

**Long-term cardiovascular safety of febuxostat compared with allopurinol in patients with gout
a multicentre, prospective, randomized, open-label, non-inferiority trial¹
FAST Trial Summary¹**

SUMMARY

Febuxostat was seen to be non-inferior to allopurinol with respect to a composite of cardiovascular (CV) death, hospitalization for non-fatal myocardial infarction or biomarker-positive acute coronary syndrome, or non-fatal stroke. A) A previous RCT raised the CV safety issue with febuxostat. B) In this RCT, febuxostat had a numerically lower HR, and was found to be non-inferior to ...based on a non-inferiority margin of 1.3. C) However febuxostat had higher rates of discontinuation (35% vs 17%, NNH=5.5) as well as all cause death. Serious adverse events (SAE) were also slightly higher for febuxostat. D) The results may have been affected (biased) by the release of the CARES trial. CARES found potential CV harm with febuxostat and this may have impacted the trial by biasing towards premature stopping of febuxostat in CV-risk patients;. During the time of this study, the trial was released and advice to avoid febuxostat in patients with pre-existing cardiovascular disease. This may have been a factor in the increased discontinuation rate of febuxostat as new regulatory advice given to primary care professionals to stop treatment in their patients involved.

Bottom Line: We now have one RCT that suggests CV harm with febuxostat, and another that suggests CV safety. At best the CV results are mixed providing some reassurance; at worst, the CV safety findings are highly suspect given the open-label nature of the trial and the mid-trial release of *bad news* for febuxostat with publication of the CARES trial. Some caution may still be warranted especially for those with a CV event history.

BACKGROUND

- Both allopurinol and febuxostat are xanthine oxidase inhibitors used as ULT for patients with gout. There has been concern about the cardiovascular safety of febuxostat and more evidence on its cardiovascular safety compared to allopurinol was recommended by the European Medicine Agency.

TRIAL DESIGN AND POPULATION (SEE ORIGINAL ARTICLE/SUPPLEMENT FOR FULL CRITERIA)

DESIGN:

- Randomized, open-label blinded endpoint, active control; stratified; allocation concealed (web-based randomization facility-centralized); multi-site/country, 18 regional centres across 4 countries; lead-in phase with allopurinol for dose optimization towards achieving a serum urate concentration of less than 0.357 mmol/L (<6 mg/dL); on-treatment non-inferiority (HR margin 1.3), mITT (all patients who did not withdraw consent and had taken at least 1 dose of the medication they were assigned) non-inferiority and superiority if both mITT and on-treatment both non-inferior; median follow-up 1467 days (IQR 1029-2052), on-treatment 1324 days (IQR 870-1919).
- Funded by** University of Dundee and received support from Ipsen and Teijin Pharma (no protocol changes)

POPULATION: n = 6128

- Inclusion criteria:** age 60 or older, 1 additional CV risk factor (see list pg 5 of supplement), received 60 or more days of allopurinol or filled 2 or more prescriptions of allopurinol in past 6 months, deemed by physician or study site coordinator to be eligible for ULT
- Exclusion criteria:** contraindicated to febuxostat or allopurinol or any of the components of their formulations, not receiving allopurinol as ULT, severe renal impairment (< 30mL/min creatinine clearance), moderate or severe hepatic impairment (see supplement pg 6), life-threatening co-morbidity or with a significant medical condition and/or conditions that would interfere with the treatment, safety or compliance with the protocol, receiving treatment for malignancy in the previous 5 years (excluding those treated for minor skin cancer and indolent cancers that are not thought to be life threatening), MI or stroke within 6 months prior to screening, CHF class III or IV (NYHA), Behaviour or lifestyle would render them less likely to comply with study medications, current gout flare or within 14 days of resolution of flare.
- POPULATION at baseline:** age 71, male 85%, white 99%, evidence of CVD 33%, HTN 78%, current or past smoker 65%, previous gout flare in past 12 months 26%, median treatment of allopurinol at time of inclusion 6 years (IQR 2.1-14.7).

INTERVENTION/COMPARISON:

- 2 study arms: **Febuxostat vs Allopurinol** specifically:
 - Febuxostat 80mg daily 97.5%, 2.5% on 120mg daily
 - Allopurinol average daily dose of 279mg (50.9% on 300mg daily, 84.2% on doses between 100,200, and 300 mg)
- Is the comparison fair? Modestly
 - Both are xanthine oxidase inhibitors, but more dose variation with allopurinol group
 - Much larger discontinuation in febuxostat group (973 vs 503); all patients were previously on and presumably tolerated allopurinol in lead-in phase.

OUTCOMES: - median follow-up ~3 years on-treatment (data collection from 2011-2019)

- Primary: Composite endpoint of Cardiovascular death, hospitalization for non-fatal myocardial infarction or biomarker-positive acute coronary syndrome, or non-fatal stroke.

RESULTS	n = 3063	n = 3065		
Clinical Endpoints	Febuxostat	Allopurinol	Hazard Ratio (95% CI)	Comments
1' Composite: cardiovascular death; hospitalization for non-fatal myocardial infarction or biomarker-positive acute coronary syndrome; or non-fatal stroke (mITT)	256 (8.4%)	285 (9.3%)	0.89 (0.75-1.06)	Other secondary endpoints: Hospitalization for arrhythmia with no evidence of ischemia was statistically significant in mITT analysis 1.51 (1.05-2.17) All-cause death was statistically significant in the on-treatment analysis, 3.5% vs 5.7%; HR = 0.75 (0.59-0.95), favouring febuxostat.
On treatment analysis 1' Composite endpoint (on-treatment)	172 (5.6%)	241 (7.9%)	0.85 (0.70-1.03)	
Cardiovascular Death	117 (3.8%)	122 (4.0%)	0.96 (0.74-1.23)	
Hospitalization for non-fatal myocardial infarction or biomarker-positive acute coronary syndrome	102 (3.3%)	110 (3.6%)	0.93 (0.71-1.21)	Remember that the release of the CARES trial findings (increased CV events) and subsequent increase in discontinuations in the febuxostat arm could seriously bias the results of this RCT (those with high CV risk more likely to have therapy discontinued during the trial).
Non-fatal Stroke	80 (2.6%)	87 (2.8%)	0.92 (0.68-1.25)	
Secondary Endpoint: All cause death	222 (7.2%)	263 (8.6%)	0.84 (0.71-1.01)	

STRENGTHS, LIMITATIONS, AND UNCERTAINTIES**STRENGTHS:**

- Large study group
- Outcomes of importance to patients
- Prospective multi-year study to give a bigger window to capture events

LIMITATIONS:

- Open label; patients, physicians, and site staff not blinded
- Large discontinuation rate in febuxostat group
- Primary composite endpoint shifts data in favor of febuxostat
- No placebo group to demonstrate baseline primary events in the study population
- Did not meet estimated events expected resulting in the study being under powered (77% study design was to be 80% powered)
- During this trial, the [CARES](#) trial released findings to avoid febuxostat in patients with pre-existing major cardiovascular disease as practitioners were not blinded; it is thought to contribute to the discontinuation rate of febuxostat.
- Majority of patients were white (HLA-B*5801 gene is common in patients of Asian descent and are at higher risk of adverse events).

UNCERTAINTIES:

- Events in the febuxostat group seemed to be less than expected when looking at other trials involving its CV risks, uncertainties remain as there was a large discontinuation rate in the febuxostat group that are included in the analysis
- When looking at secondary outcomes, hospitalization for arrhythmia with no evidence of ischemia was statistically significant in favor of allopurinol, but the study was not powered for this outcome.
- ? Efficacy of treat-to-target ULT

Other notes of interest:

Costs (per 30 days of therapy): **Allopurinol:** ~ \$19-28 (100-800mg daily) average dose of 300mg daily ~ \$21
Febuxostat: ~ \$26-30 (80-120mg daily)

¹Mackenzie IS, Ford I, Nuki G, et al. Long-term cardiovascular safety of febuxostat compared with allopurinol in patients with gout (FAST): a multicentre, prospective, randomised, open-label, non-inferiority trial. *Lancet*. 2020;396(10264):1745-1757. doi:10.1016/S0140-6736(20)32234-0

Other related RxFiles materials: [Gout Treatment Chart](#)

ACKNOWLEDGEMENTS: Prepared By Cole Binsfeld, PharmD Student. Reviewed by Loren Regier and the RxFiles academic detailing team.

DISCLAIMER: The content of this newsletter represents the research, experience and opinions of the authors and not those of the University of Saskatchewan (U of S). Neither the authors nor any other party who has been involved in the preparation or publication of this work warrants or represents that the information contained herein is accurate or complete, and they are not responsible for any errors or omissions or for the result obtained from the use of such information. Any use of the newsletter will imply acknowledgment of this disclaimer and release any responsibility of the U of S, its employees, servants or agents. Readers are encouraged to confirm the information contained herein with other sources. Additional information and references online at www.RxFiles.ca Copyright Oct 2026 – RxFiles, University of Saskatchewan (U of S)

Abbreviations and Definitions: IHD: Ischemic heart disease, HTN: Hypertension, TD2M: Type 2 diabetes, HF: Heart failure, PVD: Peripheral vascular disease, eGFR: Estimated glomerular filtration rate, BMI: Body mass index, IQR: Interquartile range, CKD: Chronic kidney disease, SU: Serum urate, RCT: Randomized control trial, NSAID: non-steroidal anti-inflammatory drug, LDL: Low density lipoprotein, ACEi: Angiotensin-converting enzyme inhibitors, ARB: Angiotensin II receptor blockers, VAS: Visual analogue scale, HAQ: Health Assessment Questionnaire, AE: Adverse effect, ULT: Urate lowering treatment, NYHA: New York Heart association, MI: Myocardial Infarction