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Implications of the cardiovascular safety of febuxostat and allopurinol in patients with gout and cardiovascular morbidities (CARES) trial and associated FDA public safety alert

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Abstract

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Recently, the FDA issued a public safety alert, responding to results of the now-published Cardiovascular Safety of Febuxostat and Allopurinol in Patients With Gout and Cardiovascular Morbidities (CARES) trial. CARES showed no significant difference between allopurinol and febuxostat in the primary composite endpoint of cardiovascular (CV) events in subjects with gout and established cardiovascular comorbidities at baseline. However, there was significantly increased risk of cardiac and all-cause mortality with febuxostat. Urate lowering therapy (ULT) is central to long-term management of gout, and xanthine oxidoreductase inhibitor (XOI) therapy is the consensus first line approach. Allopurinol is generally the first XOI employed, but febuxostat is an effective XOI option, and is commonly used when allopurinol is not tolerated. These data are further relevant since CV co-morbidities are common in gout. Here, we examine why the CARES trial was done, and discuss other, ongoing comparative studies of febuxostat and allopurinol whose results are awaited. We assess strengths and limitations of CARES, and appraise robustness and biologic plausibility of the results. CARES does not prove that febuxostat raises CV mortality risk, but suggests greater risk with febuxostat than allopurinol. CARES results do not support first line use of febuxostat ULT, and raise questions on febuxostat placement at various pharmacologic ULT decision tree branches. Alternatives to febuxostat that are frequently effective include allopurinol dose-escalation, and uricosuric therapy alone or combined with allopurinol. The FDA safety alert highlights the need for shared ULT medical decision with gout patients, including discussion of CV safety of febuxostat.

Keywords

xanthine oxidase inhibitor; mortality; myocardial infarction; probenecid; uricosuric

Introduction

In November 2017, U.S. FDA issued a public safety alert concerning febuxostat for management of hyperuricemia in gout, citing a signal for increased risk of CV- and all-cause mortality (1). This notice was in response to preliminary results of the CARES clinical trial. Full CARES results were published in *NEJM* in March, 2018 (2).

Urate lowering therapy (ULT) is central to long-term management of gout (3–6). Use of an inhibitor of the dual enzyme xanthine oxidoreductase (commonly known as xanthine oxidase) is the consensus first line therapeutic strategy for ULT (3–6). In clinical practice, allopurinol is generally employed as the first line XOI in gout. The XOI febuxostat is commonly employed in ULT when allopurinol is not tolerated, or when the maximum allopurinol dose chosen has not achieved urate lowering to the chosen target level. Since risk factors and manifestations of CV disease are particularly common in gout (7), questions raised by the CARES trial findings are fundamentally important to clinical practice. From our perspective as rheumatologist gout researchers, we recap the original purpose of the CARES trial, evaluate the study results, and cite and discuss other relevant recent and ongoing trials. We also examine potential ramifications of the CARES trial results for clinical practice.

Why was the CARES trial done?

The febuxostat CV safety issue originated from concerns about potential CV signals in APEX (Febuxostat, Allopurinol and Placebo-Controlled Study in Gout Subjects)(8), FACT (Febuxostat versus Allopurinol Controlled Trial)(9), a Phase II trial (10), and two long-term extension studies (11,12). Specifically, there was numerical imbalance in rate of CV events, with febuxostat higher in comparison to allopurinol or placebo. However, definitive conclusions could not be drawn from these earlier trials. The number of events were too small to make meaningful inferences, no dose-response was noted, the long-term extension studies had a limited number of participants on active control allopurinol, and Antiplatelet Trialists Collaboration (APTC) events had been evaluated in a post hoc manner (13).

In a subsequent 6-month randomized controlled trial (RCT) of febuxostat compared to allopurinol in 2269 participants (termed CONFIRMS), CV adverse events were prospectively defined with a 3-person committee that adjudicated the APTC events (14). At baseline in CONFIRMS, comorbid conditions were common, including mild-moderate renal impairment in 65%, history of diabetes in 13.8%, hyperlipidemia in 42%, and hypertension in 53%. Adjudicated cardiovascular event rates were 0% for febuxostat 40 mg, 0.4% for febuxostat 80 mg, and 0.4% for allopurinol (P=0.41 for allopurinol vs. febuxostat)(14). No CV deaths occurred in either of the febuxostat groups, with 2 CV deaths in the allopurinol group.

Subsequent to CONFIRMS, febuxostat was approved in 2009 by the FDA for management of hyperuricemia in gout, but FDA required the drug manufacturer to perform a post-marketing RCT of adequate size and duration to compare febuxostat and allopurinol for risk of serious adverse CV events. Similarly, the European Medicines Agency (EMA) requested a post-licensing CV safety study comparing febuxostat to allopurinol in gout, termed FAST: febuxostat versus allopurinol streamlined trial. This RCT is ongoing in the UK and Denmark (15). An ongoing RCT in Japan is distinct, in large part, by studying patients with asymptomatic hyperuricemia (FREED: febuxostat for cerebral and cardio-renovascular events prevention study)(16)(Table 1).

What did CARES show?

CARES was a very large, multicenter, double-blind, non-inferiority RCT of people with gout and established CV disease, comparing febuxostat to allopurinol (2). The primary endpoint was a composite of major adverse CV events (MACE): CV death, nonfatal MI, nonfatal stroke, and unstable angina with urgent revascularization (Table 1). Investigators determined sample size based on a non-inferiority upper margin of 1.3, with the plan being to accrue 624 MACEs (17). CARES subjects were randomized 1:1 to receive febuxostat 40 mg/day or allopurinol stratified on baseline renal function. Febuxostat dose was increased to 80 mg/day if serum urate concentration was above 6 mg/dL at week 2 study visit. Starting dose of allopurinol was dependent on renal function, and allopurinol dose escalation, based upon reaching target serum urate <6 mg/dL was implemented in 100 mg/day increments monthly over the first 10 weeks to maximum dose of 600 mg daily (400 mg daily in those with estimated creatinine clearance 30–<60ml/min). Gout flare prophylaxis was provided for

the first 6 months, preferentially with colchicine. Naproxen, other NSAID, or prednisone use were permissible alternatives.

CARES followed 6190 randomized participants, documenting a total of 656 primary endpoints (2). Median duration of febuxostat and allopurinol exposure were comparable (728 vs. 719 days, respectively), with follow-up duration also comparable (968 vs. 942 days, respectively). The investigators reported no increased risk related to febuxostat compared with allopurinol for their primary endpoint (hazard ratio (HR) 1.03 [95% CI 0.87–1.23]). However, pre-specified secondary analyses revealed increased risk of CV death (HR, 1.34; 95% CI, 1.03–1.73) and death from any cause (HR, 1.22; 95% CI, 1.01–1.47), with all-cause mortality mainly due to CV mortality (Table 1). Sudden cardiac death, the most common cause of CV death in both groups, occurred in 2.7% on febuxostat and 1.8% on allopurinol. The risk of CV death that occurred during treatment or within 30 days after discontinuation of treatment was higher among those on febuxostat than on allopurinol.

Gout flare rates over the study period were similar in the two groups in CARES (2). Although more participants in the febuxostat group had serum urate <5mg/dL, the rates of participants achieving the serum urate treatment target of <6mg/dL was similar between the two groups at all time points after two weeks. Below, we summarize key aspects of CARES, and uncertainties from the trial results (Table 2).

Strengths of the CARES design

CARES was double-blinded and randomized, with a state-of-the-art adjudication process for relevant CV disease endpoints. As such, it was designed to be free from confounding, performance bias, and detection bias, which are strengths compared to multiple prior observational studies of XOIs and CV disease in gout (18–22). CARES studied a relevant study population (i.e., people with gout and established CV disease), and was able to observe a sufficient number of relevant CV and mortality events during the study period. Moreover, the direct comparison of allopurinol and febuxostat dose titration, including allopurinol dosing to above 300 mg/day even in those with moderate renal impairment, and use of initial gout flare prophylaxis, and preferably with colchicine rather than NSAIDs, to diminish systemic inflammation due to gout flares, were noteworthy in CARES (2). NSAIDs may have substantial CV event risk, particularly in people with established CV disease (23). Moreover, in pre-specified subgroup analyses, NSAID use and low dose aspirin non-use during the study were associated with significantly elevated risk ratio for CV mortality in CARES (2).

What uncertainties arise from the results of CARES ?

Impact of high discontinuation rate and loss to follow-up

In the CARES trial, 57% of participants discontinued treatment prematurely and 45% were lost to follow-up regardless of their treatment status, though the rates were similar between the 2 groups. These findings are applicable to clinical practice, since rates of long-term continuation of ULT are low (24). However, from an experimental perspective, premature discontinuation of treatment assignment would generally bias safety signals towards the null.

This could in turn threaten the validity of the CARES trial primary endpoint result on risk of MACE composite endpoints. Furthermore, although loss to follow-up rates were similar between the two groups and the measured characteristics did not appear to be associated with loss to follow-up, it is conceivable that participants who developed the endpoint events were more often lost to follow-up in one group than the other. Additional ascertainment of the mortality status suggests this was the case. When the post-hoc ascertainment efforts added 199 deaths to the original 442 deaths (45%), 21 more deaths were added to allopurinol than febuxostat (110 vs. 89), nullifying the hazard ratio (i.e., 1.09 [95% CI; 0.94 to 1.28], as opposed to the original 1.22 [1.01 to 1.47])(2). These concerns appear to call for assessments of the potential impact of the large loss to follow-up rate, to quantify the level of threat to the validity of primary as well as secondary endpoint results.

Lack of data on temporal course and severity of gout flares

In theory, the intense inflammation pathophysiology of gout flares, with potential for associated pro-thrombotic status, and acute pain-related stress responses could impact on CV mortality. However, we do not know if there were undefined differences in temporal course and severity of gout flares between the febuxostat and allopurinol groups in the CARES trial.

Questions regarding biologic plausibility of the CARES results

Xanthine oxidoreductase and excess soluble urate, the joint targets of XOI treatment, can exert noxious effects in the vasculature and other tissues (25–28). Hence, CARES leaves us with more questions than answers with respect to XOI effects on CV mortality. Xanthine oxidoreductase has wide tissue expression, can be released into the circulation, and binds the surface of endothelial cells (25). XOI drugs directly reduce superoxide generation by the oxidase state of the enzyme, and limit oxidative stress and alter nitric oxide-redox balance, endothelial cell and mononuclear phagocyte activation, and inflammation *in vitro* and *in vivo* (25–28). Furthermore, XOI treatment inhibits experimental atherogenesis *in vivo* in mice (27).

With respect to the effects of pharmacologic serum urate-lowering, a large body of *in vitro* and *in vivo* evidence supports pro-inflammatory effects, and toxic effects in the vasculature, of high levels of soluble urate (28). These collective findings are buttressed by many human observational studies that have reported association between elevated serum urate levels and CV disease event risk, all-cause mortality, and CHF (18–22). On the other hand, Mendelian randomization analysis, though possessing a variety of limitations, has not supported the concept that urate-lowering would lower the risk of CV disease (29). To this date, human treatment studies of hyperuricemia, including use of XOIs, and assessment of CV disease, are inconclusive (22,23,28).

It remains possible that allopurinol may have beneficial effects on CV mortality, and also that the higher observed CV mortality rates in the febuxostat group in CARES could have been similar to background rates. However, this hypothesis has not been directly tested in a RCT, and would be ethically challenging to address in a long-term RCT of patients with gout. We also note that in a biologic sense, the differences in the findings between fatal and

non-fatal CV endpoints in the CARES trial (2) were unexpected and difficult to explain. For example, only 37 of the 234 CV deaths, and 63 of the 442 all-cause deaths occurred while on study drug, meaning that ~85% of these deaths occurred off study drugs (2). In additional analyses, the investigators reported that 103 CV deaths and 164 all-cause deaths occurred while on treatment or within 30 days after discontinuation of treatment. It is unclear why ~23–28% of CV-related and all-cause deaths occurred within 30 days after treatment discontinuation in CARES.

Subtle differences in allopurinol and febuxostat need to be considered when positing biologic explanations for differing CV mortality results in CARES. In this regard, febuxostat is a selective XOI, whereas the purine-like backbone of allopurinol and its active metabolite oxypurinol allow them to serve as substrates for several enzymes involved in purine and pyrimidine metabolism, leading to generation of a variety of ribonucleotides (30). It is possible that biologic effects of such ribonucleotides, and other intracellular actions of allopurinol and oxypurinol on purine and pyrimidine metabolism, could account for effects of allopurinol on CV disease distinct from those of febuxostat in CARES (30), and possibly other RCTs (18).

What would the differences in mortality be for either XOI drug compared to a non-XOI ULT control group or to placebo?

Although the CARES trial addressed comparative safety between 2 XOIs, the results lead to new questions on how the mortality signal with either XOI agent would have compared to no ULT use (e.g., placebo) or to use of a non-XOI, urate-lowering agent such as a uricosuric. From a clinical trials design perspective, lack of a placebo was entirely appropriate, noting that allopurinol is the most widely used ULT agent, and a placebo arm would have been considered unethical for long-term study in gout. However, the lack of placebo limits our ability to determine whether the mortality results of the CARES study are due to beneficial effects of allopurinol or deleterious effects of febuxostat. With respect to uricosuric ULT, a large observational study using Medicare data compared CV risk for allopurinol and probenecid (7). Those with gout who initiated probenecid had lower risk of hospitalization for MI or stroke compared with allopurinol initiators (HR 0.80, 95% CI 0.69–0.93), with consistent results regardless of baseline CKD or CV status (7). However, without performance of a prospective RCT with similar design features to CARES, including assessment of serum urate lowering and gout flares, the Medicare study results cannot be compared to CARES.

Where do we go from here in current clinical practice?

Despite aforementioned uncertainties related to the CARES study, the FDA public safety alert appears justified, and is likely to have substantial impact on clinical practice. Specifically, clinicians and patients must take notice of the new, major findings of the CARES trial of increased risk of CV mortality by 34% and all-cause mortality by 22% with febuxostat compared with allopurinol. If we take at face value the point estimates reported in the CARES trial, febuxostat, compared to allopurinol, is calculated to have a number needed

to harm (NNH) of 91 for CV deaths and 71 for all-cause deaths among patients with gout and established CVD over 2.7 years.

The ongoing European and Japanese febuxostat trials with CV endpoints may provide more clarity (Table 1), which may lead regulatory agencies to take more definitive action than the current febuxostat warning about CV risk. Results of a large-scale trial (the All Heart Study) also are awaited to assess potential allopurinol CV endpoint and mortality benefits in subjects without gout. In that study, allopurinol 600 mg/day is added to therapeutic regimens of patients with ischemic heart disease (31). The ongoing VA STOP GOUT comparative effectiveness RCT of allopurinol vs. febuxostat does not appear likely to meaningfully impact interpretation of the CARES results, since gout flare rate is the primary endpoint of VA STOP GOUT, and the study is not specifically powered for CV event risk (32).

Ways in which we believe the new CARES results and FDA alert impact on clinical practice are summarized in Table 3. Patients are likely to ask the practicing clinician questions, including: (i) should I continue my febuxostat?; (ii) does taking febuxostat increase my risk of mycocardial infarction?; what are the alternatives to febuxostat? In this era of shared medical decision making, it is advisable to discuss with patients the comparative CV mortality risks of allopurinol and febuxostat, and other safety risks of allopurinol, febuxostat, and uricosurics, such as risks of side effects from severe drug hypersensitivity and drug-drug interactions, and renal adverse events including urolithiasis. The decisions made are based upon the best available information and the personal values and preferences of each patient.

Clearly, both clinicians and patients should bear in mind that CARES does not prove that taking febuxostat raises CV mortality risk in gout. Instead, the data suggest greater mortality risk with febuxostat than allopurinol in patients with pre-existing CV disease. In this light, CARES results do not support first line use of febuxostat in ULT. The results also raise new questions on febuxostat placement at various pharmacologic ULT decision tree branches, since there are several efficacious first-line and second-line options other than febuxostat (Table 3). For those clinical situations where febuxostat may be the most effective, or in a few scenarios, the only effective oral ULT option appropriate to use, engaging in shared medical decision making helps patients make informed decisions about the risks and benefits of initiating and maintaining different therapy options.

All four recent major rheumatology society gout management guidelines have recommended febuxostat as a ULT option (3–6). In our opinion, systematic updates of gout ULT management guidelines by relevant professional organizations, employing appropriate committee processes and methodologies, are now needed to help guide decision-making on febuxostat and alternatives in oral pharmacologic ULT. This need arises from more than the new CARES study data and associated FDA safety alert. First, there are new data, from other RCTs, that support efficacy of treat to urate target pharmacologic ULT strategies for clinically and structurally meaningful endpoints in gout (33,34). Second, we note that the efficacy data for serum urate lowering, and the gout flares endpoints, were close between dose-titrated allopurinol and febuxostat in CARES (2). Third, more evidence now exists to support allopurinol as a relatively safe urate-lowering drug when risk factors for allopurinol

hypersensitivity syndrome are taken into appropriate consideration (35). Fourth, there is increased evidence of clinical efficacy and safety, of allopurinol dose-escalation in gout, commonly reaching doses above 300 mg/day, and operable in the patient subset with stage 3 chronic kidney disease (31, 36–38). Fifth, allopurinol dose-escalation was effective in the majority of patients with gout in a recent RCT (34). Last, uricosuric monotherapy, and combinations of allopurinol with certain uricosurics (eg, probenecid, lesinurad), also are effective in many patients (3–6,39,40).

Conclusion

The newly published signal for increased CV- and all-cause mortality with febuxostat compared with allopurinol in patients with gout in CARES, and the associated FDA public safety alert, arose from a large, and well-designed RCT powered to study CV events. There remain several uncertainties about the CARES trial findings. We await results of further ongoing RCTs, and there is the potential for further regulatory action. In the interim, CARES does not support first line use of febuxostat in ULT, and raises new questions on where febuxostat placement should be at different branches in the oral pharmacologic ULT decision tree for gout. New evidence has emerged in recent years for efficacy of alternative options in many patients with gout, such as allopurinol dose escalation and combination of allopurinol with uricosuric therapy. Moreover, uricosuric therapy remains a viable ULT option in many. Timely updates are now needed for gout ULT management guidelines by relevant professional organizations, using appropriate committee processes and methodologies.

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Table 1

Randomized Controlled Trials of Febuxostat for Cardiovascular Endpoints (Completed and Ongoing)

STUDY	STUDY POPULATION	N	COMPARISON	DURATION	RESULTS/COMMENTS
CARES Trial NEJM 2018 (Double-Blinded RCT)	Adult patients with **gout** and history of major CVD Mean age: 64.5 years old Men: 84.0% BMI ≥30: 66.0% Tophi: 21.3% Mean SUA: 8.72 mg/dL	6190	1. Febuxostat 40mg or 80mg depending on SUA monitoring 2. Allopurinol 200mg to 600mg depending on renal function and SUA **Primary endpoint:** MACE composite endpoint **Secondary endpoint:** **1** APTC event • CV death • Non-fatal MI • Non-fatal stroke **2** All-cause mortality **3** Serum Uric Acid (SUA) **4** Gout flares	Median duration of follow-up = 32 months (Up to 85 months)	**Primary Endpoint**: No ↑ risk on the MACE composite endpoint (hazard ratio, 1.03; upper limit of the one-sided 98.5% confidence interval [CI], 1.23; P = 0.002 for noninferiority). **Secondary Endpoints**: ↑ risk in CV mortality and all-cause mortality (hazard ratio for cardiovascular death, 1.34 [95% CI, 1.03 to 1.73]; hazard ratio for death from any cause, 1.22 [95% CI, 1.01 to 1.47]). **SUA <6 mg/dL at month 72**: Febuxostat: 74.5% Allopurinol 75.0% **Flare rates**: ≤1 year: Febuxostat: 1.33 flares/PY Allopurinol 1.20 flares/PY >1 year: Febuxostat: 0.35 flares/PY Allopurinol: 0.34 flares/PY
FAST Trial (PROBE design RCT)	Patients > 60 years, prescribed allopurinol for **symptomatic hyperuricaemia** and have at least one additional cardiovascular risk factor.	~6,000	1. Febuxostat 80mg or 120mg depending on SUA monitoring 2. Allopurinol 100mg to 900mg depending on SUA monitoring **Primary endpoint**: APTC composite endpoint **Secondary endpoints**: **1** - CV death • Non-fatal MI • Non-fatal stroke • Other CVD endpoints **2** All-cause mortality **Exploratory efficacy endpoints**: The proportion of patients whose urate level is ≥6.0, <6.0 and <5.0 mg/dL after 1, 2 and 3 years of treatment.	Mean duration of follow-up =3 years	Completed recruitments
FREED Trial (PROBE design RCT)	Patients > 60 years, with **asymptomatic hyperuricemia** (ie, elevated SUA without gout) and have at least one additional cardiovascular risk factor	1,000	1. Febuxostat 40 mg/day (target dose, after dose escalation from 10 mg/day) 2. Consider allopurinol 100 mg/day if SUA is elevated **Primary endpoint**: Composite endpoint consisting of fatal and non-fatal cerebral or cardiorenal vascular events plus all deaths other than cerebral or cardiorenal vascular Disease **Secondary endpoints**:	Planned follow-up =3 years	Patient enrolment was started in November 2013 and was completed in October 2014.

STUDY	STUDY POPULATION	N	COMPARISON	DURATION	RESULTS/COMMENTS
			Individual endpoint of cerebral, cardiovascular, and renal vascular events, and subgroup analysis by SUA levels and history of CVD		

Abbreviations: CVD, cardiovascular disease; PY, patient year, SUA, serum uric acid

Table 2

Our assessment of CARES strengths, and uncertainties arising from the results

Strengths of the study
• Large, double-blinded, and randomized study of relevant population (i.e., patients with gout and established CV disease), powered for cardiovascular events • State-of-the-art adjudication process for relevant CV disease endpoints • Direct comparison of allopurinol and febuxostat dose titration, including allopurinol dosing above 300 mg/day • Use of initial gout flare prophylaxis (preferably with colchicine)
Uncertainties arising from the results
• Particularly high dropout rate of ~50% on average (45–57%) in the treatment groups • Inconsistent findings between fatal and non-fatal CV endpoints • ~85% of deaths occurred off study drugs • Without a placebo comparator, the study design does not answer the question whether allopurinol or febuxostat independently carry an increased risk of CV disease and mortality • Questions about biologic plausibility, due to anti-inflammatory and anti-atherogenic effects of XOIs, and comparable primary mechanism of action of allopurinol and febuxostat on xanthine oxidoreductase • Lack of data on temporal course and severity of gout flares, which can exert systemic effects potentially pertinent to CV mortality

Table 3

Implications for clinical practice of the new CARES trial results and FDA public alert on febuxostat safety

- Informative discussions with patients on febuxostat CV mortality risk, when initiating and maintaining the drug, are an important part of shared decision making
- The CARES CV mortality signal does not support first line use of febuxostat in ULT
- CARES raises new questions on where febuxostat should be placed at different branches in the oral pharmacologic ULT decision tree, when compared to alternatives that work in many gout patients, as supported by:
  - Evidence for efficacy of allopurinol dose-escalation in the majority of patients with gout
  - Evidence for efficacy of uricosuric monotherapy, and of combinations of allopurinol with certain uricosurics
  - Specific recommendations in the 2012 ACR, 2016 EULAR, and 2017 BSR gout management guidelines
- ULT treatment algorithms in gout now need re-consideration by relevant professional organizations, using appropriate committee processes and methodologies

Abbreviations: ACR (American College of Rheumatology); EULAR (European League Against Rheumatism); BSR (British Society of Rheumatology)