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Cardiovascular Safety of Febuxostat versus Allopurinol in Complex Patient Populations

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Abstract

The cardiovascular safety of xanthine oxidase inhibitors in complex patient populations has emerged as a critical clinical consideration following conflicting evidence from major trials. This review synthesizes current evidence on the cardiovascular safety of febuxostat versus allopurinol in patient populations characterized by comorbidities, including chronic kidney disease, diabetes mellitus, and Asian ethnicity. There are raised concerns about the increased cardiovascular and all-cause mortality with febuxostat in gout patients with cardiovascular disease, while the subsequent non-inferior cardiovascular safety in a moderate-risk population. Recent evidence revealed heterogeneous effects across subgroups: in Asian populations, febuxostat is associated with significantly increased risks of acute coronary syndrome and atrial fibrillation, with particularly elevated risks among Asian subgroups for cardiovascular death and all-cause mortality. In patients with chronic kidney disease, evidence suggests that febuxostat may decrease cardiovascular events. In contrast, association with concomitant diabetes mellitus and chronic kidney disease exhibited higher risks of heart failure hospitalization and cardiovascular interventions with febuxostat. Interestingly, achieving serum urate control below 5 mg/dL appears independently associated with reduced cardiovascular risk regardless of the agent used. These findings highlight that cardiovascular safety comparisons cannot be generalized across populations; rather, risk-benefit assessments must integrate ethnicity, renal function, diabetic status, and baseline cardiovascular disease. Future research should prioritize prospective studies in underrepresented populations and elucidate mechanisms underlying differential treatment effects.

Keywords: Gout, Hyperuricemia, Cardiovascular diseases, Febuxostat, Allopurinol

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Introduction

Gout is an inflammatory and metabolic disorder caused by chronic hyperuricemia, which leads to deposition of urate crystals in joints and soft tissues, forming tophi, acute arthritis, and renal disorders (Ragab *et al*., 2017; Singh & Gaffo, 2020; Grant & Wallace, 2024). Also, hyperuricemia may increase the risk of cardiovascular diseases such as hypertension, ischemic heart disease, stroke, or heart failure, making cardiovascular disease (CVD) a major cause of mortality and morbidity in those patients (Tao *et al*., 2023; Kunie *et al*., 2025).

A reactive oxygen species (ROS) is increased in patients with gout due to the oxidation process of hypoxanthine to xanthine, which occurs by the xanthine oxidase (XO) enzyme (Liu *et al*., 2021; Osluf *et al*., 2024; Morgan *et al*., 2025). Accordingly, inhibition of this enzyme decreases oxidative stress, providing a mechanistic rationale for cardiovascular benefit by uric acid lowering (Cicero *et al*., 2020).

Today, the most common xanthine oxidase inhibitors (XOIs) used clinically are the purine analogue allopurinol and febuxostat, which is a non-purine, more selective inhibitor (Wang *et al*., 2021). Allopurinol is safer than febuxostat, while febuxostat is a more potent alternative for patients who are intolerant of or insufficiently controlled by allopurinol (Lindstrom *et al*., 2025; Zhang & Wang, 2025).

However, cardiovascular outcome trials have produced conflicting results. The CARES trial (2018) reported higher rates of cardiovascular and all-cause mortality with febuxostat compared with allopurinol, prompting safety warnings (Choi *et al*., 2018; Anunziata & Cussa, 2024). In contrast, the later FAST trial (2020) and several meta-analyses found no significant difference in major adverse cardiovascular events between the two drugs (Mackenzie *et al*., 2020; Clark & Foster, 2025). These differences in cardiovascular effects among these drugs may be related to several factors, including the dose, duration of therapy, sex-related biological and pharmacokinetic factors, in addition to co-existing diseases such as chronic kidney disease, heart failure, and hypertension. Understanding these modifiers is essential to clarify true drug effects (Si *et al*., 2021; Wang *et al*., 2021; Ganea *et al*., 2024). This review aims to summarise and interpret available evidence regarding the impacts of these factors on cardiovascular safety and the efficacy of febuxostat and allopurinol in gout patients.

Mechanisms of Cardiovascular Action

Protective Mechanisms of XO Inhibition

Xanthine oxidase inhibitors decrease the level of reactive oxygen species production and serum uric acid concentrations, both of which are significant causes of endothelial dysfunction and vascular injury (Sekizuka, 2022; Raza *et al*., 2025). In purine catabolism, processes mediated by xanthine oxidase generate superoxide and hydrogen peroxide, which scavenge nitric oxide (NO), diminish endothelial relaxation, enhance lipid peroxidation, and activate inflammatory pathways (George & Struthers, 2009). XO inhibition consequently restores NO bioavailability, enhances endothelial function, and mitigates vascular stiffness (Liu *et al*., 2021; Ribeiro *et al*., 2024; Ming *et al*., 2025).

Allopurinol causes vasodilation, improves endothelial function of coronary vessels, and improves ventricular function independently of urate reduction (George & Struthers, 2009; Rekhraj *et al*., 2013; Cuenca-Martínez *et al*., 2025). XOIs protect mitochondrial function by decreasing damage by ROS and increasing energy production, and regulating cytokine expression (Liu *et al*., 2021; Mickevičius *et al*., 2024).

Cardioprotective mechanisms of XOIS include lowering of oxidative stress by decreased superoxide levels and lipid peroxidation (Sekizuka, 2022), enhancement of nitric oxide bioavailability causing vasodilation (George & Struthers, 2009; Jabin & Guthrie, 2025), decrease of vascular inflammation by formation of cytokines and endothelial activation (Liu *et al*., 2021), and improvement diastolic function and decreased left ventricular mass (Rekhraj *et al*., 2013; Hsiao *et al*., 2024).

Potential Harmful Mechanisms of Febuxostat

Febuxostat produces more potent and sustained xanthine oxidase inhibition compared with allopurinol, resulting in more profound suppression of urate and purine metabolism (Xie *et al*., 2023). Excessive XO inhibition may alter hypoxanthine and xanthine recycling, potentially affecting ATP regeneration and reducing adenosine-mediated coronary vasodilation (Battelli *et al*., 2018; Xie *et al*., 2023; Wong *et al*., 2025).

Decreasing pathological reactive oxygen species (ROS) has cardioprotective effects. Still, excessive decrease of ROS may alter physiological redox signaling required for mitochondrial homeostasis and endothelial function, so stronger XO inhibition with febuxostat, particularly at higher doses, may therefore disrupt endothelial adaptive mechanisms more than allopurinol (Pacher *et al*., 2006; Alhossan *et al*., 2024).

The CARES trial shows elevated cardiovascular and all-cause mortality with febuxostat compared with allopurinol in patients with already cardiovascular disease, despite no increase in nonfatal major adverse cardiovascular events (White *et al*., 2018; Novak & Dvorak, 2025). Sudden cardiac death may occur due to myocardial energy imbalance, electrophysiological instability, or microvascular dysfunction (Cicero *et al*., 2019; Solmell *et al*., 2024). Allopurinol has been shown to improve myocardial oxygen efficiency, reduce left ventricular workload, and enhance endothelial function in cardiovascular disease, effects not consistently reproduced with febuxostat (George & Struthers, 2009; Schneider & Krüger, 2025). Differences in myocardial energetics may therefore contribute to divergent clinical outcomes in advanced cardiovascular disease.

Recent in vitro evidence suggests that high-dose febuxostat may suppress ROS-dependent signaling necessary for Nrf2 activation, mitochondrial biogenesis, and nitric oxide production, thereby impairing adaptive antioxidant responses (Miciak & Jurkiewicz, 2024; Zhang & Wang, 2025). Febuxostat undergoes hepatic metabolism primarily via UGT and CYP pathways, which may influence oxidative balance differently compared with the renally cleared allopurinol and its active metabolite oxypurinol (George & Struthers, 2009; Rani & Gehrke, 2025). These pharmacokinetic differences may contribute to variable cardiovascular responses in patients with hepatic or renal dysfunction.

Influence of Dose and Duration

Allopurinol with a high dose (≥300 mg/day) significantly decreases xanthine oxidase function, thereby increasing antioxidant, endothelial, and cardiac function. In contrast, low doses may not provide cardiovascular advantages (Rekhraj *et al*., 2013; Iriti *et al*., 2024). Febuxostat has maximum xanthine oxidase inhibition at a low dose of (40–80 mg/day), but doses greater than 120 mg/day cause inhibition of physiological antioxidant pathways. The ideal benefit–to–risk ratio seems to be more constrained for febuxostat, particularly in individuals with severe cardiovascular disease (White *et al*., 2018; Alnabulsi *et al*., 2025).

Long-term use of xanthine oxidase inhibitors elevates antioxidant effects and endothelial functions. However, the FAST study shows that long-term febuxostat treatment (>4 years) does not increase cardiovascular risk compared with allopurinol in healthy patients (Mackenzie *et al*., 2020; Jaafar *et al*., 2024). But CARES studies exhibit increased mortality over the initial year, possibly attributable to inadequate adherence, discontinuation of the drug, and disease severity (White *et al*., 2018). Extended XO inhibition (>2 years) caused enhanced vascular outcomes and reduced ischemic event rates in an observational cohort study (Saito *et al*., 2021; Shen & Bao, 2025).

Sex Differences and Pharmacokinetics

Patients' sex may affect xanthine oxidase expression, drug metabolism, glomerular filtration rate, and oxidative stress levels. Women typically exhibit less XO activity and decreased renal clearance of oxypurinol, so they have increased systemic exposure at comparable doses (Chang *et al*., 2021; Bao *et al*., 2025). This may improve urate-lowering efficacy but also increase the risk of hypersensitivity, especially in the elderly or women with renal insufficiency. Allopurinol is metabolized to oxypurinol, which is the active form, and is mainly excreted by the kidneys and possesses a prolonged half-life (Feig *et al*., 2008). Marginally diminished female GFR and variations in body composition may consequently lead to elevated drug exposure. Febuxostat is extensively metabolized hepatically through UGT and CYP (1A2, 2C8, 2C9) and exhibits dual excretion by hepatic and renal pathways (George & Struthers, 2009; Uneno *et al*., 2024).

While total exposure is comparable across men and women, women exhibit increased plasma concentrations due to decreased CYP activity and a smaller volume of distribution (George & Struthers, 2009). Moreover, estrogen may lower XO activity and oxidative stress, thus decreasing the cardiovascular advantages of robust XO inhibition in premenopausal women (Budhiraja *et al*., 2003). Significant cardiovascular outcome trials, including CARES and FAST, had a restricted percentage of women, hence constraining conclusive sex-specific insights (White *et al*., 2018; Mackenzie *et al*., 2020). Nevertheless, due to pharmacokinetic differences and differing baseline risks, personalized dose and vigilant monitoring are advisable, particularly for older women and individuals with hepatic or renal disease.

Co-existing Diseases in the Cardiovascular Effects of Febuxostat and Allopurinol

The presence of comorbid conditions changes the cardiovascular safety and effectiveness profile of Xanthine oxidase inhibitors. Hypertension, chronic kidney disease (CKD), diabetes mellitus, obesity, metabolic syndrome, and coronary artery disease (CAD) change drug metabolism, urate management, oxidative equilibrium, and vascular responsiveness, thus affecting both adverse and therapeutic outcomes (Feig *et al*., 2008; George & Struthers, 2009).

Chronic Kidney Disease (CKD)

Chronic renal disease is prevalent in gout and significantly changes the pharmacokinetics of xanthine oxidase inhibitors. The kidneys eliminate allopurinol metabolite (Oxypurinol); buildup transpires in chronic kidney disease, so a dosage adjustment is necessary. Nevertheless, many studies indicate cardioprotective and nephroprotective effects by decreased oxidative stress and enhanced endothelial function (Feig *et al*., 2008; Stern *et al*., 2024). Febuxostat is primarily metabolized hepatically, it retains efficacy across stages of chronic kidney disease without necessitating formal dose adjustments; however, in patients with advanced renal failure and significant vascular damage, elevated rates of cardiovascular events have been documented in certain investigations (White *et al*., 2018), due to baseline XO activity and oxidative stress change, so decreasing physiological ROS signaling that required for endothelial homeostasis.

Hypertension and Endothelial Dysfunction

Uric acid plays a role in endothelial dysfunction, arterial stiffness, and elevated vascular resistance (Feig *et al*., 2008). Allopurinol has been shown to reduce blood pressure and enhance flow-mediated dilatation by lowering vascular XO-derived superoxide and retaining NO activity (Feig *et al*., 2008). Febuxostat, although efficient in reducing urate levels, exhibits variable endothelial advantages due to its primary hepatic action and insufficient suppression of vascular XO activity (George & Struthers, 2009).

Diabetes Mellitus and Metabolic Syndrome

Chronic inflammation and oxidative stress increase vascular damage in diabetes and metabolic disorders (Feig *et al*., 2008). Allopurinol enhances microvascular function, insulin sensitivity, and oxidative equilibrium in many experimental and clinical studies.

Febuxostat demonstrates significant urate-lowering efficacy; nevertheless, there is limited evidence on its metabolic advantages, and it may have a modest impact on hepatic lipid metabolism (George & Struthers, 2009).

Coronary Artery Disease (CAD) and Heart Failure (HF)

In coronary artery disease and heart failure, xanthine oxidase-derived reactive oxygen species contribute to myocardial dysfunction. Allopurinol boosts myocardial function, improves exercise tolerance, and decreases left ventricular hypertrophy, presumably by inhibition of myocardial xanthine oxidase and the decrease of reactive oxygen species (Feig *et al*., 2008). Febuxostat has yielded mixed results: the CARES study indicated an increase in cardiac mortality in patients with pre-existing cardiovascular disease (White *et al*., 2018). But the FAST study observed no additional risk in more stable and intensively followed individuals (Mackenzie *et al*., 2020).

Effect of Xanthine Oxidase Inhibitors in a Patient with Polypharmacy

Co-administration with Non-Steroidal Anti-Inflammatory Drugs

NSAIDs make vascular damage worse by changing the balance of oxidative and nitrosative stress in the endothelial tissue by cyclooxygenase inhibition-dependent and -independent processes (Mohammad *et al*., 2025a, 2025b). XO inhibition does not completely decrease NSAID-associated cardiovascular risk, especially in high-risk patients (Schmidt *et al*., 2018).

Co-administration with Diuretics

Loop diuretics and thiazides increase uric acid levels by reducing renal urate excretion. Diuretic-induced hyperuricemia correlates with an increase in gout attacks and endothelial damage (Feig *et al*., 2008). Allopurinol may enhance vascular function and reduce left ventricular mass in hypertensive individuals (Rekhraj *et al*., 2013). Concurrent thiazide medication may increase the risk of allopurinol hypersensitivity syndrome, especially in patients with chronic renal disease (Mach *et al*., 2019).

Co-administration with Statins

Statins decrease cardiovascular risk and are recommended for patients with gout (Mach *et al*., 2019). Febuxostat increases rosuvastatin exposure by inhibiting its BCRP-mediated efflux in the small intestine, while allopurinol has no interaction. Febuxostat may serve as a useful index inhibitor of BCRP in drug-drug interaction studies in humans. Moreover, concomitant use of febuxostat may increase the exposure to BCRP substrate drugs and, thus, the risk of dose-dependent adverse effects (Lehtisalo *et al*., 2020).

Conclusion

More and more data indicate that xanthine oxidase inhibitors' effects on the heart are not always the same. They are highly affected by dose, duration of treatment, sex-related pharmacokinetics, other diseases, and medicines taken at the same time. Allopurinol helps the heart, blood vessels, and myocardium by blocking xanthine oxidase and the antioxidant properties of its active metabolite, oxypurinol, especially for people with hypertension, chronic kidney impairment, coronary artery disease, and heart failure. Besides dropping urate, these benefits also include increased nitric oxide bioavailability, lower oxidative stress, and better myocardial energetics.

Febuxostat, on the other hand, has a more urate-lowering effect, which is helpful for people who can't handle allopurinol or who have a mild renal problem. However, research from high-risk groups, especially the CARES trial, shows that too much xanthine oxidase inhibition (febuxostat), changed redox signaling, poor purine–adenosine homeostasis, and possible mitochondrial and electrophysiological instability may all lead to higher cardiovascular and all-cause mortality in people who already have advanced cardiovascular disease and severe renal dysfunction. The FAST study indicates that these adverse effects of febuxostat did not occur in healthy groups. This ensures the idea that the cardiovascular risk related to febuxostat is specific to each patient's state and not a general drug effect.

Sex effect on xanthine oxidase activity, metabolism, and renal function. If patients have other diseases like diabetes, chronic kidney disease, or metabolic syndrome, it can also make oxidative stress and vascular risk worse. Also, polypharmacy in the elderly, especially NSAIDs, statins, and diuretics, can cause pharmacological interactions and increase the adverse effects of allopurinol and febuxostat.

The cardiovascular effect of allopurinol and febuxostat is determined not only by decreasing uric acid level but also by a complex interplay of redox biology, patient sex, comorbidities, and co-administered drugs. Further studies are needed to clarify the mechanism that links febuxostat to increased mortality in advanced CVD. Make randomized trials specifically targeting high-risk cardiovascular and CKD subgroups. Explore dose-response relationships beyond urate reduction, especially on vascular oxidative balance. More trials focusing on cardiovascular risk patients and renal problem subgroups, sex-difference outcomes, and mechanistic biomarkers (mitochondrial function, oxidative stress, and arrhythmia risk) are needed.

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