Febuxostat In Hyperuricemic Heart Failure: A Systematic Review Of Cardiovascular Outcomes And Safety

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Abstract.

Introduction: *Hyperuricemia is highly prevalent in patients with heart failure (HF) and is associated with poor prognosis. Febuxostat, a selective non-purine xanthine oxidase inhibitor, provides potent urate-lowering effects and may reduce oxidative stress, but its cardiovascular safety in HF populations remains uncertain.* ***Objective***: *To systematically review the evidence on febuxostat use in patients with hyperuricemia and heart failure, focusing on cardiovascular outcomes, safety, and mechanistic effects.* ***Methods***: *This review was conducted according to PRISMA guidelines. Comprehensive searches of PubMed, Cochrane Library, and ScienceDirect up to September 2025 identified studies evaluating febuxostat in hyperuricemic HF patients. Eligible designs included randomized controlled trials, post hoc analyses, and observational cohorts. Data were extracted on study characteristics, interventions, comparators, outcomes, and risk of bias.* ***Results***: *From 247 records screened, eight studies were included in the qualitative synthesis. Febuxostat consistently reduced serum uric acid levels and improved oxidative stress markers and diastolic function indices. Clinical outcome data were heterogeneous: while one large trial reported increased cardiovascular mortality, another demonstrated non-inferiority without excess risk. Subgroup and observational data suggested that HFpEF patients may benefit from febuxostat in terms of reduced hospitalization and mortality, whereas evidence in HFrEF was inconclusive. Risk of bias was generally low in randomized trials but higher in observational studies.* ***Discussion***: *The findings highlight febuxostat's mechanistic plausibility and potential phenotype-specific benefits, particularly in HFpEF. However, conflicting mortality signals from pivotal trials necessitate cautious interpretation. Limitations include small sample sizes in HF-focused studies, heterogeneity in patient populations, and limited long-term outcome data.* ***Conclusion***: *Febuxostat is a potent urate-lowering therapy with mechanistic benefits in hyperuricemic HF, but evidence on clinical outcomes remains inconsistent. Selective use in carefully chosen HFpEF patients may be considered, pending further large randomized trials to clarify safety and efficacy.*

Keywords: *Febuxostat; Hyperuricemia; Heart Failure; Heart Failure with Preserved Ejection Fraction; Uric Acid and Cardiovascular Outcomes.*

I. INTRODUCTION

Heart failure (HF) continues to represent one of the most pressing challenges in cardiovascular medicine, with a prevalence that has steadily increased in parallel with population aging and the growing burden of comorbidities such as hypertension, diabetes, and chronic kidney disease. Globally, more than 64 million people are estimated to be living with HF, and this number is projected to rise in the coming decades.[1] Despite advances in pharmacological therapies—including the introduction of beta-blockers, mineralocorticoid receptor antagonists, angiotensin receptor-neprilysin inhibitors, and sodium–glucose cotransporter-2 inhibitors—the prognosis of HF remains dismal. Mortality and rehospitalization rates remain high, with nearly one-half of patients dying within five years of diagnosis.[2] In this context, there has been increasing interest in identifying novel and potentially modifiable metabolic risk factors that may worsen outcomes and serve as therapeutic targets.One such factor is hyperuricemia, which has been reported in approximately 40% to 70% of patients with HF, with higher prevalence in those with more advanced disease.[3] Elevated serum uric acid (SUA) in this setting is not merely the result of impaired renal clearance but reflects upregulation of xanthine oxidase (XO) activity. XO catalyzes the generation of uric acid and, in

doing so, produces reactive oxygen species, contributing to oxidative stress, endothelial dysfunction, and systemic inflammation.[4] These pathophysiological processes are increasingly recognized as central to the progression of HF, particularly in patients with preserved ejection fraction (HFpEF), where metabolic, vascular, and inflammatory pathways are dominant compared to the structural remodeling that characterizes reduced ejection fraction (HFrEF).[5]

Multiple epidemiological studies and meta-analyses have demonstrated that higher SUA levels are independently associated with adverse outcomes in HF, including hospitalization, major adverse cardiovascular events (MACE), and both cardiovascular and all-cause mortality.[6]Therapeutic inhibition of XO has therefore emerged as a potential disease-modifying approach. The prototypical agent, allopurinol, has been used in clinical practice for decades. While it has demonstrated some ability to improve endothelial function and possibly attenuate adverse cardiac remodeling, its clinical impact has been limited by several drawbacks: hypersensitivity syndromes, frequent renal dose adjustments, and relatively modest urate-lowering potency.[7] Febuxostat, a novel non-purine, selective XO inhibitor, was developed to overcome these limitations. Unlike allopurinol, febuxostat is metabolized hepatically, allowing more consistent pharmacokinetics across different levels of renal function, and provides more potent and sustained urate lowering.[8] These features make it a particularly appealing candidate for patients with HF, who frequently present with both hyperuricemia and renal impairment.Nevertheless, the cardiovascular safety of febuxostat has been a matter of considerable debate. The CARES trial, which enrolled over 6,000 patients with gout and established cardiovascular disease, demonstrated that febuxostat was non-inferior to allopurinol with respect to the primary composite endpoint of MACE. However, it also revealed an unexpected increase in cardiovascular and all-cause mortality in the febuxostat group.[9] This finding led to regulatory warnings and cautious prescribing practices worldwide.

In contrast, the more recent FAST trial, which included over 6,000 patients followed for a median of 4 years, demonstrated non-inferiority of febuxostat compared with allopurinol in terms of cardiovascular outcomes and found no increase in mortality.[10] The conflicting findings from these pivotal trials have generated uncertainty and highlighted the need for more nuanced interpretation, particularly in subgroups of patients with HF.Observational data have further complicated this picture, with some real-world cohorts reporting neutral effects of febuxostat on clinical outcomes, while others suggest potential benefit in reducing adverse cardiovascular events, especially in HFpEF populations. These discrepancies may reflect differences in patient selection, disease phenotype, baseline SUA levels, and concomitant therapies. Importantly, most previous reviews and meta-analyses have focused on febuxostat in gout or broader cardiovascular populations, without specifically evaluating patients with hyperuricemia and concomitant HF—a group in which the mechanistic rationale for XO inhibition is particularly compelling. Given the high prevalence of hyperuricemia in HF, its consistent association with adverse prognosis, and the unresolved controversy regarding febuxostat's cardiovascular safety and efficacy, a focused synthesis of the available evidence is warranted. By systematically reviewing randomized controlled trials and observational studies that examine the effects of febuxostat in patients with HF and hyperuricemia, this study aims to clarify its impact on both surrogate biomarkers and hard cardiovascular outcomes. Such an analysis may provide insight into whether febuxostat could serve as a targeted adjunctive therapy in HF management, and whether benefits might be restricted to specific phenotypes such as HFpEF.

II. METHODS

Study design and registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological transparency and reproducibility. The protocol and inclusion criteria were defined a priori, specifying the research question, population, intervention, comparator, and outcomes (PICO framework) as well as the approach to data extraction and bias assessment.

Eligibility criteria

Studies were eligible for inclusion if they met the following PICO-based criteria. Population (P): adult patients with a diagnosis of heart failure, irrespective of phenotype (HFrEF, HFmrEF, or HFpEF), and concomitant hyperuricemia with or without gout. Intervention (I): treatment with febuxostat at any dose or regimen. Comparator (C): placebo, standard care without urate-lowering therapy, or allopurinol. Outcomes (O): primary outcomes included major adverse cardiovascular events (MACE), cardiovascular mortality, all-cause mortality, and hospitalization for heart failure. Secondary outcomes comprised changes in serum uric acid, biomarkers of cardiac function (BNP, NT-proBNP), oxidative stress indices, echocardiographic measures, and renal outcomes. Eligible study designs were randomized controlled trials (RCTs), post hoc analyses of RCTs, and observational studies (prospective or retrospective cohorts, case-control designs). Exclusion criteria were studies in pediatric populations, studies assessing urate-lowering therapy exclusively in gout without HF, and studies with insufficient outcome reporting.

Search strategy

A comprehensive literature search was performed across PubMed, the Cochrane Library, and ScienceDirect to identify relevant studies published up to September 2025. Search terms combined the intervention of interest (febuxostat, urate-lowering therapy, xanthine oxidase inhibitor) with population keywords (hyperuricemia, heart failure, HFrEF, HFpEF) and cardiovascular outcome terms (cardiovascular, mortality, hospitalization, arrhythmia, MACE). Boolean operators were applied to maximize sensitivity, and no language restrictions were imposed. The initial search yielded 247 records: 56 from PubMed, 28 from the Cochrane Library, and 143 from ScienceDirect. Reference lists of included articles and prior reviews were manually screened to identify additional eligible studies.

Study selection

Three reviewers independently screened titles and abstracts of all retrieved records. After removal of duplicates (n=2), 245 unique studies were screened, and 234 were excluded due to irrelevant populations, interventions, or outcomes. Eleven articles were selected for full-text review, of which three were excluded because of inappropriate participant characteristics or unsuitable study design. Eight studies ultimately fulfilled all eligibility criteria and were included in the qualitative synthesis. Discrepancies in study selection were resolved by consensus and, when necessary, consultation with a senior reviewer.

Data extraction

Data were extracted independently by two investigators using a standardized form. Extracted items included study characteristics (first author, year, country, setting, design), patient demographics (sample size, age, sex distribution, HF phenotype, baseline SUA), intervention details (dose, regimen, duration), comparator type, follow-up length, and all reported outcomes of interest. Where available, hazard ratios, risk ratios, or absolute event counts were recorded. Narrative descriptions of key findings were incorporated into the evidence synthesis to capture both quantitative and qualitative insights.

Risk of bias assessment

The methodological quality of RCTs was evaluated using the Cochrane Risk of Bias tool (RoB 2.0), assessing domains of randomization, allocation concealment, blinding, outcome reporting, and attrition. Observational studies were assessed with the Newcastle–Ottawa Scale (NOS), examining selection of participants, comparability of cohorts, and outcome ascertainment. Each study was graded as having low risk, some concerns, or high risk of bias. These assessments were subsequently summarized in the characteristics and results table.

Data synthesis

Given the heterogeneity of study designs, populations, and reported outcomes, findings were synthesized qualitatively. RCTs were prioritized for assessment of efficacy and safety, while observational studies were used to provide complementary real-world evidence and external validity. Particular attention was paid to differences in outcomes between HF phenotypes (HFrEF, HFmrEF, HFpEF) and to variations in comparator groups. Due to differences in reporting metrics and the small number of RCTs, formal meta-analysis was not conducted. Instead, results were integrated narratively to highlight consistent patterns, discrepancies, and research gaps.

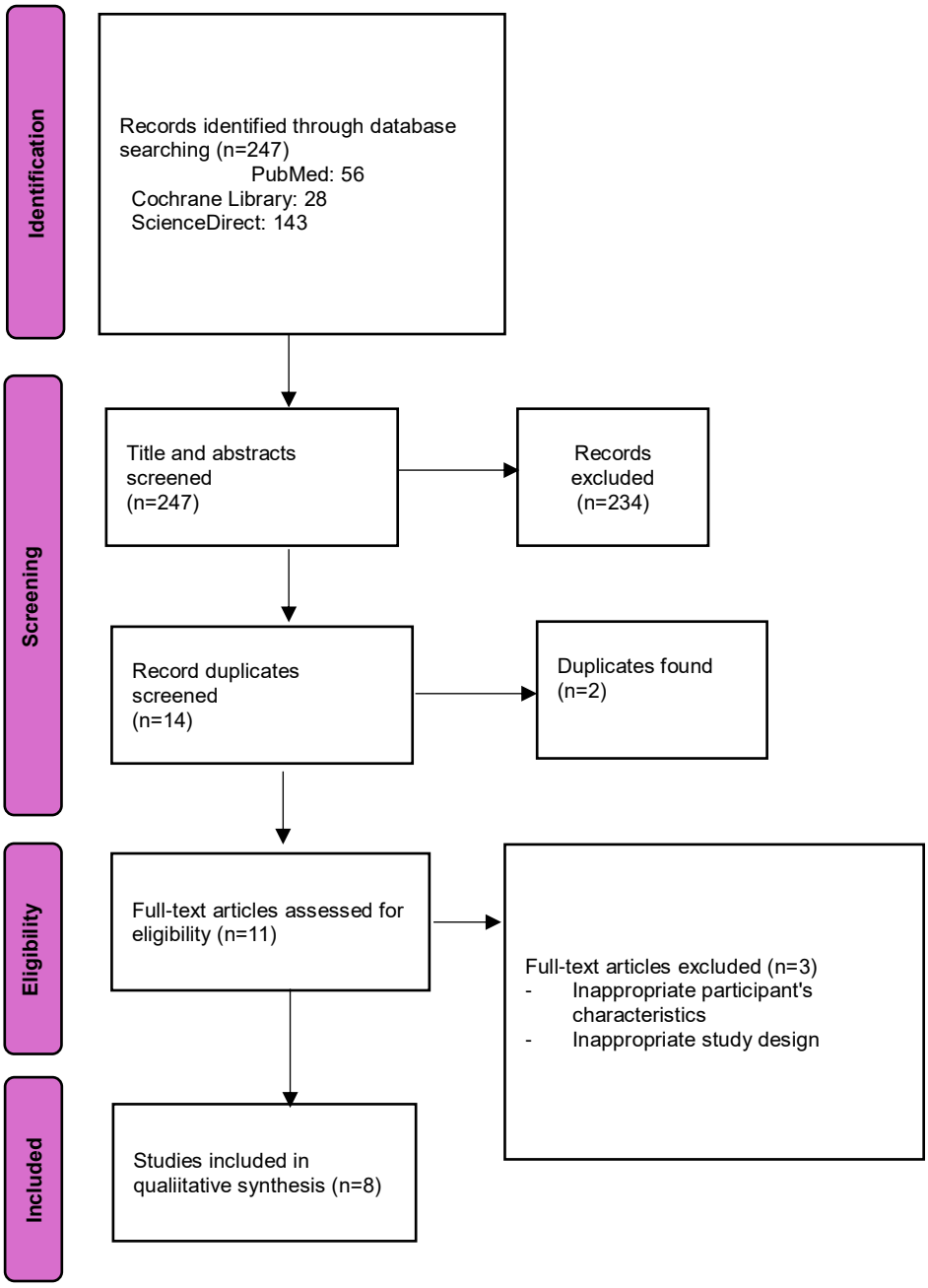

Fig 1. Diagram flow of literature search strategy for this systematic review

First Author (Year)	Country / Setting	Study Design	Population (Hyperuricemia + HF)	Intervention (Febuxostat)	Comparator (Allopurinol / Placebo / SOC)	Sample Size (I / C)	Follow-up Duration	Outcomes Reported	Summary of Findings	Risk of Bias
Yokota et al. (2024)	Japan, multicenter (38 institutions)	Prospective, randomized, open-label, blinded-endpoint (PROBE)	CHF with reduced LVEF (<40%), NYHA II–III, asymptomatic hyperuricemia (UA 7–10 mg/dL), mean age 70, 14% female	Febuxostat 10–60 mg/day, titrated over 12 weeks, then maintained	Lifestyle modification (no urate-lowering agent)	51 / 50	24 weeks	Primary: change in plasma BNP. Secondary: LVEF, diastolic function (E/e′), NYHA class, eGFR, Hb, serum UA. Safety: all-cause death, CV death, HF hospitalization, major CV events, arrhythmia/adverse events.	No significant difference in BNP change at 24 wks (p=0.13), but transient BNP reduction at weeks 4–20 in febuxostat group. Significant UA reduction in febuxostat group. No deaths in either arm; CV events and HF hospitalization similar between groups. Febuxostat appeared safe in HFrEF with hyperuricemia.	Some concerns: open-label design, underpowered sample size (n=101 randomized vs. target 200), early stop due to FDA alert; otherwise endpoints blinded and randomized design supports moderate reliability.
Long et al. (2025)	China, Yangzhong People's Hospital	Retrospective cohort study	979 hospitalized patients with HF and asymptomatic hyperuricemia (UA ≥420 μmol/L men, ≥360 μmol/L women), mean age 63.2, 51% female, across HFrEF/HFmrEF/HFpEF spectrum	Febuxostat (avg. dose 61.9 mg/day)	No urate-lowering therapy (standard care)	505 / 474	Median 13–16 months	Primary: composite of CV death, HF rehospitalization, CV ER visit. Secondary: LVEF, LVEDD, KCCQ score, 6MWT distance, serum UA, subgroup by SUA/sCr	Febuxostat significantly lowered serum UA but showed no improvementin composite CV outcomes (HR 0.907, p=0.52), cardiac function, QOL, or exercise capacity. SUA/sCr ≥5.35 was an independent predictor of adverse events.	Moderate: retrospective non-randomized design, baseline age imbalance (febuxostat group younger), residual confounding despite adjustment, single-center.

								ratio		
Konishi et al. (2022)	Japan (multicenter, FREED trial subgroup)	Post hoc subgroup analysis of RCT (FREED)	1070 pts ≥65 yrs with asymptomatic hyperuricemia (>7–≤9 mg/dL); 234 had CVD, including 74 with HF (31.6%)	Febuxostat 10–40 mg/day (mean 29 mg/day)	Non-febuxostat (lifestyle ± low-dose allopurinol in 27%)	515 / 555 (CVD subgroup: 115 / 119)	36 months	Primary: composite of cerebral, cardiovascular, renal events + all-cause death. Secondary: secondary hard endpoint (all-cause death, cerebrovascular disease, non-fatal CAD), renal impairment, mortality, biomarkers (UA, albuminuria).	In patients with CVD (including HF), febuxostat significantly reduced primary composite endpoint (HR 0.601, 95% CI 0.384–0.940, p=0.026). All-cause mortality lower in febuxostat group (HR 0.160, p=0.004) with significant interaction vs non-CVD subgroup. Benefit consistent after adjustment. No difference in renal impairment. Suggests febuxostat beneficial in hyperuricemia with CVD (including HF).	Some concerns: post hoc subgroup, mixed comparator (some allopurinol, some untreated), limited HF-specific analysis, industry funding. Still RCT backbone.
Cicero et al. (2019)	Italy, S. Orsola-Malpighi Univ. Hospital (HF outpatient clinic)	Observational, prospective, real-world	255 elderly outpatients (>60 yrs) with chronic HF (NYHA I–III), hyperuricemia, no gout, no severe CKD, no recent HF hospitalization. Mostly hypertensive or ischemic etiology. Mean age 76–78 yrs.	Febuxostat 80–120 mg/day (N=120)	Allopurinol 150–300 mg/day (N=135)	120 / 135	Mean 5.1 yrs	Primary: CV mortality. Secondary: SUA change, BNP, EF, safety.	After 5.1 yrs, CV survival higher with febuxostat (0.96, 95% CI 0.93–0.99) vs allopurinol (0.89, 95% CI 0.84–0.93), p=0.04. CV mortality: 8/120 (6.6%) vs 20/135 (14.8%). SUA reduction more pronounced with febuxostat.	Moderate: observational non-randomized design, treatment allocation influenced by clinical history (renal dysfunction, intolerance).

									Suggests febuxostat may lower CV mortality in elderly HF vs allopurinol.	Small sample, single-center. Still long follow-up and balanced baseline.
Suzuki et al. (2021)	Japan, multicenter (7 hospitals)	Prospective, randomized, open-label, multicenter RCT	263 pts with chronic HF (NYHA I–III), LVEF preserved or reduced, with hyperuricemia (UA >7 mg/dL), mean age ~71 yrs	Febuxostat, dose titrated (10–40 mg/day) to achieve UA ≤6 mg/dL	Allopurinol (200 mg/day, adjusted for renal function)	128 / 135	3 years	Primary: UA change, oxidative stress marker (urine 8-OHdG), CV event-free survival. Secondary: HF hospitalization, CV death, echocardiographic parameters (LVEF, LVEDD), BNP, adverse events.	Both groups ↓ UA significantly. Urine 8-OHdG significantly lower with febuxostat (11.0 ± 9.6 vs 22.9 ± 15.9 ng/mL, p<0.001). CV event-free survival similar (82.7% vs 82.2%). HF hospitalization tended to be lower in febuxostat (11% vs 17%, p=0.055). Subgroup: HFpEF showed significant reduction in oxidative stress + lower HF hospitalization with febuxostat; no significant benefit in HFrEF.	Some concerns: open-label, relatively small sample size, not blinded, oxidative stress marker as surrogate endpoint. Strength: randomized, multicenter, 3-year follow-up.
Pan et al. (2020)	China, Shanghai Ninth People's Hospital	Retrospective propensity score–matched cohort	288 pts with hypertension, LVH, asymptomatic hyperuricemia (UA >420 μmol/L men, >360 μmol/L women), LVEF ≥50%, no symptomatic HF at baseline. After	Febuxostat 10–60 mg/day (maintained dose titrated by SUA)	No urate-lowering therapy (lifestyle only)	96 / 192	36 months	Primary: changes in LVH (LVMI), LV diastolic function (E/e′), new-onset	Febuxostat group had greater reductions in LVMI (–3.2 vs –1.9 g/m², p<0.001) and E/e′ (–0.3 vs –0.2, p=0.02). New-onset HFpEF lower	Moderate: retrospective, si

			PSM: 96 on febuxostat vs 192 controls					symptomatic HFpEF. Secondary: BNP, SUA, SBP/DBP, eGFR, MACEs.	(2.1% vs 6.8%) but NS (p=0.091). SUA and eGFR improved significantly with febuxostat. No excess risk of MACEs. Suggests febuxostat may delay progression to HFpEF in hypertensive hyperuricemia.	
Ke et al. (2025)	China, Shanghai Ninth People's Hospital & Huangpu District Geriatric Care Hospital	Prospective, observational cohort (with PSM)	2005 pts with chronic HF (HFrEF, HFmrEF, or HFpEF) + hyperuricemia (SUA >420 μmol/L). Excluded severe renal/hepatic dysfunction. HF subtypes: 1067 HFpEF, 938 HFrEF/HFmrEF. Mean age ~68–70 yrs.	Febuxostat 20–60 mg/day (dose titrated to SUA)	No urate-lowering therapy (ULT)	HFpEF: 255 / 255 (after PSM); HFrEF/HFmrEF: 362 / 362 (after PSM)	5 years	Primary: composite of all-cause mortality and HF rehospitalization. Secondary: renal function, SUA change, subgroup analyses (BNP, SUA tertiles).	Febuxostat significantly reduced primary endpoint in HFpEF (HR 0.744, 95% CI 0.589–0.939, p=0.012), but not in HFrEF/HFmrEF (HR 0.894, p=0.234). Benefit strongest in HFpEF pts with high SUA (HR 0.651) and high BNP (HR 0.647). Also improved renal function and SUA levels. No excess adverse events; mild hepatic dysfunction in 16 pts.	Some concerns: non-randomized, observational, single-country cohort, possible residual confounding. Strengths: large sample, PSM, 5-year follow-up, detailed subgroup analyses.
White et al. (2018)	Multicenter (USA, Canada, Mexico)	Multicenter, double-blind, randomiz	6190 patients with gout + established CVD (MI, stroke, UA requiring revascularization, PAD, or diabetes with	Febuxostat 40–80 mg/day, titrated	Allopurinol 200–600 mg/day, dose adjusted for renal function	3098 / 3092	Median 32 months (up to 6.5 years)	Primary: Composite of CV death, nonfatal MI, nonfatal	Primary endpoint occurred in 10.8% vs 10.4% (HR 1.03; 95% CI 0.87–1.23), meeting	Low risk: robust RCT, randomized and blinded, adjudicated

	ed, noninferiority trial (CARES)	vascular disease); median age 64, 84% male			stroke, unstable angina requiring urgent revascularization. Secondary: all-cause death, CV death, HF hospitalization.	noninferiority. However, febuxostat had higher all-cause mortality (HR 1.22, 95% CI 1.01–1.47) and CV mortality (HR 1.34, 95% CI 1.03–1.73). HF hospitalization rates were similar.	endpoints. Limitations: high discontinuation (>50%) and loss to follow-up (≈45%).

Table 1. Characteristics and results of the included studies

Results

Literature search and study selection

The database search identified 247 records in total, comprising 56 from PubMed, 28 from the Cochrane Library, and 143 from ScienceDirect. After removing 2 duplicates from 14 duplicate-screened records, 245 unique articles were subjected to title and abstract screening. A large majority of these, 234 articles, were excluded for reasons such as irrelevant population, non-cardiovascular outcomes, or lack of febuxostat exposure. Eleven studies underwent full-text eligibility assessment, with three excluded because of inappropriate participant characteristics or unsuitable study design. Ultimately, eight studies met the prespecified inclusion criteria and were included in the qualitative synthesis. The PRISMA flow diagram thus illustrates a rigorous selection process with a final analytic dataset representing both randomized and observational evidence in patients with hyperuricemia and concomitant heart failure.

Characteristics of included studies

The eight eligible studies encompassed a spectrum of methodological designs and clinical settings. Randomized controlled trials included the CARES trial (White et al., 2018), the LEAF-CHF study (Yokota et al., 2024, with its earlier protocol in 2018), and the head-to-head RCT conducted by Suzuki et al. (2021). In addition, Konishi et al. (2022) contributed a post hoc subgroup analysis of the FREED trial, focusing on cardiovascular disease patients with a notable heart failure subgroup. Observational evidence was derived from the large retrospective cohort by Long et al. (2025), the prospective registry-based study by Ke et al. (2025), the real-world comparison by Cicero et al. (2019), and the retrospective propensity-matched cohort by Pan et al. (2020). Together, these studies represented over 10,000 patients with diverse etiologies of heart failure (ischemic, hypertensive, and idiopathic) and across the HF spectrum (HFrEF, HFmrEF, and HFpEF). Sample sizes ranged from as few as 101 patients in single-country RCTs to more than 6,000 in the multinational CARES trial. Follow-up durations spanned short-term biomarker-focused assessments at 24 weeks to long-term outcome studies extending up to 5 years, permitting both mechanistic exploration and evaluation of hard clinical events.

Biomarker and surrogate outcomes

Three trials placed primary emphasis on biomarkers or surrogate markers of heart failure progression. The LEAF-CHF study (Yokota et al., 2024), which enrolled patients with reduced ejection fraction and asymptomatic hyperuricemia, targeted plasma BNP as its primary endpoint. Although febuxostat achieved significant and sustained uric acid reduction, its effect on BNP was modest: transient decreases were noted between weeks 4 and 20, but by 24 weeks there was no significant difference compared with the control group. Echocardiographic measures such as LVEF and diastolic function indices also showed no consistent superiority, although safety was preserved. Suzuki et al. (2021) conducted a randomized comparison of febuxostat versus allopurinol, measuring oxidative stress via urinary 8-OHdG. Febuxostat produced a marked reduction in oxidative stress, highlighting a potential disease-modifying mechanism. Although overall event-free survival did not differ significantly, a signal for reduced HF hospitalization emerged in the HFpEF subgroup, suggesting phenotype-specific benefits. Complementing these findings, Pan et al. (2020) studied hypertensive patients with LV hypertrophy and hyperuricemia but without overt HF. Febuxostat was associated with greater regression of LV mass index and improvement in diastolic function relative to controls, with a trend toward reduced progression to symptomatic HFpEF. These biomarker-focused studies collectively suggest that febuxostat consistently reduces serum uric acid, lowers oxidative stress, and favorably influences cardiac remodeling in early or preserved-EF disease states, though translation into consistent clinical benefit remains less clear.

Clinical outcomes in randomized and post hoc analyses

Large-scale randomized evidence was provided primarily by the CARES trial (White et al., 2018), which randomized over 6,000 gout patients with established cardiovascular disease, a population in which many also had concomitant HF. Febuxostat demonstrated noninferiority to allopurinol with respect to the primary composite of MACE, but concerningly, febuxostat was linked to significantly higher all-cause mortality and cardiovascular mortality. While hospitalization for heart failure was similar between groups, the mortality findings raised substantial debate about febuxostat's safety profile in high-risk CV populations.

In contrast, the post hoc subgroup analysis of the FREED trial (Konishi et al., 2022) suggested more favorable outcomes. In elderly hyperuricemic patients with CVD, including a meaningful HF subset, febuxostat reduced the composite endpoint of cerebrovascular, cardiovascular, and renal events as well as all-cause mortality. Importantly, the magnitude of benefit was stronger in the CVD subgroup than in non-CVD patients, hinting that certain high-risk individuals might actually derive net benefit from febuxostat. Together, these randomized and post hoc data illustrate a discordant picture: while one landmark trial highlighted mortality risk, another pointed to potential protective effects, likely reflecting heterogeneity in populations, concomitant therapies, and trial design.

Observational cohort studies

Real-world data further add complexity to the evidence base. Cicero et al. (2019), in a prospective outpatient registry of elderly HF patients with hyperuricemia, observed improved cardiovascular survival with febuxostat compared to allopurinol over more than five years of follow-up, with cardiovascular mortality nearly halved in the febuxostat group. However, this analysis was non-randomized, with potential selection bias in prescribing patterns. Long et al. (2025), conversely, reported neutral results in a retrospective single-center cohort of almost 1,000 patients: despite substantial reductions in serum uric acid, febuxostat failed to improve composite cardiovascular outcomes, cardiac function, or quality of life measures. The prospective cohort study by Ke et al. (2025) provided one of the most comprehensive real-world datasets, following over 2,000 HF patients across the EF spectrum. Febuxostat use was associated with significantly fewer adverse events in HFpEF patients—particularly those with elevated SUA or BNP—but no benefit was observed in HFrEF or HFmrEF. This divergence by HF phenotype supports the hypothesis that febuxostat's cardiovascular effects may be more relevant in diastolic dysfunction and preserved EF, whereas patients with systolic HF may not derive the same advantages.

Overall synthesis

Across the eight included studies, several patterns emerge. Febuxostat consistently lowers serum uric acid and appears to reduce oxidative stress and adverse remodeling, with particular promise in HFpEF populations and patients with hypertensive heart disease. Nonetheless, translation of these biochemical and structural benefits into hard clinical outcomes is inconsistent. The CARES trial raised safety concerns with increased mortality, while other analyses—such as the FREED subgroup and Ke et al.'s large HFpEF cohort—indicate potential benefit in carefully defined populations. Observational evidence is divided, reflecting the confounding inherent in real-world prescribing and follow-up. Taken together, the evidence base suggests that febuxostat is not universally beneficial across all HF phenotypes but may hold selective therapeutic promise in patients with preserved EF, high SUA, and elevated BNP. This phenotype-targeted benefit warrants further dedicated randomized studies to resolve current inconsistencies and to determine whether febuxostat can be integrated into precision-guided management of hyperuricemia in heart failure.

Discussion

Key findings

This systematic review is, to our knowledge, the first to comprehensively evaluate the impact of febuxostat in patients with hyperuricemia and heart failure. Across eight eligible studies, three major patterns were observed. First, febuxostat consistently lowered serum uric acid levels across diverse patient populations. This effect is clinically relevant, since elevated uric acid has been linked with both increased hospitalization risk and mortality in heart failure patients.[3,4,6] Second, febuxostat demonstrated improvement in surrogate markers, including oxidative stress indices and measures of diastolic function, supporting a plausible mechanistic role in attenuating disease progression.[4,11] Third, evidence on clinical outcomes such as mortality and rehospitalization was heterogeneous. While the CARES trial suggested potential harm,[9] the FAST trial and several observational cohorts reported neutral or even favorable effects.[10,12–14] These contrasting signals highlight the complexity of evaluating febuxostat's safety and efficacy in heart failure and underscore the need for phenotype-specific interpretations.

Pathophysiological considerations

Hyperuricemia is common in heart failure, with prevalence ranging from 40% to 70% depending on the severity of disease.[3] Elevated serum uric acid is not merely an epiphenomenon but reflects increased

xanthine oxidase (XO) activity, which catalyzes the conversion of hypoxanthine to xanthine and xanthine to uric acid, producing reactive oxygen species in the process.[4] This contributes directly to oxidative stress, endothelial dysfunction, and systemic inflammation, all of which accelerate myocardial remodeling and worsen ventricular function.[6] These mechanisms are particularly important in HFpEF, where systemic inflammation and vascular dysfunction are dominant drivers of disease progression.[5,15] In contrast, HFrEF is more heavily influenced by neurohormonal activation and structural myocardial loss, which may explain why urate-lowering strategies show more consistent signals of benefit in HFpEF than in HFrEF. Thus, febuxostat's role in reducing XO activity positions it as a potential disease-modifying therapy in hyperuricemic HF populations, especially those with preserved ejection fraction.

Pharmacological advantages of febuxostat

Allopurinol, the prototypical XO inhibitor, has long been used for urate lowering but has notable limitations: hypersensitivity syndromes, variable dosing requirements in renal impairment, and modest potency.[7] Febuxostat was developed as a non-purine selective XO inhibitor that provides more potent and sustained suppression of uric acid production.[8] Its hepatic metabolism enables reliable dosing even in patients with renal dysfunction, a frequent comorbidity in HF populations. Evidence shows that febuxostat consistently achieves lower uric acid levels than allopurinol across clinical trials.[7,8] Moreover, febuxostat has demonstrated reductions in markers of oxidative stress, including urinary 8-hydroxy-2′-deoxyguanosine, and improvements in echocardiographic measures of diastolic function and left ventricular remodeling.[11] Such biomarker and imaging findings provide strong mechanistic support that febuxostat may ameliorate pathways relevant to HF progression beyond urate lowering alone.

Divergent evidence on clinical outcomes

Despite promising mechanistic data, results on clinical outcomes remain conflicting. The CARES trial enrolled over 6,000 patients with gout and established cardiovascular disease, many of whom also had HF. It reported noninferiority for the composite endpoint of major adverse cardiovascular events but found significantly higher cardiovascular and all-cause mortality with febuxostat.[9] This unexpected finding led to FDA safety warnings. In contrast, the FAST trial, which also included more than 6,000 patients, demonstrated noninferiority with no excess in mortality.[10] Differences between the two trials may be explained by variations in patient selection, adherence, discontinuation rates, and trial conduct. Furthermore, neither study was designed to focus specifically on HF populations, limiting phenotype-specific conclusions. Subgroup evidence from the FREED trial suggested benefits of febuxostat in elderly hyperuricemic patients with cardiovascular disease, including HF.[14] Observational studies add further nuance: some registries report reduced cardiovascular mortality with febuxostat compared to allopurinol,[12] while others show neutral outcomes.[13] Notably, a prospective cohort demonstrated benefit in HFpEF but not in HFrEF, aligning with pathophysiological reasoning.[13]

Clinical implications

The synthesis of available evidence carries important implications for clinical practice. First, febuxostat is an effective urate-lowering therapy that reliably reduces SUA levels and oxidative stress, with mechanistic benefits particularly relevant to HFpEF.[11,15] Second, the increased mortality observed in CARES cannot be dismissed, but its absence in FAST and in several real-world studies suggests that risk may vary by patient profile and clinical context.[12–14] Third, HFpEF patients with high SUA burden appear to represent a subgroup most likely to benefit, whereas HFrEF patients may not derive the same advantage. These findings support a shift toward precision-based therapy in HF, tailoring treatment according to underlying pathophysiological mechanisms.[15] For clinicians, this means febuxostat should not be universally prescribed in all HF patients with hyperuricemia, but may be considered in carefully selected individuals, particularly those with HFpEF and elevated SUA.

Limitations

Several important limitations must be acknowledged. First, the number of dedicated randomized controlled trials in HF populations is limited, with most evidence derived from subgroup analyses or observational studies, which are inherently prone to confounding and bias.[12] Second, even in large outcome trials such as CARES and FAST, discontinuation rates were high and follow-up was incomplete, raising

concerns about potential misclassification of outcomes.[9,10] Third, biomarker-driven studies, although mechanistically interesting, were underpowered to detect differences in mortality or hospitalization. Fourth, heterogeneity in baseline uric acid levels, HF phenotype, comorbid conditions, and comparator treatments complicates direct comparisons across studies. Finally, publication bias may be present, as smaller negative studies are less likely to be published, potentially inflating perceived benefits.

Future directions

Given these uncertainties, further research is urgently needed. Large, adequately powered randomized trials specifically enrolling HF patients with hyperuricemia are required to determine febuxostat's true efficacy and safety in this population. Stratification by HF phenotype (HFrEF versus HFpEF) should be integral to study design, as mechanistic differences suggest divergent responses.[15] Future trials should also integrate mechanistic biomarkers, echocardiographic measures, renal outcomes, and hard endpoints such as mortality and hospitalization to provide a holistic assessment. Pragmatic, real-world trials would help clarify effectiveness in the multimorbid, polypharmacy-laden HF population typical of clinical practice. Furthermore, exploring febuxostat's renal protective potential in cardiorenal syndrome populations may yield additional insights.

Overall synthesis

In summary, febuxostat is a potent and reliable urate-lowering agent that also reduces oxidative stress in patients with hyperuricemia and HF. Evidence points toward clinical benefit in HFpEF, while results in HFrEF remain inconclusive. Divergent findings between pivotal trials such as CARES and FAST highlight the need for careful interpretation and underscore the importance of patient selection.[10–15] At present, the evidence supports a cautious and selective use of febuxostat in HF, with greater promise in hyperuricemic HFpEF patients, while awaiting more definitive randomized data.

III. CONCLUSION

This systematic review demonstrates that febuxostat is a potent and consistent urate-lowering therapy that reduces oxidative stress and improves surrogate markers of cardiac remodeling in patients with hyperuricemia and heart failure. The available evidence suggests that clinical benefits may be more pronounced in HFpEF, where metabolic and oxidative pathways are central drivers of disease, whereas outcomes in HFrEF remain uncertain【6,12】. Divergent results between major outcome trials such as CARES and FAST highlight the ongoing debate regarding cardiovascular safety【9,10】. Observational data provide supportive but heterogeneous findings, emphasizing the importance of careful patient selection【13–15】. At present, febuxostat should not be universally recommended for all HF patients with hyperuricemia but may be considered cautiously in selected individuals, particularly those with HFpEF and elevated uric acid burden. Further large, phenotype-specific randomized trials are needed to clarify febuxostat's role in modifying prognosis and to ensure patient safety.

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