Long-term cardiovascular safety of febuxostat compared with allopurinol in patients with gout (FAST): a multicentre, prospective, randomised, open-label, non-inferiority trial

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Summary

Background Febuxostat and allopurinol are urate-lowering therapies used to treat patients with gout. Following concerns about the cardiovascular safety of febuxostat, the European Medicines Agency recommended a post-licensing study assessing the cardiovascular safety of febuxostat compared with allopurinol.

Methods We did a prospective, randomised, open-label, blinded-endpoint, non-inferiority trial of febuxostat versus allopurinol in patients with gout in the UK, Denmark, and Sweden. Eligible patients were 60 years or older, already receiving allopurinol, and had at least one additional cardiovascular risk factor. Those who had myocardial infarction or stroke in the previous 6 months or who had severe congestive heart failure or severe renal impairment were excluded. After a lead-in phase in which allopurinol dose was optimised towards achieving a serum urate concentration of less than 0·357 mmol/L (<6 mg/dL), patients were randomly assigned (1:1, with stratification according to previous cardiovascular events) to continue allopurinol (at the optimised dose) or start febuxostat at 80 mg/day, increasing to 120 mg/day if necessary to achieve the target serum urate concentration. The primary outcome was a composite of hospitalisation for non-fatal myocardial infarction or biomarker-positive acute coronary syndrome; non-fatal stroke; or cardiovascular death. The hazard ratio (HR) for febuxostat versus allopurinol in a Cox proportional hazards model (adjusted for the stratification variable and country) was assessed for non-inferiority (HR limit 1·3) in an on-treatment analysis. This study is registered with the EU Clinical Trials Register (EudraCT 2011-001883-23) and ISRCTN (ISRCTN72443728) and is now closed.

Findings From Dec 20, 2011, to Jan 26, 2018, 6128 patients (mean age 71·0 years [SD 6·4], 5225 [85·3%] men, 903 [14·7%] women, 2046 [33·4%] with previous cardiovascular disease) were enrolled and randomly allocated to receive allopurinol (n=3065) or febuxostat (n=3063). By the study end date (Dec 31, 2019), 189 (6·2%) patients in the febuxostat group and 169 (5·5%) in the allopurinol group withdrew from all follow-up. Median follow-up time was 1467 days (IQR 1029–2052) and median on-treatment follow-up was 1324 days (IQR 870–1919). For incidence of the primary endpoint, on-treatment, febuxostat (172 patients [1·72 events per 100 patient-years]) was non-inferior to allopurinol (241 patients [2·05 events per 100 patient-years]; adjusted HR 0·85 [95% CI 0·70–1·03], p<0·0001). In the febuxostat group, 222 (7·2%) of 3063 patients died and 1720 (57·3%) of 3001 in the safety analysis set had at least one serious adverse event (with 23 events in 19 [0·6%] patients related to treatment). In the allopurinol group, 263 (8·6%) of 3065 patients died and 1812 (59·4%) of 3050 had one or more serious adverse events (with five events in five [0·2%] patients related to treatment). Randomised therapy was discontinued in 973 (32·4%) patients in the febuxostat group and 503 (16·5%) patients in the allopurinol group.

Interpretation Febuxostat is non-inferior to allopurinol therapy with respect to the primary cardiovascular endpoint, and its long-term use is not associated with an increased risk of death or serious adverse events compared with allopurinol.

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Introduction

Gout is a metabolic disorder in which prolonged elevation of serum urate can lead to the deposition of crystals of monosodium urate, tophus formation, chronic inflammatory arthritis, urolithiasis, and nephropathy, as well as to recurrent flares of acute arthritis and bursitis. Gout is frequently associated with comorbidities such as chronic kidney disease, obesity, diabetes, hypertension, and cardiovascular disease, and with increased mortality.[1–3] In addition to the treatment of acute flares with anti-inflammatory drugs, management of gout requires long-term urate-lowering therapy to persistently reduce serum urate below its crystallisation threshold in order to dissolve crystal deposits and prevent further crystal

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed on Sept 17, 2020, using the search terms "febuxostat", "allopurinol", and "cardiovascular outcomes". We searched, with no date or language restrictions, for reports of any randomised clinical trials comparing febuxostat with allopurinol in terms of cardiovascular outcomes in more than 500 participants. We found one trial, the CARES trial, which involved 6190 randomised patients with gout and coexisting major cardiovascular conditions and reported that febuxostat was non-inferior to allopurinol with respect to rates of adverse cardiovascular events. However, the risks of death from any cause (hazard ratio 1·22 [95% CI 1·01–1·47]) and of cardiovascular death (1·34 [1·03–1·73]) in a modified intention-to-treat analysis were higher in the febuxostat group than in the allopurinol group.

Added value of this study

The Febuxostat versus Allopurinol Streamlined Trial (FAST) was a large, multicentre, prospective, randomised, open-label, blinded-endpoint, non-inferiority trial to compare the cardiovascular safety of febuxostat versus allopurinol in patients with gout, at least one additional cardiovascular risk factor, and who were already being treated with allopurinol. The population studied was generally at lower cardiovascular risk than that in the CARES trial, with only about a third of patients in FAST having previous major cardiovascular comorbidity. Daily doses of febuxostat in FAST were higher (80 mg/day or 120 mg/day) than in CARES (40 mg/day or 80 mg/day), and dose ranges of allopurinol were wider in FAST (100–900 mg/day) than in CARES (200–600 mg/day). Only 5·8% of patients in FAST withdrew from all follow-up, and discontinuation of randomised treatment was less frequent (16·5% in the allopurinol group and 32·4% in the febuxostat group) than in the CARES trial (in which 45·0% of patients did not complete all trial visits and 56·6% of patients discontinued randomised treatment prematurely). FAST used record linkage to national health-care databases to complement other methods of reporting for the detection of hospitalisations and deaths. We found that febuxostat was non-inferior to allopurinol for the primary composite endpoint (hospitalisation for non-fatal myocardial infarction or biomarker-positive acute coronary syndrome; non-fatal stroke; or cardiovascular death) during a median on-treatment period of 1324 days (IQR 870–1919; 3·63 years). In contrast to CARES, FAST found that treatment with febuxostat was not associated with an increase in cardiovascular death or all-cause death. Overall there were fewer deaths in the febuxostat group than in the allopurinol group.

Implications of all the available evidence

Although the CARES study suggested that febuxostat therapy might be associated with higher risks of all-cause death and cardiovascular death than allopurinol, FAST, with better ascertainment of events, found no increase in these risks.

deposition, recurrent flares of gout, and progressive joint damage. The most widely used urate-lowering medications are the xanthine oxidase inhibitors allopurinol and febuxostat. Prophylaxis against acute flares of gout is recommended when urate-lowering therapy is initiated or following dose increases of a xanthine oxidase inhibitor, typically for a period of up to 6 months.[4]

Initial clinical trials comparing febuxostat to allopurinol or placebo identified a numerically higher risk of cardiovascular events in patients taking febuxostat.[5–8] Marketing authorisation for febuxostat was granted after a subsequent 6-month randomised controlled trial of febuxostat compared with allopurinol in 2269 participants (the CONFIRMS trial)[9] showed equal frequencies (0·4%) of adjudicated cardiovascular events with febuxostat (80 mg) and allopurinol, and no cardiovascular deaths in febuxostat-treated patients. However, because of lingering concerns about the possibility of increased cardiovascular risk with febuxostat, the European Union Risk Management Plan for febuxostat indicated that a post-authorisation safety study should be done in Europe in patients with gout to evaluate the cardiovascular effects of febuxostat versus standard urate-lowering therapy with allopurinol. The Febuxostat versus Allopurinol Streamlined Trial (FAST) was approved to fulfil this requirement.

Methods

Study design and participants

We did a prospective, randomised, open-label, blinded-endpoint multicentre trial in patients with gout at 18 regional centres in the UK (Scotland and England), Denmark, and Sweden.[10] The trial was designed to assess the cardiovascular safety of febuxostat in comparison with allopurinol. Allopurinol was chosen as the comparator because it is the long-established, first-line urate-lowering therapy for gout.

Patients were mainly recruited from 850 primary care practices in the UK and Denmark (by a search of primary care records for potentially eligible patients), but also from two secondary care centres in Scotland, and via two clinical research organisations in Sweden. Eligible patients were aged 60 years or older, had gout,[11] and, in the opinion of the recruiting physician, required urate-lowering therapy. No patients with asymptomatic hyperuricaemia were recruited to the study. Eligible participants also had at least one additional cardiovascular risk factor (appendix p 6) and were already receiving allopurinol therapy. Patients with a history of myocardial infarction or stroke in the previous 6 months and those with congestive heart failure (New York Heart Association [NYHA] class III or IV) or severe renal impairment were excluded. A full list of inclusion and exclusion criteria is detailed in the appendix (pp 4–5).

The study protocol (appendix pp 157–217) was approved by ethics committees and regulatory authorities in each country. All participants gave written informed consent.

The study Clinical Co-ordination Centre was MEMO Research at the University of Dundee (Dundee, UK) and the study Data and Biostatistical Centre was at the Robertson Centre for Biostatistics at the University of Glasgow (Glasgow, UK). Trial monitoring was carried out or subcontracted by the University of Dundee as study sponsor.

Randomisation and masking

Following a lead-in phase in which allopurinol dose was optimised, or immediately after the screening visit for patients who were already controlled to the target urate concentration, patients were randomly allocated (1:1) to receive either allopurinol or febuxostat, using a central web-based randomisation facility located at the Robertson Centre for Biostatistics, University of Glasgow. The randomisation system could be accessed via an interactive voice response system or by a web-based application. The randomisation list was created by a statistician in the Robertson Centre and was based on randomised permuted blocks of size four, stratified according to previous cardiovascular events (myocardial infarction, stroke, or hospitalisation for congestive heart failure or peripheral vascular disease). Participants, site staff, and treating physicians were not masked to therapy allocation, but the endpoint adjudication committee were masked.

Procedures

At the screening visit before randomisation, serum urate concentration was measured. If serum urate was not controlled to the European League Against Rheumatism (EULAR) target of less than 0·357 mmol/L (<6 mg/dL)[12] on the patient's pre-study allopurinol dose, the patient commenced a lead-in phase in which the dose was increased by 100 mg/day every 2 weeks until the patient's urate concentration was at target or until they reached the maximum licensed dose (900 mg/day) or maximum tolerated dose of allopurinol. This dose increase was done because 80 mg febuxostat is a more potent urate-lowering therapy than low-dose allopurinol. Patients could continue in the study even if the target urate concentration had not been reached after the maximum dose increase.

Allopurinol and febuxostat were supplied directly by post to participants from the research pharmacy at the University of Dundee (except in Sweden, where they were supplied from the Dundee research pharmacy via a local pharmacy). Patients in the allopurinol group were given allopurinol orally (100 mg or 300 mg tablets; Salutas Pharma [Barleben, Germany] or Teva Pharmaceutical Works [Debrecen, Hungary]) at the optimised dose determined pre-randomisation. Patients in the febuxostat group were given febuxostat orally (80 mg and 120 mg tablets; Patheon France [Bourgoin Jallieu, France] or Menarini [Dresden, Germany]) at 80 mg daily for the first 2 weeks after randomisation. After 2 weeks, serum urate concentration was measured and, if not controlled to the EULAR target, the febuxostat dose was increased to 120 mg daily. Patients in both groups had a washout period of 7–21 days after randomisation before starting the randomised therapy.

Although the majority of patients remained on the daily dose assigned at randomisation, the daily dose of allopurinol or febuxostat could be reduced or increased by a physician within the licensed daily dose limits on the basis of clinical discretion (eg, reduced because of tolerability issues or increased because of inadequate control of urate concentrations identified during annual visits).

6 months of prophylaxis against gout flares was offered to all patients at the start of their randomly allocated therapy. Prophylaxis was started earlier in any patients whose allopurinol dose was increased during the allopurinol lead-in phase and was offered again at any time during the study when a patient's dose of urate-lowering therapy was increased. First-line gout flare prophylaxis was with colchicine (0·5 mg once or twice daily), and second-line alternatives were non-steroidal anti-inflammatory drugs (NSAIDs; naproxen, diclofenac, or meloxicam) with gastric protection (omeprazole or ranitidine). Patients could decline or discontinue gout flare prophylaxis at any time. Any gout flares that occurred during the study were managed at the discretion of the patient's local treating physician according to local guidelines.

All patients had an annual follow-up visit during which serum urate, urea, creatinine, and electrolyte concentrations were measured and liver function tests were done. In addition, all patients had follow-up contacts every 2 months with the study team. Adverse events could be reported at any time by patients or health professionals. Record linkage to centralised databases for records of hospitalisations, deaths, and cancer diagnoses was done at regular intervals during the study in the UK (Public Health Scotland and NHS Digital databases) and Denmark (Danish Health Data Board [Sundhedsdatastyrelsen] database), except for in the last year of study follow-up in Denmark. Despite significant attempts by the investigators, it was not possible to obtain similar record-linkage data in Sweden.

Because the primary event rates were lower than predicted during the study, the trial recruitment period was extended beyond the 2 years originally planned, and the follow-up period was also extended.

Outcomes

The primary outcome was a composite of hospitalisation for non-fatal myocardial infarction or biomarker-positive acute coronary syndrome; non-fatal stroke (whether reported to have led to hospitalisation or not, or to have occurred during a hospitalisation); or death due to a cardiovascular event.

The secondary outcomes were hospitalisation for non-fatal myocardial infarction or biomarker-positive acute coronary syndrome; non-fatal stroke (whether reported to have led to hospitalisation or not, or to have occurred during a hospitalisation); death due to a cardiovascular event; all-cause death; hospitalisation for heart failure; hospitalisation for unstable, new, or worsening angina; hospitalisation for coronary revascularisation; hospitalisation for cerebral revascularisation; hospitalisation for transient ischaemic attack; hospitalisation for non-fatal cardiac arrest; hospitalisation for venous and peripheral arterial vascular thrombotic event; and hospitalisation for arrhythmia with no evidence of ischaemia.

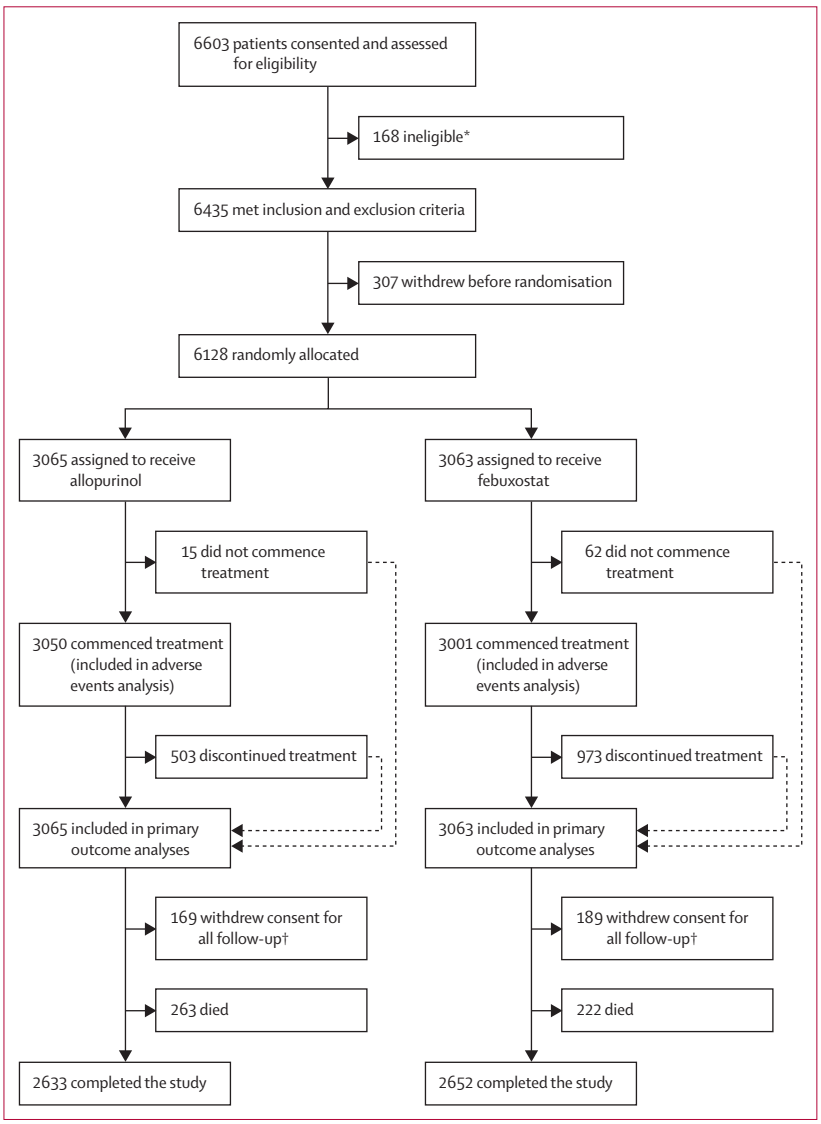

Figure 1: **Trial profile**
14 randomised patients and one non-randomised patient recruited from a single UK site are not included in these numbers because their data were deleted following instruction from the sponsor due to concerns about the validity of their consent and inclusion of their data following a monitoring visit. *88 withdrew or were excluded before completion of inclusion and exclusion criteria assessment; 61 met the inclusion criteria but were excluded on at least one exclusion criterion; 19 were excluded on at least one inclusion and at least one exclusion criterion. †Reasons for withdrawal of consent are listed in the appendix (p 30).

Minor amendments to two components of the primary outcome were made during the trial: hospitalised stroke was amended to include strokes that were non-hospitalised or occurred during a hospitalisation, and myocardial infarction was updated to include myocardial infarction or biomarker-positive acute coronary syndrome (which are largely considered to be the same outcome nowadays).

An independent clinical events classification committee based at the University of Glasgow, whose members were unaware of the trial group assignments, assessed all the components of the primary composite outcome, secondary cardiovascular outcomes, and death. These events are defined in the clinical event definitions (appendix pp 7–25).

As exploratory efficacy endpoints, we also assessed the proportions of patients whose serum urate concentration was less than 0·357 mmol/L (<6 mg/dL) or less than 0·297 mmol/L (<5 mg/dL) after each year of treatment.

Serious adverse events occurring during and up to 28 days after the end of the study were recorded unless participants had withdrawn consent. Gout flares and any treatment-related adverse events were also recorded.

For adverse events that were potential study endpoints, more detailed information was collected from medical records and death certificates and an anonymised endpoint package was prepared for adjudication by an independent adjudication committee.

Statistical analysis

We calculated that 456 first primary events were required to show non-inferiority of febuxostat compared with allopurinol, assuming a non-inferiority limit for the hazard ratio (HR) of 1·3 with 80% power and a one-sided α of 0·025. The non-inferiority margin of 1·3 was selected and approved by the European Medicines Agency as representing a minimal difference of clinical interest and was based on previous regulatory guidance and precedent. Previous and ongoing cardiovascular safety studies—including cardiovascular safety trials of novel treatments for diabetes, trials comparing celecoxib with other NSAIDs, and current trials of novel renal treatments[13–17]—have used similar values, which have been accepted by regulators. With an expected primary event rate of about 10% over 3 years in the allopurinol group (based on events observed in observational databases), we estimated that 2282 patients would be required in each treatment group. Assuming a dropout rate of 20% from the on-treatment population, the enrolment of 2853 patients in each treatment group (5706 total) was predicted to provide the required number of primary events with an average follow-up period of 3 years. Baseline characteristics are shown according to treatment groups as mean (SD) or median (IQR) for continuous variables and as number and percentage for categorical variables.

All clinical outcomes were analysed on a time-to-first-event basis using Cox proportional hazards models, with the exception of the frequency of flares of gout, for which all recurrent events were counted and analysed with use of a negative binomial regression model. All analyses were adjusted for the stratification variable and country. Treatment effect for febuxostat relative to allopurinol was estimated as HR (95% CI) for the Cox models and incidence rate ratio (95% CI) for the negative binomial model. p values were calculated from Wald statistics.

The primary analysis was an on-treatment analysis. In on-treatment analyses, we censored follow-up at the time of permanent discontinuation of the original randomly allocated therapy, death from any cause not included in the endpoint being considered, date of withdrawal of all consent to participate further in the study, or end of study (Dec 31, 2019), whichever occurred first. In the intention-to-treat analyses, we censored follow-up after death from any cause not included in the endpoint being considered, date of withdrawal of all consent to participate further in the study, or end of study, whichever occurred first.

The primary outcome was assessed first in an on-treatment non-inferiority analysis with a non-inferiority limit for the HR of 1·3. A supporting intention-to-treat analysis was done and, if non-inferiority was shown in both these analyses, an intention-to-treat superiority analysis was also done. This hierarchical testing process meant that there was no need for adjustment for multiple testing. Prespecified subgroup analyses were also done for the primary endpoint. p values for the test of interaction between the variable defining the subgroup

	Febuxostat (n=3063)	Allopurinol (n=3065)
Age, years	71·0 (6·4)	70·9 (6·5)
Sex		
Male	2619 (85·5%)	2606 (85·0%)
Female	444 (14·5%)	459 (15·0%)
Country		
Scotland	1211 (39·5%)	1173 (38·3%)
England	840 (27·4%)	834 (27·2%)
Denmark	947 (30·9%)	996 (32·5%)
Sweden	65 (2·1%)	62 (2·0%)
Ethnicity		
White	3034 (99·1%)	3036 (99·1%)
Asian	11 (0·4%)	14 (0·5%)
Afro-Caribbean	10 (0·3%)	8 (0·3%)
Oriental	2 (0·1%)	1 (<0·1%)
Other	6 (0·2%)	6 (0·2%)
Smoking history		
Current	252 (8·2%)	234 (7·6%)
Former	1743 (56·9%)	1766 (57·6%)
Never	1068 (34·9%)	1065 (34·7%)
Systolic blood pressure, mm Hg	138·2 (18·3)	138·0 (17·3)
Diastolic blood pressure, mm Hg	75·6 (12·0)	75·2 (11·3)
Body-mass index, kg/m²	31·0 (5·1); n=3060	31·2 (5·3); n=3062
Total cholesterol, mmol/L	4·6 (1·2); n=3000	4·5 (1·2); n=2998
LDL cholesterol, mmol/L	2·9 (1·1); n=2999	2·8 (1·0); n=2998
Baseline urate, mmol/L*	0·297 (0·048); n=3000	0·297 (0·046); n=3050
Cardiovascular history		
Previous myocardial infarction	308 (10·1%)	348 (11·4%)
Acute coronary syndrome (other than myocardial infarction)	317 (10·3%)	302 (9·9%)
Coronary revascularisation	358 (11·7%)	367 (12·0%)
Angina pectoris requiring medical treatment	361 (11·8%)	370 (12·1%)
Previous stroke	167 (5·5%)	141 (4·6%)
Previous transient ischaemic attack	156 (5·1%)	149 (4·9%)
Established peripheral vascular disease	147 (4·8%)	148 (4·8%)
High blood pressure	2345 (76·6%)	2439 (79·6%)
Heart failure	142 (4·6%)	146 (4·8%)
Evidence of cardiovascular disease†	1038 (33·9%)	1008 (32·9%)
Other medical history		
Renal disease	504 (16·5%)	483 (15·8%)
Asthma	334 (10·9%)	358 (11·7%)
Chronic obstructive pulmonary disease	211 (6·9%)	228 (7·4%)
Diabetes	661 (21·6%)	719 (23·5%)
Gout history		
Age at gout symptom onset, years	56·4 (12·8)	55·8 (13·1)
Tophi	299 (9·8%)	329 (10·7%)
Any episodes of acute gout in past 12 months	787 (25·7%)	813 (26·5%)
Median duration of allopurinol treatment at inclusion, years (IQR)	6·0 (2·1–14·0)	6·0 (2·2–14·7)
Concomitant medication ongoing at inclusion		
Statins	1824 (59·5%)	1769 (57·7%)
Angiotensin-converting enzyme inhibitors	1224 (40·0%)	1244 (40·6%)
Antiplatelet agents (including aspirin)	1098 (35·8%)	1072 (35·0%)
Aspirin	922 (30·1%)	906 (29·6%)
Non-steroidal anti-inflammatory drugs	815 (26·6%)	914 (29·8%)
Colchicine	110 (3·6%)	94 (3·1%)

Data are mean (SD) or n (%) unless otherwise stated. *Measured immediately pre-randomisation. †Defined as history of myocardial infarction, stroke, transient ischaemic attack, acute coronary syndrome, coronary revascularisation, angina pectoris, or heart failure.

Table 1: **Baseline characteristics in all randomly allocated participants**

and randomised treatment allocation were calculated. Similar analyses were done for other time-to-event secondary endpoints.

Time-to-event curves are presented as cumulative incidence functions adjusting for the competing risk of deaths not included in the endpoint being plotted.

Between-group differences in serum urate concentrations were assessed annually by ANCOVA, adjusting for baseline concentrations, the stratification variable, and country.

The type I error rate was set at 2·5% (one-sided) for the one-sided non-inferiority analyses and at 5% for two-sided superiority analyses. No formal interim analyses were done and therefore no p value penalties are required. No adjustments were made for the multiplicity of statistical comparisons. Thus, analyses other than that for the primary endpoint should be considered exploratory.

All validly randomly allocated participants were included in the on-treatment and intention-to-treat analyses. The safety analysis was done for all patients who took at least one dose of the allocated medication. The incidence of serious treatment-emergent adverse events is summarised by MedDRA system organ class for each treatment group.

Analyses and graphical displays were done using SAS for Windows version 9.4 and R version 3.6.1. All cardiovascular outcomes were adjudicated by an independent clinical endpoint committee (appendix p 34), except coronary revascularisation, cerebral revascularisation, and transient ischaemic attack, which were reviewed and classified by physicians at the University of Dundee.

Trial safety was overseen by an independent data-monitoring committee (appendix p 34). This trial is registered with the EU Clinical Trials Register (EudraCT 2011-001883-23) and ISRCTN (ISRCTN72443728).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From Dec 20, 2011, to Oct 17, 2017, 6603 patients consented to be enrolled in the trial and were assessed for eligibility, of whom 475 were excluded before randomisation. Separate from these 6603 patients, data for 14 randomly allocated patients and one non-allocated patient (all recruited at one UK site) were deleted from the study database following instruction by the sponsor because of concerns identified at a monitoring visit regarding the validity of consent and inclusion of these patients and their data. These 15 patients are excluded from all summaries and analyses. 6128 patients were randomly assigned to receive febuxostat (n=3063) or

	Events				HR (95% CI)	$p_{non\text{-}inferiority}$
	Febuxostat (n=3063)		Allopurinol (n=3065)			
	Patients, n (%)	Rate per 100 patient-years	Patients, n (%)	Rate per 100 patient-years		
Primary endpoint (composite): cardiovascular death; hospitalisation for non-fatal myocardial infarction or biomarker-positive acute coronary syndrome; or non-fatal stroke	172 (5·6%)	1·723	241 (7·9%)	2·054	0·85 (0·70–1·03)	<0·0001
Cardiovascular death	62 (2·0%)	0·610	82 (2·7%)	0·677	0·91 (0·66–1·27)	0·018
Hospitalisation for non-fatal myocardial infarction or biomarker-positive acute coronary syndrome	77 (2·5%)	0·767	98 (3·2%)	0·824	0·94 (0·70–1·27)	0·016
Non-fatal stroke	58 (1·9%)	0·574	80 (2·6%)	0·670	0·87 (0·62–1·21)	0·0092
All-cause death	108 (3·5%)	1·062	174 (5·7%)	1·438	0·75 (0·59–0·95)	<0·0001
Hospitalisation for heart failure	65 (2·1%)	0·645	89 (2·9%)	0·745	0·88 (0·64–1·21)	0·0077
Hospitalisation for unstable, new, or worsening angina	4 (0·1%)	0·039	12 (0·4%)	0·099	0·39 (0·13–1·22)	0·019
Hospitalisation for coronary revascularisation	65 (2·1)	0·648	78 (2·5%)	0·654	1·00 (0·72–1·39)	0·059
Hospitalisation for cerebrovascular revascularisation	2 (0·1%)	0·020	8 (0·3%)	0·066	0·30 (0·06–1·42)	0·032
Hospitalisation for transient ischaemic attack	18 (0·6%)	0·177	23 (0·8%)	0·191	0·94 (0·51–1·74)	0·15
Hospitalisation for non-fatal cardiac arrest	2 (0·1%)	0·020	6 (0·2%)	0·050	NA	0·29
Hospitalisation for venous and peripheral arterial vascular thrombotic event	29 (0·9%)	0·287	35 (1·1%)	0·291	0·99 (0·61–1·62)	0·14
Hospitalisation for arrhythmia with no evidence of ischaemia	55 (1·8%)	0·546	45 (1·5%)	0·375	1·47 (0·99–2·18)	0·73

Non-inferiority p values are based on a non-inferiority limit for the HR of 1·3, with the one-sided type I error rate set at 2·5%. HRs were from Cox proportional hazards models adjusted for the stratification variable (previous cardiovascular events) and country. Where the total number of events was less than ten, the p value is from a Fisher's exact test and HR is not given. HR=hazard ratio. NA=not applicable.

Table 2: **Primary and secondary outcomes in the on-treatment analysis**

allopurinol (n=3065; figure 1). The final randomisation took place on Jan 26, 2018. The study reached the end of its contracted period on Dec 31, 2019, at which point patients discontinued their allocated treatment; the decision to end the trial then was made at a time when the number of adjudicated primary events that had occurred was still uncertain. The final number of primary events was below the target number because of uncertainties about whether some events had occurred while patients were on treatment (which were later clarified) and because the number of potential events (for which information was still being gathered) that were subsequently adjudicated as positive events was lower than expected. Final record-linkage data and supporting information on endpoints resulted in the trial completion being Aug 31, 2020. Median follow-up time in the study was 1467 days (IQR 1029–2052) and median on-treatment follow-up period was 1324 days (IQR 870–1919). 189 (6·2%) patients in the febuxostat group and 169 (5·5%) in the allopurinol group withdrew from all follow-up.

The two treatment groups were well balanced with respect to baseline characteristics (table 1) and baseline cardiovascular risk factors (appendix p 26), with the exception of a slightly higher proportion of patients with history of diabetes in the allopurinol group than in the febuxostat group. The overall mean age was 71·0 years (SD 6·4), 5225 (85·3%) participants were male, 903 (14·7%) were female, and 6070 (99·1%) were white. 2384 (38·9%) were recruited in Scotland, 1674 (27·3%) in England, 1943 (31·7%) in Denmark, and 127 (2·1%) in Sweden. 2046 (33·4%) patients had a history of cardiovascular disease (defined as myocardial infarction, stroke, transient ischaemic attack, acute coronary syndrome, coronary revascularisation, angina pectoris, or heart failure). 1380 patients (22·5%) had a history of diabetes.

At the time of screening, 3593 (58·6%) patients were taking statins, 2170 (35·4%) were taking antiplatelet agents (including 1828 [29·8%] taking aspirin), and 2468 (40·3%) were taking an angiotensin-converting enzyme inhibitor.

The median duration of allopurinol therapy at time of screening was 6·0 years [IQR 2·1–14·0]. At the screening visit, most participants were taking a 100–300 mg daily dose of allopurinol (1951 [31·8%] patients on 100 mg; 1066 [17·4%] on 200 mg; 2749 [44·9%] on 300 mg). In the allopurinol lead-in phase, 2201 (35·9%) patients required an increase in allopurinol dose to reach EULAR target serum urate concentration. The daily doses of allopurinol taken by participants immediately before randomisation are shown in the appendix (p 27). At the end of the lead-in phase, the mean daily dose of allopurinol was 278 mg in the allopurinol group and 274 mg in the febuxostat group, and 2983 (97·3%) patients of 3065 in the allopurinol group and 2978 (97·3%) of 3062 with available data in the febuxostat group were at the target urate concentration. After randomisation, 97·5% of febuxostat daily doses were 80 mg and 2·5% were 120 mg. For allopurinol daily doses, 10·0% were 100 mg, 23·3% were 200 mg, 50·9% were 300 mg, 11·9% were 400 mg, and 3·9% were 500–900 mg. The mean daily dose of febuxostat during the trial was 81 mg. The mean daily dose of allopurinol during the trial was 279 mg.

In the primary on-treatment analysis, febuxostat therapy was non-inferior to allopurinol therapy for

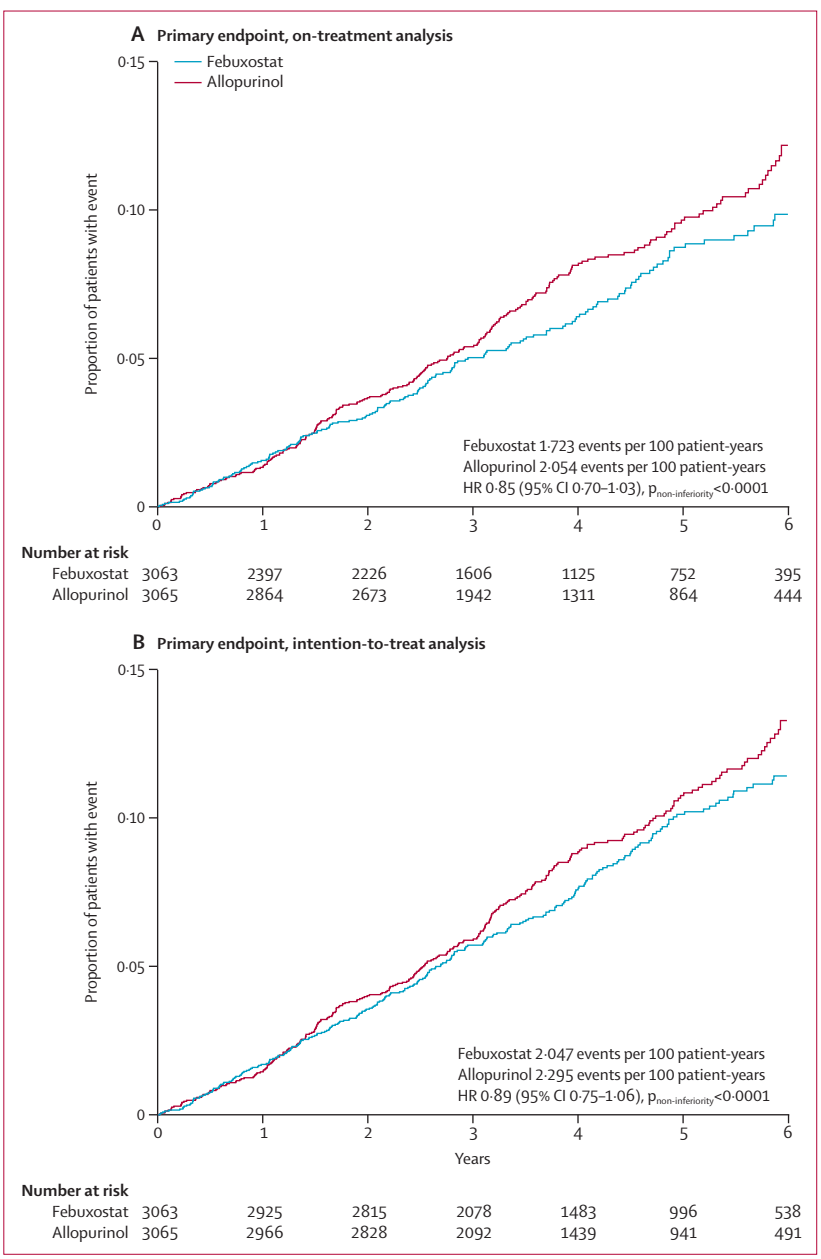

Figure 2: **Cumulative incidence functions for the primary composite endpoint (n=6128)**
The primary composite endpoint consisted of cardiovascular death; hospitalisation for non-fatal myocardial infarction or biomarker-positive acute coronary syndrome; or non-fatal stroke. Analyses were adjusted for the competing risk of deaths not included in the endpoint. (A) On-treatment analysis. (B) Intention-to-treat analysis. HR=hazard ratio.

	Events				HR (95% CI)	$p_{non\text{-}inferiority}$	$p_{superiority}$
	Febuxostat (n=3063)		Allopurinol (n=3065)				
	Patients, n (%)	Rate per 100 patient-years	Patients, n (%)	Rate per 100 patient-years			
Primary endpoint (composite): cardiovascular death; hospitalisation for non-fatal myocardial infarction or biomarker-positive acute coronary syndrome; or non-fatal stroke	256 (8·4%)	2·047	285 (9·3%)	2·295	0·89 (0·75–1·06)	<0·0001	0·185
Cardiovascular death	117 (3·8%)	0·911	122 (4·0%)	0·949	0·96 (0·74–1·23)	0·0088	0·730
Hospitalisation for non-fatal myocardial infarction or biomarker-positive acute coronary syndrome	102 (3·3%)	0·808	110 (3·6%)	0·873	0·93 (0·71–1·21)	0·0067	0·573
Non-fatal stroke	80 (2·6%)	0·629	87 (2·8%)	0·687	0·92 (0·68–1·25)	0·013	0·591
All-cause death	222 (7·2%)	1·728	263 (8·6%)	2·045	0·84 (0·71–1·01)	<0·0001	0·063
Hospitalisation for heart failure	92 (3·0%)	0·724	102 (3·3%)	0·805	0·90 (0·68–1·19)	0·0047	0·441
Hospitalisation for unstable, new, or worsening angina	5 (0·2%)	0·039	12 (0·4%)	0·094	0·41 (0·14–1·16)	0·015	0·092
Hospitalisation for coronary revascularisation	87 (2·8%)	0·689	83 (2·7%)	0·656	1·05 (0·78–1·42)	0·080	0·761
Hospitalisation for cerebrovascular revascularisation	3 (0·1%)	0·023	8 (0·3%)	0·062	0·38 (0·10–1·42)	0·033	0·148
Hospitalisation for transient ischaemic attack	20 (0·7%)	0·156	25 (0·8%)	0·195	0·79 (0·44–1·42)	0·048	0·430
Hospitalisation for non-fatal cardiac arrest	5 (0·2%)	0·039	6 (0·2%)	0·047	0·84 (0·26–2·77)	0·238	0·779
Hospitalisation for venous and peripheral arterial vascular thrombotic event	36 (1·2%)	0·282	40 (1·3%)	0·313	0·90 (0·57–1·41)	0·054	0·640
Hospitalisation for arrhythmia with no evidence of ischaemia	74 (2·4%)	0·583	49 (1·6%)	0·385	1·51 (1·05–2·17)	0·796	0·024

Non-inferiority p values are based on a non-inferiority limit for the HR of 1·3, with the one-sided type I error rate set at 2·5%. The type I error rate was set at 5% for the superiority analyses. HRs were from Cox proportional hazards models adjusted for the stratification variable (previous cardiovascular events) and country. HR=hazard ratio.

Table 3: **Primary and secondary outcomes in the intention-to-treat analysis**

incidence of the primary composite endpoint (allopurinol 2·054 events per 100 patient-years; febuxostat 1·723 events per 100 patient-years; adjusted HR 0·85 [95% CI 0·70–1·03], p<0·0001; table 2; figure 2A). The intention-to-treat analysis confirmed that febuxostat was non-inferior to allopurinol with respect to the primary endpoint (p<0·0001; table 3; figure 2B), and the two-sided superiority analysis showed no significant difference in risk of the primary endpoint between groups (p=0·185; table 3).

Results obtained in the on-treatment and intention-to-treat analyses of secondary outcomes (tables 2, 3) showed that febuxostat was non-inferior to allopurinol with respect to all-cause death (figure 3A, B); each individual component of the primary outcome, including cardiovascular death (figure 3C, D); hospitalisation for heart failure; and hospitalisation for unstable, new, or worsening angina. However, the intention-to-treat analysis also showed a nominally significant increase in hospitalisation for arrhythmia with no evidence of ischaemia (0·385 events per 100 patient-years in the allopurinol group *vs* 0·583 events per 100 patient-years in the febuxostat group; adjusted HR 1·51 [1·05–2·17], $p_{superiority}$=0·024).

3001 (98·0%) patients in the febuxostat group and 3050 (99·5%) patients in the allopurinol group took at least one dose of the study medication and were included in the safety population (n=6051). 973 patients (32·4%) in the febuxostat group and 503 patients (16·5%) in the allopurinol group discontinued randomised therapy. The excess withdrawals of consent and withdrawals from treatment in the febuxostat group occurred in the first year of follow-up, with most occurring in the first 6 months (appendix pp 44–45). Colchicine was the most commonly dispensed drug for gout flare prophylaxis and was dispensed to 2223 (71·4%) patients in the febuxostat group and 1603 (52·6%) in the allopurinol group in the safety analysis set (appendix p 29).

222 (7·2%) patients died and 1720 (57·3%) had at least one serious adverse event in the febuxostat group, and 263 (8·6%) died and 1812 (59·4%) had at least one serious adverse event in the allopurinol group (table 4; appendix pp 30–32). The incidence of endocrine disorders was higher and incidence of neoplasms (benign, malignant, and unspecified, including cysts and polyps) was lower in the febuxostat group compared with in the allopurinol group.

804 (33·6%) of 2394 patients in the febuxostat group and 878 (30·9%) of 2846 in the allopurinol group had at least one value above the upper limit of normal for creatinine concentration (>106 µmol/L in men and >80 µmol/L in women).

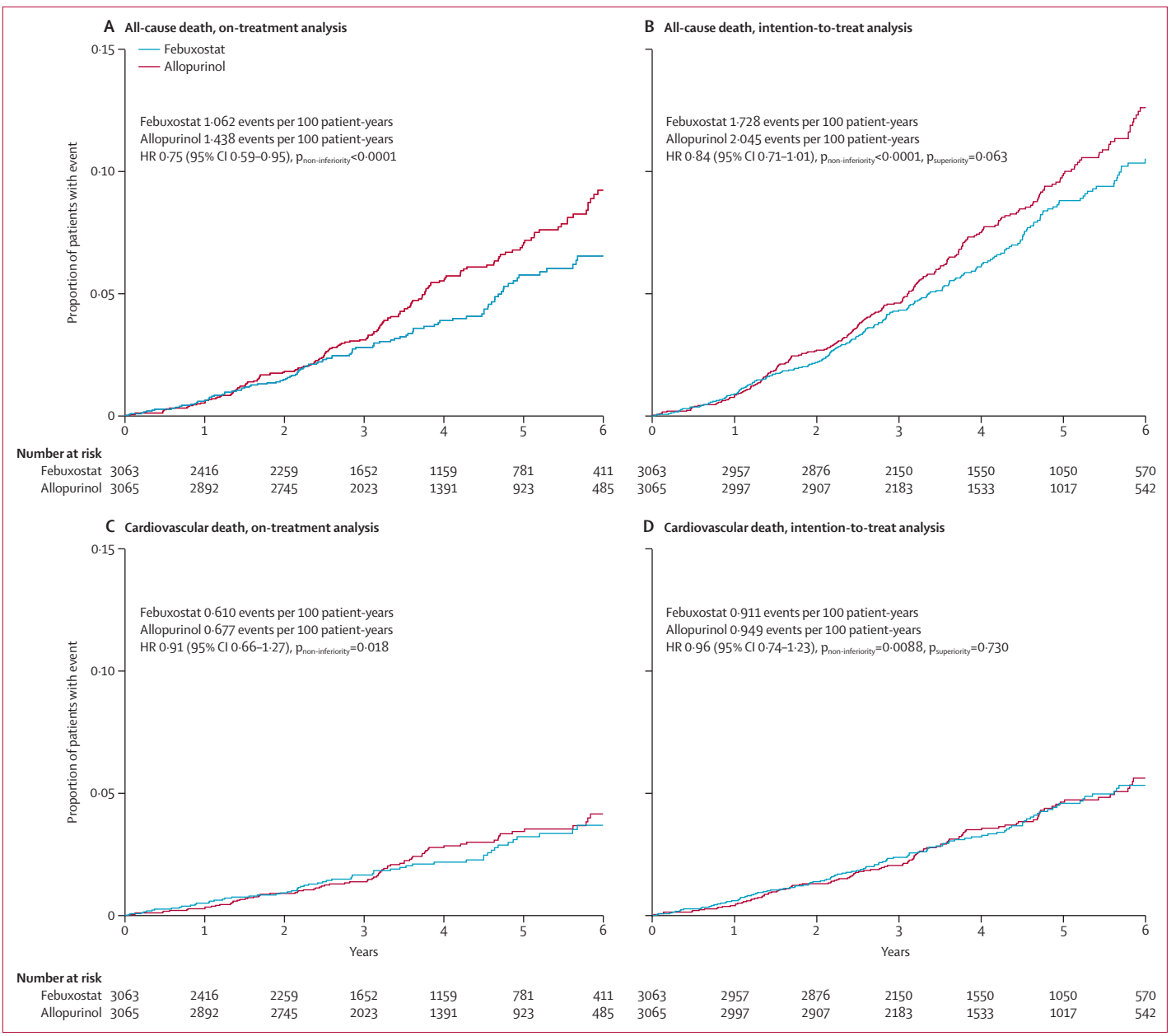

Figure 3: **Cumulative incidence functions for selected secondary endpoints (n=6128)**
(A) All-cause death in the on-treatment analysis. (B) All-cause death in the intention-to-treat analysis. (C) Cardiovascular death in the on-treatment analysis, adjusting for the competing risk of deaths not included in the endpoint. (D) Cardiovascular death in the intention-to-treat analysis, adjusting for the competing risk of deaths not included in the endpoint. HR=hazard ratio.

24 patients had serious adverse events that were considered to be related to treatment: 19 (0·6%) in the febuxostat group (with 23 events in total) and five (0·2%) in the allopurinol group (five events). The largest difference between treatment groups with respect to the incidence of treatment-related serious adverse events was in gastrointestinal disorders (eight [0·3%] patients in the febuxostat group *vs* one [<0·1%] in the allopurinol group). In the allopurinol group, the treatment-related serious adverse events were angina (two [0·1%] patients), thrombocytopenia, dyspepsia, and arthralgia (each one [<0·1%] patient), and all patients recovered. In the febuxostat group, four patients had serious treatment-related pancreatitis (five episodes total), of whom one patient recovered, two recovered with sequelae, and one patient recovered but subsequently had a further episode of pancreatitis plus gastrointestinal perforation, circulatory collapse, and death. In addition, the treatment-related serious adverse events in this group included three cases of diarrhoea (all recovered), one of which was

	Febuxostat (n=3001)	Allopurinol (n=3050)	Difference (95% CI)*
Any event	1720 (57·3%)	1812 (59·4%)	2·1% (–0·4 to 4·6)
Blood and lymphatic system disorders	37 (1·2%)	44 (1·4%)	0·2% (–0·4 to 0·8)
Cardiac disorders	414 (13·8%)	441 (14·5%)	0·7% (–1·1 to 2·4)
Congenital, familial, and genetic disorders	13 (0·4%)	13 (0·4%)	–0·0% (–0·3 to 0·3)
Ear and labyrinth disorders	13 (0·4%)	11 (0·4%)	–0·1% (–0·4 to 0·2)
Endocrine disorders	15 (0·5%)	2 (0·1%)	–0·4% (–0·7 to –0·2)
Eye disorders	178 (5·9%)	183 (6·0%)	0·1% (–1·1 to 1·3)
Gastrointestinal disorders	256 (8·5%)	285 (9·3%)	0·8% (–0·6 to 2·3)
General disorders and administration site conditions	164 (5·5%)	185 (6·1%)	0·6% (–0·6 to 1·8)
Hepatobiliary disorders	75 (2·5%)	75 (2·5%)	–0·0% (–0·8 to 0·7)
Immune system disorders	8 (0·3%)	9 (0·3%)	0·0% (–0·2 to 0·3)
Infections and infestations	376 (12·53%)	430 (14·1%)	1·6% (–0·1 to 3·3)
Injury, poisoning, and procedural complications	224 (7·5%)	247 (8·1%)	0·6% (–0·7 to 2·0)
Investigations	36 (1·2%)	46 (1·5%)	0·3% (–0·3 to 0·9)
Metabolism and nutrition disorders	124 (4·1%)	144 (4·7%)	0·6% (–0·4 to 1·6)
Musculoskeletal and connective tissue disorders	222 (7·4%)	234 (7·7%)	0·3% (–1·1 to 1·6)
Neoplasms (benign, malignant, and unspecified, including cysts and polyps)	344 (11·5%)	407 (13·3%)	1·9% (0·2 to 3·5)
Nervous system disorders	245 (8·2%)	264 (8·7%)	0·5% (–0·9 to 1·9)
Psychiatric disorders	29 (1·0%)	36 (1·2%)	0·2% (–0·3 to 0·7)
Renal and urinary disorders	129 (4·3%)	135 (4·4%)	0·1% (–0·9 to 1·2)
Reproductive system and breast disorders	31 (1·0%)	30 (1·0%)	–0·0% (–0·6 to 0·5)
Respiratory, thoracic, and mediastinal disorders	190 (6·3%)	217 (7·1%)	0·8% (–0·5 to 2·0)
Skin and subcutaneous tissue disorders	21 (0·7%)	26 (0·9%)	0·2% (–0·3 to 0·6)
Social circumstances	6 (0·2%)	8 (0·3%)	0·1% (–0·2 to 0·3)
Surgical and medical procedures	214 (7·1%)	239 (7·8%)	0·7% (–0·6 to 2·0)
Vascular disorders	156 (5·2%)	160 (5·3%)	0·0% (–1·1 to 1·2)

Numbers are patients with at least one event (overall and within each system organ class). *Difference in percentage (allopurinol group minus febuxostat group).

Table 4: **Serious adverse events in the safety analysis set**

additionally associated with acute renal failure (recovered); three cases of atrial fibrillation (two recovered, one not recovered); two cases of cholecystitis (one recovered, one recovered with sequelae); single cases of haematuria, gastro-oesophageal reflux disease, and non-cardiac chest pain (all recovered); and single cases of worsening renal failure, abnormal liver function tests, rotator cuff syndrome, and pneumonia (all recovered with sequelae). Because all patients were taking allopurinol at baseline, those allocated to the allopurinol group were inherently less likely to have treatment-related serious adverse events during the trial than were those allocated to receive febuxostat (a novel treatment).

Overall, more patients were reported to have a malignant neoplasm in the allopurinol group (384 [12·6%]) than in the febuxostat group (322 [10·7%]; appendix p 31). In the 28-day period following the end of the study, four (0·1%) patients in the febuxostat group and four (0·1%) in the allopurinol group died.

We did prespecified subgroup analyses of the primary outcome (both on-treatment and intention-to-treat) based on 28 categories of baseline characteristics (appendix pp 46–49). Only one subgroup analysis (for subgroups defined by pre-randomisation urate concentrations <0·297 mmol/L [<5 mg/dL] and ≥0·297 mmol/L [≥5 mg/dL]) reached statistical significance in the interaction test: a nominally significant reduction in risk of the primary endpoint (adjusted HR 0·66 [95% CI 0·51–0·86]) was found with febuxostat compared with allopurinol in the subgroup with urate concentration less than 0·297 mmol/L, whereas no such difference (1·13 [0·90–1·42]) was found in the other subgroup (on-treatment analysis $p_{interaction}$=0·0013; intention-to-treat analysis $p_{interaction}$=0·0026). Incidence of the primary endpoint in the subgroup of patients with a history of myocardial infarction, stroke, or acute coronary syndrome was similar between the febuxostat group (65 [9·5%] of 684 patients) and the allopurinol group (83 [11·8%] of 705; adjusted HR 1·02 [95% CI 0·74–1·42], $p_{interaction}$=0·202) in the on-treatment analysis, and results were similar in the intention-to-treat analysis (febuxostat 103 [15·1%]; allopurinol 102 [14·5%]; 1·07 [0·81–1·41], $p_{interaction}$=0·119).

Additional subgroup analyses were carried out on the basis of initial gout flair prophylaxis treatment, and concomitant treatment with aspirin, non-steroidal anti-inflammatory drugs and colchicine. There were no significant interactions between randomised treatment and any of these subgroups (appendix pp 50–51).

We did a sensitivity analysis (on-treatment and intention-to-treat) of the composite primary endpoint but replacing cardiovascular death with all-cause death, as well as an on-treatment analysis of the same endpoint but extending the on-treatment period by 90 days, and found non-inferiority of febuxostat relative to allopurinol in each instance, consistent with the results of the main analyses (appendix pp 36–37). In another on-treatment analysis of this composite endpoint (including all-cause death) with additional adjustment for age, sex, LDL and HDL cholesterol concentrations, high-sensitivity troponin I levels, systolic blood pressure, smoking status (current, former, or never), and histories (present or absent) of each of diabetes, hypertension, and cardiovascular disease, febuxostat remained non-inferior to allopurinol (appendix p 38).

Changes in urate concentration from baseline were compared statistically between the two treatment groups each year for years 1–7. Reductions in urate concentration were greater on febuxostat treatment than on allopurinol treatment, with significant differences between the two groups (p<0·0001) each year and mean differences greater than 0·08 mmol/L for years 1–6 (appendix p 34). After randomisation, 1017 patients in the febuxostat group had at least one gout flare (event rate 17·95 per 100 patient-years), compared with 1044 patients in the allopurinol group (19·85 per 100 patient-years).

Discussion

In this study of more than 6000 patients with gout, who had been receiving urate-lowering therapy with a xanthine

oxidase inhibitor at doses designed to lower urate concentration to EULAR target levels (<0·357 mmol/L) for up to 7 years, febuxostat was non-inferior to allopurinol with regard to the occurrence of major cardiovascular outcomes, including the primary outcome of hospitalisation for non-fatal myocardial infarction or biomarker-positive acute coronary syndrome, non-fatal stroke, or death due to a cardiovascular event. Non-inferiority was shown in both the primary on-treatment and intention-to-treat analyses. Importantly, there was no signal of increased death, with lower incidences of all-cause death and cardiovascular death reported in the febuxostat group than in the allopurinol group. The findings contrast with those of the CARES trial,[17] in which the secondary endpoints of adverse cardiovascular outcomes, all-cause death, and cardiovascular death occurred at significantly higher rates with febuxostat than with allopurinol in patients with gout and established cardiovascular comorbidities at baseline, despite febuxostat being non-inferior to allopurinol with respect to rates of the primary endpoint (a composite of death from cardiovascular causes, myocardial infarction, stroke, or unstable angina with urgent revascularisation). However, when efforts were made to trace patients in CARES who were lost to follow-up, this difference in deaths was no longer seen, and it was unclear why increased deaths were associated with lower doses of febuxostat. This difference could simply have been due to information bias caused by the inability to adequately follow up those who withdrew from CARES. The supporting analyses of CARES in which private investigators followed up the vital status of those who withdrew found that the signal of increased deaths in the febuxostat group was no longer significant, and supports this view.[17]

Although the studies were of similar size, there were several differences between CARES and FAST. All patients in CARES had established cardiovascular disease, whereas only 33% of patients in FAST had cardiovascular disease at baseline. CARES included patients with severe heart failure who might have had particularly poor cardiovascular prognosis, whereas FAST excluded patients with NYHA III or IV heart failure. The prevalence of tophi was greater in the CARES population, suggesting more severe gout at baseline. Additionally, CARES allowed inclusion of newly treated patients, whereas FAST only recruited patients who were already established on allopurinol therapy and might therefore have had a lower urate crystal burden, which might be important for cardiovascular risk. To what extent the results of FAST are generalisable to patients with gout who have not previously been treated with urate-lowering therapy or to patients with severe heart failure is not clear. The doses of study medication were different in the two trials, with a lower dose of febuxostat being used in CARES (40–80 mg/day) than in FAST (80–120 mg/day), and the range of doses of allopurinol differed (200–600 mg/day in CARES *vs* 100–900 mg/day in FAST), reflecting the different dose ranges for the two xanthine oxidase inhibitors approved by regulatory agencies in North America and Europe. In CARES, 56·6% of patients discontinued randomised treatment prematurely and 45·0% of patients withdrew and did not complete all trial visits, and were therefore not followed up until the end of the trial). In FAST, there were lower rates of treatment discontinuation (32·4% in the febuxostat group and 16·5% in the allopurinol group) and much better rates of patient follow-up, with only 5·8% of patients in FAST withdrawing from all follow-up.

The results of the CARES study led to regulators issuing alerts from 2017 onwards and subsequently changing prescribing advice for febuxostat and recommending that treatment with febuxostat should be avoided in patients with pre-existing major cardiovascular diseases (eg, myocardial infarction, stroke, or unstable angina), unless no other therapeutic options are appropriate. At the time that this advice was released in Europe and the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) requested that the FAST investigators should provide an updated risk–benefit assessment about whether the study should continue. An independent risk–benefit assessment led to the MHRA making the recommendation in 2018 that FAST should continue unchanged. However, it is likely that the regulatory advice released to health-care professionals at this time increased withdrawals from randomised medication in the febuxostat group of the study. Notably, no increased risk of adverse cardiovascular events was found in the FAST subgroup of patients with previous myocardial infarction, stroke, or acute coronary syndrome, who were very similar to the patients included in the CARES study.

The FAST study finished underpowered for the required number of primary events, with 413 events instead of the planned target of 456 events. The lower number of primary events will have resulted in only a modest reduction in statistical power from 80% to approximately 77% to exclude a non-inferiority limit of 1·3, or alternatively, 80% power to exclude a non-inferiority limit of 1·315.

The primary analysis of FAST, endorsed by the European Medicines Agency, was an on-treatment rather than intention-to-treat analysis, as is commonly the case in a non-inferiority safety trial. In such trials, on-treatment analysis results in a comparison that is undiluted by periods in which the medications under investigation were not taken. In FAST, our research pharmacy had regular contact with all trial participants about adherence so our ascertainment of exposure to randomised medications was good. However, an on-treatment analysis might not have provided a true, unbiased analysis of the randomised population if there were differential discontinuation rates, as indeed there were in FAST, with higher discontinuation rates and earlier discontinuations of febuxostat than allopurinol.

This difference could have been influenced by the increased use of colchicine in patients allocated to receive febuxostat, and the fact that switching from any established drug therapy to a new drug therapy usually results in more discontinuations in trials. For this reason, a supporting intention-to-treat analysis was also done. Because we were able to follow up patients until the end of the trial by telephone and other personal contact and by record linkage to national hospitalisation and death records (except in the small proportion of patients who withdrew completely), our ascertainment of outcomes in the intention-to-treat analysis was very good. Both analyses provided similar findings with respect to deaths.

Although an association between serum urate concentrations and cardiovascular disease is well established from numerous observational studies, the hypothesis that hyperuricaemia has a direct causal role in the aetiopathogenesis of comorbid cardiovascular disease remains controversial and is not supported by mendelian randomisation studies.[18,19]

Colchicine use was greater in the febuxostat group, probably because more patients switching therapy to febuxostat chose to accept gout flare prophylaxis than those continuing on allopurinol. Although some recent trials have shown that treatment with colchicine can improve outcomes in patients with recent myocardial infarction and with chronic coronary disease, published evidence that treatment with colchicine might be associated with improvements in cardiovascular outcomes has been inconsistent.[20–23] In FAST, although prophylaxis against flares of gout was offered to all patients, only some accepted it, those who took it mainly did so at the very beginning of the trial, and it is likely that some patients chose to take it for less than the 6 months provided. It is unlikely that the relatively short-term administration of low-dose colchicine or NSAIDs as prophylaxis, or any differences in concomitant use of colchicine or NSAIDs, even with the imbalances between treatment groups, had any major effect on the long-term outcomes of FAST. The effects of prophylaxis or concomitant use of NSAIDs or colchicine are shown in the appendix (pp 50–51).

Because neither FAST nor CARES had a placebo group for comparison against active treatment with a xanthine oxidase inhibitor, either or both xanthine oxidase inhibitors might actually protect patients with gout against cardiovascular disease and death. Notably, the cardiovascular event rates in FAST were lower than anticipated. A large randomised trial comparing allopurinol (600 mg/day) therapy versus usual care, the ALL-HEART study,[24] is currently underway in the UK to determine whether allopurinol has a beneficial effect on major cardiovascular outcomes in patients with ischaemic heart disease. Should allopurinol be of benefit in ischaemic heart disease, a case could be made to carry out a randomised trial of febuxostat versus usual care or placebo in patients with cardiovascular disease.

Other findings of FAST deserve further research. One possibility is to investigate the findings of numerically higher incidence of non-cardiovascular deaths and malignancies that occurred in the allopurinol group compared with the febuxostat group. Another is to investigate the higher rate of hospitalisations for arrhythmias without evidence of ischaemia.

In summary, we found that febuxostat at doses of 80–120 mg/day was non-inferior to allopurinol at 100–900 mg/day with respect to its effect on adverse cardiovascular events. In contrast to a previous large study, we found no signal of increased all-cause or cardiovascular deaths with febuxostat. In light of these findings, regulatory advice to avoid the use of febuxostat in patients with cardiovascular disease should be reconsidered and modified.

Contributors

This study was conceived by TMM. TMM, IF, and GN formed the Executive Committee of the trial. TMM, IF, GN, and ISM participated in designing the study. MR and IF did the statistical analysis. ISM wrote the first draft of the manuscript with input from IF and TMM. IF and MR accessed and verified the data underlying the study. All authors participated in the interpretation of the data and critical review of the manuscript. All authors have read and approved the final version.

Declaration of interests

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Data sharing

Once the investigators have been given the opportunity to publish further papers, the steering committee will be happy to consider applications for de-identified information. Requests should be made to the corresponding author.

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