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Reassessing the cardiovascular safety of febuxostat: implications of the FAST study

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Short Summary for Pubmed

The US FDA-mandated CARES trial, published in 2018, reported increased all-cause and cardiovascular (CV) death in participants randomized to febuxostat compared with allopurinol. The subsequent FDA Drug Safety Communication and Boxed Warning resulted in substantial reductions in febuxostat use in the US. The EMA-mandated Febuxostat versus Allopurinol Streamlined Trial (FAST), published in 2020, found no increased risk of composite CV events, CV mortality or all-cause mortality for febuxostat, compared with allopurinol. This commentary discusses implications of these new findings for gout management.

Keywords: gout, febuxostat, allopurinol, cardiovascular disease, mortality

The US Federal Drug Administration (FDA)-mandated Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities trial (CARES), published in 2018, reported increased all-cause and cardiovascular (CV) death in participants randomized to febuxostat compared with allopurinol (1). The outcome of this trial and the subsequent FDA Drug Safety Communication and Boxed Warning (2) resulted in substantial reductions in febuxostat use in the US (3). The European Medicines Agency (EMA)-mandated Febuxostat versus Allopurinol Streamlined Trial (FAST), published in 2020, found no increased risk of composite CV events, CV mortality or all-cause mortality for febuxostat, compared with allopurinol (4). We discuss implications of these new findings for gout management.

CARES findings

As described in our previous commentary (5), CARES was a multicentre, double-blind, non-inferiority CV outcomes trial of 6190 patients with gout and established CVD, with median 32 months follow-up (**Table 1**) (1). Though CARES was a large clinical trial, there were important limitations including very high rates of study medication discontinuation (>50% of participants), large amounts of missing data (45% did not complete all trial visits), and concerns about incomplete capture of CV and mortality events. Moreover, the vast majority of mortality events in CARES (~85%) occurred when participants were not taking urate lowering therapy (ULT). Hence, results of the EMA-mandated Febuxostat versus Allopurinol Streamlined Trial (FAST) study were widely anticipated.

The FAST study

FAST was a prospective, randomised, open-label, blinded-endpoint, non-inferiority, CV outcomes trial of 6,128 participants with gout and at least one additional CV risk factor, who were already receiving allopurinol (**Table 1**) (4). Following a run-in period in which allopurinol doses were optimized to achieve a serum urate <6mg/dL, participants were randomized to resume allopurinol at the optimized dose or commence febuxostat 80mg/day (increasing to 120mg daily if required to achieve serum urate<6mg/dl) after a washout period of 7-21 days. During the median follow-up of approximately 43 months, the primary (on-treatment) analysis of major adverse cardiovascular events (MACE) (**Table 1**) found that febuxostat was non-inferior to allopurinol with an adjusted hazard ratio (HR) 0.85 (95% CI, 0.70–1.03). In the febuxostat group 3.8% of participants died (of any cause), compared with 5.7% in the allopurinol group (HR 0.75; 95% CI, 0.59–0.95).

Febuxostat (median dose 80mg/day) led to lower serum urate levels than allopurinol (median dose 300mg/day) throughout study follow-up (mean 3.6 vs. 5.0 mg/dL, respectively). FAST was an open-label trial with endpoints assessed in a blinded manner by an independent clinical events classification committee.

FAST participant retention was excellent (94%). However, there was differential withdrawal of ULT (32.4% febuxostat group vs. 16.5% allopurinol group) during the first year, and more participants in the febuxostat group (71.4%) received colchicine as gout flare prophylaxis than in the allopurinol group (52.6%). The fact that participants had previously been receiving allopurinol (for a median duration of 6 years), and had achieved the target urate level of <6mg/dL by the time of randomization, likely contributed to higher intolerance or discontinuation of febuxostat in this open-label study. Additional intention to treat (ITT) analyses, which kept the original trial assignment until the end of the follow-up without differential loss, had consistent results with the primary findings (HR for MACE 0.89 [95% CI, 0.75 to 1.06] and HR for all-cause death 0.84 [95% CI, 0.71 to 1.01]), which support the trial's internal validity. Similarly, unblinded switching to febuxostat, which was considered more potent than allopurinol, could have contributed to more prescriptions for colchicine gout flare prophylaxis in the febuxostat arm after the post-randomization washout period. Given the CV protective effect of low-dose colchicine (6, 7), these participants could have enjoyed the CV benefits, at least while exposed to colchicine. Nevertheless, subgroup analyses of participants not exposed to colchicine for gout flare prophylaxis showed consistent findings (HR 0.84 in on-treatment analysis and 0.82 in ITT analysis) suggesting that colchicine was probably not a significant factor in the conclusion.

FAST recruitment was mainly in primary care settings, reflecting the clinical setting in which most gout is managed. As such, the study population (33% with CVD) would be broadly applicable to the gout population at-large. FAST excluded people with MI or stroke in the preceding six months, or with severe heart failure or chronic kidney disease, whereas CARES excluded MI or stroke only if within 60 days prior to screening, and all CARES participants were required have a history of major CVD. CARES also enrolled a higher proportion with tophaceous gout (21% vs. 10%), indicative of more severe disease. Considering the trial design, FAST's findings should be most generalizable to febuxostat use after allopurinol use. However, if the CV

risk is not affected by (pre-trial) allopurinol use among people with gout (thus, not causing selection bias such as depletion of susceptibles), generalizability of FAST's CV outcomes would also be analogous to that of a trial without the universal pre-trial exposure to allopurinol (e.g. CARES). To date, there is no high-level evidence for the mortality or CV impacts of allopurinol, leaving unclear the inference of the generalizability of FAST in relation to trials without a lead-in exposure to allopurinol. Overall rates of serious adverse events were similar between groups, and there were fewer neoplasms, including malignant neoplasms, in the febuxostat group in FAST. Nevertheless, we note that any adverse events and tolerability associated with the initiation of allopurinol would have been selected out before the FAST trial, while febuxostat was an incident exposure, thus not benefiting from such a selection process.

Remaining uncertainties after the FAST trial

Below we discuss some uncertainties remaining after FAST; some are more readily addressable than others.

1. The absence of a placebo arm in FAST or CARES makes it unclear whether allopurinol or febuxostat has any impact on CV events compared to no ULT use in people with gout. However, a placebo would be ethically challenging given the indications for ULT in these trial participants with gout (8).
2. While the subgroup analysis among those not exposed to colchicine prophylaxis was consistent with the main findings, formal mediation analysis of this post randomization exposure to colchicine would be valuable in this at-risk gout population.
3. A formal time-varying analysis would have been helpful to assess potential reasons for ULT discontinuation beyond postulating simple reluctance and resistance to switching to a new drug (febuxostat) from an effective drug.
4. There was a lower risk of the primary CV endpoint for febuxostat (adjusted HR 0.66 [95% CI, 0.51–0.86]) in the subgroup with baseline serum urate <5mg/dL, but no such difference among those with baseline serum urate ≥5mg/dL. Clarifying associations between serum urate levels and CV risk in FAST would be valuable.
5. Additional data on requirements for ULT, particularly after discontinuation of febuxostat, would be helpful, as findings of the ITT analysis could potentially be impacted if participants

started the other ULT agent (including restarting allopurinol after stopping febuxostat) during the trial follow-up.

6. The potential role of gout flares in CV risk remains unclear. Neither CARES nor FAST provided characterization of flare burden (severity, duration, frequency) that might mediate CV events.

Implications of the FAST findings together with CARES data

Notwithstanding some uncertainties associated with FAST, and the differences from CARES (**Table 1**), the FAST findings suggest that CARES could have been critically hampered by its severe loss-to-follow-up (45%), exemplified by its own *post hoc* ascertainment efforts nullifying the mortality risk associated with febuxostat (1). Despite the higher febuxostat doses in FAST (median 80mg daily vs 40mg daily in CARES), febuxostat tended to have a lower mortality risk than allopurinol in FAST; significantly lower in the on-treatment analysis (primary approach), by 25%, as discussed above. It remains unclear whether the further lowering serum urate with the higher febuxostat dose mediated this finding. While the FAST findings may not clarify all the concerns raised by CARES for patients with gout and established CVD, it is also important to remember that >55% of CARES participants discontinued study medication and 45% were lost to follow up. With discontinuation and loss-to-follow-up rates this extreme, it is very difficult to ensure the internal validity of the findings, as noted in the conflicting findings from the fuller *post hoc* ascertainment (1). Furthermore, CARES showed internal inconsistency between primary MACE and CV mortality endpoints, whereas FAST findings were internally consistent. Finally, several recent large-scale pharmaco-epidemiologic studies also support the FAST findings, not CARES (9-11).

If FAST had shown any hint of increased risk of mortality, it would have furthered the concerns raised by CARES. However, FAST did not show any such signal, and there actually was a suggestion of survival benefit associated with febuxostat in FAST, even with a mean doubling of the febuxostat exposure dose. While there are a number of differences between CARES and FAST, the most important one threatening internal validity is the level of loss-to-follow-up in CARES (45% CARES vs 6% FAST). To that end, FAST is considered to have superior internal validity compared to the CARES, regardless of generalizability (external validity). Naturally, generalizability matters as well; however, without internal validity, i.e., valid effect estimates,

generalizability is meaningless. Thus, based on the current evidence, it is our view that the collective verdict on the CV safety of febuxostat should rely more on FAST's results than CARES'. To that end, we support the FAST authors' suggestion for regulatory agencies to update their guidance on the CV risk of febuxostat (4).

Author contributions

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Lisa K Stamp: 1a, 2, 3

Robert Terkeltaub: 1a, 2, 3

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Table 1. Comparison of CARES and FAST

	CARES, White NEJM 2018 (1)	**FAST, MacKenzie Lancet 2020 (4)**
Trial design	Prospective, randomized, multicenter noninferiority trial	Prospective, randomized, multicenter noninferiority trial
Blinding	Double-blind, blinded-endpoint adjudication	Open-label, blinded-endpoint adjudication
Setting	USA, Mexico, Canada	Scotland, England, Denmark, and Sweden
Trial start date	April 2010	December 2011
Number of participants randomized	6,190	6,128
Study population	Gout, a history of major CVD, serum urate ≥7.0 mg/dL (0.42mmol/L) or ≥ 6.0 mg/dL (0.36mmol/L) with inadequately controlled gout	Gout, aged ≥60 years, already receiving allopurinol, with at least one additional CV risk factor.
Relevant exclusions	Myocardial infarction or stroke within 60 days prior to screening, severe renal impairment	Myocardial infarction or stroke in the previous 6 months, congestive heart failure (NYHA class III or IV), severe renal impairment
Proportion with established CVD	100%	33.4%
Proportion with tophaceous gout	21.3%	10.2%
Run-in period	No	Yes, run-in period to optimize allopurinol dose to achieve serum urate <6mg/dl (0.36mmol/L) prior to randomization
Final daily febuxostat dose	Median dose 40mg; 61.0% on 40 mg and 39.0% on 80 mg	Median dose 80mg; 97.5% on 80mg and 2.5% on 120mg
Final daily allopurinol dose	Median dose 300mg; 21.8% on 200 mg, 44.6% on 300 mg, 33.6% on ≥400 mg	Median dose 300mg; 10.0% on 100 mg, 23.3% on 200 mg, 50.9% on 300 mg, 15.8% on ≥400 mg
Primary endpoint	Composite of CV death, nonfatal myocardial infarction, nonfatal stroke, or unstable angina with urgent revascularization	Composite of hospitalization for non-fatal myocardial infarction or biomarker-positive acute coronary syndrome; non-fatal stroke; or death due to a CV event
Follow-up strategy for primary analysis	Study visits and phone follow-up	Record linkage to centralized databases for hospitalizations, deaths, and cancer diagnoses, in

		addition to study visits and phone follow-up
Primary analysis	Modified intention-to-treat non-inferiority analysis with a non-inferiority limit for the hazard ratio (HR) of 1.3	On-treatment non-inferiority analysis with a non-inferiority limit for the hazard ratio (HR) of 1.3
Median follow-up duration	Febuxostat 968 days and allopurinol 942 days	For all study participants, 1,467 days
Loss to follow-up	45.0%	5.8%
Assigned drug discontinuation	Febuxostat (57.3%); allopurinol (55.9%)	Febuxostat (32.4%); allopurinol (16.5%)
Colchicine gout flare prophylaxis (first 6 months)	Febuxostat 84.1%, allopurinol 83.8%	Febuxostat 71.4%, allopurinol 52.6%
Primary endpoint result	Primary intention-to-treat analysis: febuxostat (10.8%) was non-inferior to allopurinol (10.4%); HR 1.03 (97% CI 0.87–1.23)	Primary on-treatment analysis: febuxostat (5.6%) was non-inferior to allopurinol (7.9%); HR 0.85 (95% CI 0.70–1.03) Secondary intention-to-treat analysis: febuxostat (8.4%) was non-inferior to allopurinol (9.3%); HR 0.89 (0.75–1.06)
All-cause deaths	Primary intention-to-treat analysis: there were more deaths with febuxostat (7.8%) than allopurinol (6.4%); HR 1.22 (95% CI 1.01–1.47)	Primary on-treatment analysis: febuxostat (3.8%) was non-inferior to allopurinol (5.7%); HR 0.75 (95% CI 0.59–0.95) Secondary intention-to-treat analysis: febuxostat (7.2%) was non-inferior to allopurinol (8.6%); HR 0.84 (0.71–1.01)
Cardiovascular deaths	Primary intention-to-treat analysis: there were more deaths with febuxostat (4.3%) than allopurinol (3.2%); HR 1.34 (95% CI 1.03–1.73)	Primary on-treatment analysis: febuxostat (2.0%) was non-inferior to allopurinol (2.7%); HR 0.91 (95% CI 0.66–1.27) Secondary intention-to-treat analysis: febuxostat (3.8%) was non-inferior to allopurinol (4.0%); HR 0.96 (0.74–1.23)
Serum urate outcome	Similar proportion of participants had serum urate <6mg/dL, more with serum urate <5mg/dL with febuxostat	Mean follow-up serum urate level was 3.6mg/dL in febuxostat and 5.0mg/dL in allopurinol
Gout flare outcome	Febuxostat (0.68 flares per patient-year) vs allopurinol (0.63 flares per patient-year)	At least one gout flare for febuxostat (18 per 100 patient-years) vs allopurinol (20 per 100 patient-years)