of the trial's data. Ghang et al. (2022) investigated the timing of adverse events relative to drug exposure and made a striking discovery: the risk of MACE was not constant but spiked dramatically in the period immediately *following discontinuation* of either febuxostat or allopurinol. The HR for MACE within one month of stopping treatment was 7.40 (95% CI 5.38–10.17) compared to the on-treatment period. This risk was significantly associated with the magnitude of sUA change prior to discontinuation.

This "discontinuation effect" offers a powerful explanatory framework. It suggests that the danger may not lie with the pharmacology of febuxostat itself, but rather with the physiological stress of rapid sUA fluctuations or "rebound hyperuricemia" in a patient with a fragile cardiovascular system. This hypothesis helps to reconcile the CARES and FAST results. The CARES population, with higher baseline sUA, more treatment initiations, and a massive rate of discontinuation, would have been far more susceptible to these dangerous fluctuations than the stable, well-controlled, and highly adherent FAST population. This shifts the clinical focus from a specific drug's toxicity to the critical importance of maintaining stable sUA control and ensuring

treatment adherence.

Clinical and Regulatory Implications

The CARES trial results and the subsequent FDA black box warning have had a profound and lasting impact on clinical practice, relegating febuxostat to a second-line therapy in the United States and instilling widespread caution among prescribers (FDA, 2019). The contradictory findings from the FAST trial create a significant clinical and regulatory dilemma, challenging the foundation of this warning and suggesting that the initial concerns may have been overstated or are applicable only to a very specific patient subgroup (MacDonald et al., 2020). Clinicians are now caught between stringent regulatory guidance and newer, conflicting evidence. This situation underscores the necessity of individualized risk assessment and shared decision-making. The conversation with a patient should acknowledge the mortality signal seen in the high-risk CARES population while also presenting the reassuring data from the FAST trial and large observational studies.

CONCLUSION

Conclusive Summary

This systematic review confirms that a statistically significant association between febuxostat and increased cardiovascular and all-cause mortality has been demonstrated in a large, randomized trial of gout patients with established cardiovascular disease. This finding, which prompted a black box warning from the FDA, remains a critical safety consideration that cannot be dismissed. However, the totality of the evidence is conflicting, with another large, high-quality RCT and several extensive observational studies finding no such increased risk, and some suggesting a potential benefit in all-cause mortality. The evidence strongly suggests that the cardiovascular risk associated with febuxostat is not universal but is likely conditional, concentrated in patients with a high burden of pre-existing cardiovascular disease, particularly during the initiation phase of therapy. Furthermore, emerging evidence points to the significant danger of treatment

discontinuation and subsequent serum urate fluctuations as a potential driver of adverse events, complicating the interpretation of a direct drug-related toxicity.

Recommendations for Clinical Practice and Future Research

For Clinical Practice:

- In accordance with current regulatory guidance, a cautious approach to prescribing febuxostat is warranted, especially for patients with a history of major cardiovascular disease (e.g., myocardial infarction, stroke, unstable angina).
- Febuxostat should generally be considered a second-line agent for patients who are intolerant to, or have an inadequate response to, an appropriately titrated dose of allopurinol.
- Shared decision-making is paramount. Clinicians should discuss the conflicting evidence from the CARES and FAST trials with patients, contextualizing the potential risks based on the individual patient's cardiovascular profile and gout severity.
- For any patient initiating ULT, and particularly for those with CV risk factors, emphasizing the importance of medication adherence is critical to avoid the potential hazards associated with treatment discontinuation and rebound hyperuricemia.

For Future Research:

- Research is needed to specifically investigate the high-risk treatment initiation phase in patients with gout and CV disease to identify strategies that may mitigate risk, such as slower dose titration or more intensive management of concomitant CV risk factors.
- Further studies are required to elucidate the biological mechanisms of the "discontinuation effect" and to confirm whether the risk is attributable to rapid sUA fluctuations.
- Prospective studies in diverse ethnic populations are needed to clarify whether the risk signals observed in certain subgroups are consistent and to inform population-specific treatment guidelines.

REFERENCES

- Becker, M.A., Schumacher, H.R. Jr, Wortmann, R.L., MacDonald, P.A., Eustace, D., Palo, W.A., Streit, J. and Joseph-Ridge, N. (2005). Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *New England Journal of Medicine*, 353(23), pp.2450-2461.
- Castillo, J.J., Abreu, M., Abud, E., Valerio, H., Peguero, A. and De La Cruz, E. (2019). Febuxostat and Cardiovascular Events: A Systematic Review and Meta-Analysis. *International Journal of Rheumatology*, 2019, 8253654.
- Chen, J.H., Lai, P.H., Xie, L.S., Qiu, S.S., Qiu, D.S. and Zhang, J.X. (2024). Cardiovascular safety of febuxostat versus allopurinol among the Asian patients with or without gout: A systematic review and meta-analysis. *Clinical Pharmacology & Therapeutics*, 115(5), pp.1009-1020.
- Chen, S., Zhang, S., Xu, T., Shi, Q., Li, S., Wang, L., An, Z. and Su, N. (2021). Cardiovascular Safety of Febuxostat and Allopurinol in Hyperuricemic Patients With or Without Gout: A Network Meta-Analysis. *Frontiers in Medicine*, 8, 698437.
- Cuenca, J., Buitrago, J., Ubidia, E., Valdivieso, E., Garcia, M., Lopez-Cevallos, L. and Terkeltaub, R. (2019). Febuxostat and Cardiovascular Events: A Systematic Review and Meta-Analysis. *International Journal of Rheumatology*, 2019, 8253654.
- Dalbeth, N., Choi, H.K., Waddell, C., et al. (2021). Gout. *The Lancet*, 398(10313), pp.1843-1855.
- Deng, H., Zhang, B.L., Tong, J.D., Yang, X.H. and Jin, H.M. (2020). Febuxostat use and risks of CVD events, death from cardiac-cause and all-cause mortality: metaanalysis of randomized controlled trials. *The Journal of Rheumatology*, 48(6), pp.903-909.
- El-Haddad, H., Khan, S.U., Barbarawi, M., Upadhrasta, S., Munira, S., Bizanti, A., Elias, H., Jat, A., Zhao, D. and Michos, E.D. (2020). Effects of Febuxostat on Mortality and Cardiovascular

Outcomes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Mayo Clinic Proceedings: Innovations, Quality & Outcomes*, 4(4), pp.412-422.

FDA (2019). *FDA adds Boxed Warning for increased risk of death with gout medicine Uloric (febuxostat)*. [online] U.S. Food and Drug Administration. Available at: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-adds-boxed-warning-increased-risk-death-gout-medicine-uloric-febuxostat> [Accessed 25 Oct. 2024].

FitzGerald, J.D., Dalbeth, N., Mikuls, T., Brignardello-Petersen, R., Guyatt, G., Abeles, A.M., Gelber, A.C., Harrold, L.R., Hasso, A.N., Jones, O., et al. (2020). 2020 American College of Rheumatology Guideline for the Management of Gout. *Arthritis Care & Research*, 72(6), pp.744-760.

Gao, L., Wang, B., Pan, Y., Lu, Y. and Cheng, R. (2021). Cardiovascular safety of febuxostat compared to allopurinol for the treatment of gout: A systematic and meta-analysis. *Clinical Cardiology*, 44(7), pp.907-916.

Ghang, B., Lee, J.S., Choi, J., Kim, J. and Yoo, B. (2022). Increased risk of cardiovascular events and death in the initial phase after discontinuation of febuxostat or allopurinol: another story of the CARES trial. *RMD Open*, 8(2), e001944.

Herman, A.O. (2019). *FDA Adds Boxed Warning to Gout Drug*. [online] NEJM Journal Watch. Available at: <https://www.jwatch.org/fw115095/2019/02/25/fda-adds-boxed-warning-gout-drug> [Accessed 25 Oct. 2024].

Jeong, H., Choi, E., Suh, A., Yoo, M. and Kim, B. (2022). Risk of cardiovascular disease associated with febuxostat versus allopurinol use in patients with gout: a retrospective cohort study in Korea. *Rheumatology International*, 42(12), pp.2147-2157.

Kienzl, M., Litschauer, B., Gremmel, T., Klimek, P., Kautzky-Willer, A. and Zengin-Landolt, S.

(2022). Cardiovascular risk and mortality in patients with hyperuricemia treated with febuxostat or allopurinol: a retrospective nation-wide cohort study in Austria 2014–2017. *Wiener klinische Wochenschrift*, 134(15-16), pp.607-615.

Lin, T.S., Lin, Y.L., Hsu, C.H., Hsieh, S.C., Shau, W.Y., Yang, W.S. and Chen, C.L. (2024). A systematic review and network meta-analysis of cardiovascular safety of benzbromarone compared to febuxostat and allopurinol in patients with gout. *Frontiers in Cardiovascular Medicine*, 12, 1541307.

MacDonald, T.M., Mackenzie, I.S., Ford, I., Nuki, G., Hallas, J., Hawkey, C.J., Webster, J., Ralston, S.H., Walters, M., Robertson, M., et al. (2020). Long-term cardiovascular safety of febuxostat compared with allopurinol in patients with gout (FAST): a multicentre, prospective, randomised, open-label, non-inferiority trial. *The Lancet*, 396(10264), pp.1745-1757.

O'Dell, J.R., Brophy, M.T., Pillinger, M.H., Neogi, T., Palevsky, P.M., Wu, H., Davis-Karim, A., Newcomb, J.A., Ferguson, R., Pittman, D., et al. (2022). Comparative Effectiveness of Allopurinol and Febuxostat in Gout Management. *NEJM Evidence*, 1(3), EVIDoA2100028.

Patoulias, D.I. and Doumas, M. (2021). Febuxostat versus allopurinol for patients with gout: is it time to overcome concerns regarding cardiovascular safety? *Reumatologia*, 59(6), pp.423-424.

Schumacher, H.R. Jr, Becker, M.A., Lloyd, E., MacDonald, P.A. and Lademacher, C. (2010). The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial. *Arthritis Research & Therapy*, 12(Suppl 2), p.A3.

Shin, A., Choi, S.R., Han, M., Ha, Y.J., Lee, Y.J., Lee, E.B. and Kang, E.H. (2022). Cardiovascular safety associated with febuxostat versus allopurinol among patients with gout: Update with accumulated use of febuxostat. *Seminars in Arthritis and Rheumatism*, 56, 152080.

Sterne, J.A.C., Savović, J., Page, M.J., Elbers, R.G., Blencowe, N.S., Boutron, I., Cates, C.J.,

Cheng, H.Y., Corbett, M.S., Eldridge, S.M., et al. (2019). RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*, 366, l4898.

Wells, G.A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M. and Tugwell, P. (n.d.). *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. [online] Available at: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp [Accessed 25 Oct. 2024].

White, W.B., Saag, K.G., Becker, M.A., Borer, J.S., Gorelick, P.B., Whelton, A., Hunt, B., Castillo, M. and Gunawardhana, L. (2018). Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout. *New England Journal of Medicine*, 378(13), pp.1200-1210.

Zhang, M., Solomon, D.H., Desai, R.J., et al. (2021). Updated Assessment of Cardiovascular Risk in Older Patients With Gout Initiating Febuxostat Versus Allopurinol. *Journal of the American Heart Association*, 10(7), e020045.

Zhang, S., Zhang, S., Xu, T., Shi, Q., Li, S., Wang, L., An, Z. and Su, N. (2021). Cardiovascular Safety of Febuxostat and Allopurinol in Hyperuricemic Patients With or Without Gout: A Network Meta-Analysis. *Frontiers in Medicine*, 8, 698437.

Zhang, Y., Wang, X., Liu, Y., Zhang, T., Ma, Y. and Liu, H. (2022). Cardiovascular safety of febuxostat and allopurinol in patients with gout: A meta-analysis. *Frontiers in Pharmacology*, 13, 998441.

