Gout, Xanthine Oxidase Inhibition, and Cardiovascular Outcomes

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Gout, a chronic rheumatologic illness characterized by hyperuricemia, arthritis, tophaceous deposits, and renal calculi, is associated with increased rates of cardiovascular and chronic kidney disease. Prospective observational studies have shown that the risk of cardiovascular mortality is higher in people with gout and coronary heart disease compared with those with coronary disease who do not have gout. Epidemiological associations among hyperuricemia, gout, and risk factors for cardiovascular disease are robust, but whether hyperuricemia and gout are independent risk factors for coronary disease remains controversial. Urate has a complex relationship to oxidative stress, possessing both scavenging properties as well as oxidizing and radical-forming properties. These data have led to small, interventional studies that have shown that urate-lowering agents such as allopurinol may improve a number of cardiovascular conditions, including heart failure, hypertension, and chronic kidney disease.

The xanthine oxidase inhibitors are the mainstay of therapy for reducing serum urate levels in patients with gout. The xanthine oxidase inhibitor allopurinol was approved in 1966, and febuxostat, a nonpurine inhibitor of xanthine oxidase, was approved for the management of hyperuricemia in patients with gout in 2009. Allopurinol and its metabolites are structural analogues of both purines and pyrimidine compounds and thus can affect enzymes in both metabolic pathways, whereas febuxostat is a nonpurine inhibitor of only xanthine oxidase. In clinical practice, the pharmacological advantages of febuxostat over the commonly used doses of allopurinol have included greater serum urate-lowering efficacy, fewer reported severe hypersensitivity reactions, and no requirement for dose adjustment in patients with moderate renal impairment, a common comorbidity in gout.

During the development of febuxostat, this drug was compared to placebo and allopurinol in clinical trials involving >5000 patients with gout. These studies showed a small imbalance in the rates of major cardiovascular events occurring at 0.74 per 100 patient-years with febuxostat versus 0.60 per 100 patient-years with allopurinol. The US Food and Drug Administration approved febuxostat with the contingency that a large cardiovascular safety outcome study be performed to determine its cardiovascular profile compared to allopurinol in patients with gout. This study, the CARES trial (Cardiovascular Safety of Febuxostat and Allopurinol in Patients With Gout and Cardiovascular Morbidities), was conducted between 2010 and 2017 to determine whether febuxostat was noninferior to allopurinol on major cardiovascular events in patients with gout and cardiovascular disease. The study population for the CARES trial was limited to patients with gout who had prior evidence of cardiovascular disease, a strategy previously used in the US Food and Drug Administration-mandated cardiovascular safety studies in diabetes.

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mellitus to increase major adverse cardiovascular event rates and improve the efficiency of these trials.

The CARES trial demonstrated that treatment with febuxostat resulted in overall rates of major cardiovascular events (a composite of nonfatal myocardial infarction, nonfatal stroke, urgent revascularization for unstable angina, and death because of cardiovascular causes) comparable to those of allopurinol in patients with high cardiovascular risk gout, but cardiovascular death and deaths from any cause were higher on febuxostat. It is important to note that these findings were similar for the modified intention-to-treat analysis and a prespecified analysis of patients on drug in addition to 30 days after drug discontinuation. Also, adjudicated nonfatal events that included myocardial infarction, coronary revascularization, arrhythmias, and hospitalization for heart failure were comparable on febuxostat and allopurinol. The only heterogeneity displayed in analyses of cardiovascular mortality occurred in 2 subgroups: those with or without concomitant administration of low-dose aspirin and the use or nonuse of nonsteroidal anti-inflammatory drugs. These drugs may be associated with more frequent gout flares, which in turn could theoretically mediate proinflammatory effects that lead to increases in cardiovascular events. However, there was not a marked difference in serum urate reduction between therapies, and gout flare rates were nearly identical for the 2 drugs. The unexpected finding of an increase in cardiovascular mortality with no differences in any nonfatal cardiovascular event in CARES requires more research in the assessment of the cardiovascular safety of the xanthine oxidase inhibitors.

In this issue of Circulation, Zhang and colleagues have assessed the cardiovascular risk of febuxostat versus allopurinol in a patient population with gout derived from a US Medicare cohort. This is a high-quality, large observational study with >25 000 febuxostat initiators and >75 000 allopurinol initiators. The investigators used extensive propensity score matching to lessen confounding. The primary end point of interest was a composite of nonfatal myocardial infarction or stroke. Because of the nature of study, death because of cardiovascular causes was not obtainable, but all-cause death could be calculated. The authors also performed subgroup analyses according to a baseline history of cardiovascular disease. Patients were identified as high cardiovascular risk if the baseline criteria were similar to those of the CARES trial. The authors report a surprisingly low incidence of cardiovascular disease in the overall cohort—12%—yet 36% had a history of congestive heart failure. Hence, this population, with a median age of 76 years and with more than one-third of the population with heart failure, a well-known harbinger of mortality, was clearly at high risk for major cardiovascular events. The authors found no differences in the incidence rates for any of the nonfatal or fatal events between febuxostat and allopurinol, regardless of the presence or absence of cardiovascular disease before initiating the xanthine oxidase inhibitor. There was no heterogeneity of this neutral finding by subgroup analyses. Although the authors suggest that mortality for febuxostat versus allopurinol may have increased with longer exposure (>3 years), those findings are neither significant nor robust.

The data from the present observational study and those of CARES demonstrate similar results for the nonfatal events and disparate results for all-cause mortality. It is important to note that these are 2 very different types of studies. CARES was a randomized clinical trial with prospectively adjudicated cardiovascular end points by an expert committee blinded to treatment assignment. This allowed the causes of cardiovascular mortality to be defined, the most common of which was sudden cardiac death. The study by Zhang et al is a retrospective observational study in which events are identified through claims data and involved a population more than a decade older than the CARES population but with otherwise lower cardiovascular disease burden. In addition, the median observation period for this observational study (1.1–1.2 years) is about half that of the CARES trial.

Neither the observational study by Zhang and colleagues nor the CARES trial had a nonxanthine oxidase inhibitor control group, so neither study defined an increase in mortality risk because of febuxostat per se. Rather, the CARES data demonstrated a relative increase in mortality on febuxostat relative to allopurinol. A recent analysis by the same study group as in the present article reported a lower risk of myocardial infarction and stroke on the uricosuric agent probenicid compared with initiators of allopurinol in >39 000 Medicare beneficiaries with gout. Based on this result, the authors suggest that probenecid has the capacity to inhibit pannexin 1 channels and reduce the production of the interleukin-8, a cytokine known to increase vascular harm. More research is needed in this area as well to determine whether other urate transporter 1 inhibitors such as lesinurad lead to improved cardiovascular outcomes.

The mechanism underlying the mortality risk on febuxostat observed in the CARES trial is not known. Preclinical cardiovascular studies of febuxostat showed no propensity for the drug to alter vascular cell ion channels or affect cardiac function or metabolism. Adjudicated atrial and ventricular arrhythmias in the CARES trial were comparable on febuxostat and allopurinol, and a thorough corrected QT interval study with high doses of febuxostat showed no differences from placebo. Although investigators have considered oxidative stress associated with gout flares to be an attractive hypothesis for increases in cardiovascular mortality, an increase in acute coronary syndromes...
should also have accompanied this observation, a finding clearly not observed in the CARES trial or in the observational study by Zhang and colleagues. Some observational evaluations of the xanthine oxidase inhibitors have even suggested beneficial cardiovascular outcomes in patients with gout and cardiorenal comorbidities. Whether urate lowering through xanthine oxidase inhibition or urate transporter-1 blockers leads to cardiovascular benefit is still an open question for patients with gout because no study has had a large enough placebo treatment arm. Another highly relevant clinical question remaining is whether the mortality finding observed in the CARES trial will be reproduced in a moderate cardiovascular risk population with gout, such as the ongoing FAST (Febuxostat versus Allopurinol Streamlined Trial).

**REFERENCES**


**ARTICLE INFORMATION**

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