ORIGINAL ARTICLE

Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout

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ABSTRACT

BACKGROUND

Cardiovascular risk is increased in patients with gout. We compared cardiovascular outcomes associated with febuxostat, a nonpurine xanthine oxidase inhibitor, with those associated with allopurinol, a purine base analogue xanthine oxidase inhibitor, in patients with gout and cardiovascular disease.

METHODS

We conducted a multicenter, double-blind, noninferiority trial involving patients with gout and cardiovascular disease; patients were randomly assigned to receive febuxostat or allopurinol and were stratified according to kidney function. The trial had a prespecified noninferiority margin of 1.3 for the hazard ratio for the primary end point (a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or unstable angina with urgent revascularization).

RESULTS

In total, 6190 patients underwent randomization, received febuxostat or allopurinol, and were followed for a median of 32 months (maximum, 85 months). The trial regimen was discontinued in 56.6% of patients, and 45.0% discontinued follow-up. In the modified intention-to-treat analysis, a primary end-point event occurred in 335 patients (10.8%) in the febuxostat group and in 321 patients (10.4%) in the allopurinol group (hazard ratio, 1.03; upper limit of the one-sided 98.5% confidence interval [CI], 1.23; P=0.002 for noninferiority). All-cause and cardiovascular mortality were higher in the febuxostat group than in the allopurinol group (hazard ratio for death from any cause, 1.22 [95% CI, 1.01 to 1.47]; hazard ratio for cardiovascular death, 1.34 [95% CI, 1.03 to 1.73]). The results with regard to the primary end point and all-cause and cardiovascular mortality in the analysis of events that occurred while patients were being treated were similar to the results in the modified intention-to-treat analysis.

CONCLUSIONS

In patients with gout and major cardiovascular coexisting conditions, febuxostat was noninferior to allopurinol with respect to rates of adverse cardiovascular events. All-cause mortality and cardiovascular mortality were higher with febuxostat than with allopurinol. (Funded by Takeda Development Center Americas; CARES ClinicalTrials.gov number, NCT01101035.)

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Gout is a chronic illness characterized by hyperuricemia, arthropathy, tophus development, and urolithiasis and is associated with an increased risk of cardiovascular and chronic kidney disease.[1] The risk of cardiovascular events, including death, is substantially higher in people with gout than in those without gout.[2,3] When the Food and Drug Administration (FDA) released a guidance document outlining specific requirements for the cardiovascular safety assessment of antidiabetic therapies,[4] investigators in other therapeutic areas, including those studying gout therapies, began to explore cardiovascular safety with similarly designed trials.

Febuxostat, a nonpurine inhibitor of xanthine oxidase that is used for the management of hyperuricemia in patients with gout, inhibits both the oxidized and reduced forms of xanthine oxidase and decreases the formation of uric acid.[5] Febuxostat provides highly selective and potent inhibition of xanthine oxidase and greater hypouricemic activity than do commonly used doses of allopurinol.[6] During its development, febuxostat was compared with placebo and allopurinol in clinical trials involving more than 5000 patients with gout[5-7]; these trials suggested a modestly higher rate of cardiovascular events with febuxostat. The Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial was therefore conducted as an FDA requirement to determine whether febuxostat was noninferior to allopurinol with regard to major cardiovascular events in patients with gout and cardiovascular disease.

METHODS

TRIAL DESIGN

We conducted a multicenter, randomized, double-blind noninferiority trial; details of the design of the trial have been published previously.[8] The funder (Takeda Pharmaceuticals) participated in the trial design, conduct, and monitoring and in data collection, storage, and analyses. An independent data and safety monitoring committee monitored the trial and had access to the unblinded data. Statistical analyses were performed for the data and safety monitoring committee by an independent statistical group (WebbWrites).

The academic authors of the present article drafted the manuscript, had full access to the final trial data, and vouch for the accuracy and completeness of the data and the analyses, as well as for the fidelity of the trial to the protocol, which is available with the full text of this article at NEJM.org. The appropriate national and institutional regulatory authorities and ethics committees approved the trial design.

PATIENTS

Patients were eligible for enrollment in the trial if they had a diagnosis of gout fulfilling the American Rheumatism Association criteria[9] and a history of major cardiovascular disease before randomization (detailed inclusion and exclusion criteria are provided in Table S1 in the Supplementary Appendix, available at NEJM.org). Additional criteria for inclusion were a serum urate level of at least 7.0 mg per deciliter (420 μmol per liter), or of at least 6.0 mg per deciliter (360 μmol per liter) with inadequately controlled gout, after a 1-to-3-week washout period from previous gout therapies. Patients were regarded as having a history of major cardiovascular disease if they had had a myocardial infarction, hospitalization for unstable angina, stroke, hospitalization for transient ischemic attack, peripheral vascular disease, or diabetes mellitus with evidence of microvascular or macrovascular disease, as defined previously.[8] All participants provided written informed consent.

TREATMENT AND PROCEDURES

Patients were randomly assigned to receive febuxostat or allopurinol administered in a double-blind fashion once daily. Randomization was stratified according to the estimated creatinine clearance at baseline (≥60 ml per minute vs. ≥30 but <60 ml per minute).

Doses of allopurinol were modified according to kidney function. Patients with an estimated creatinine clearance of at least 60 ml per minute initially received allopurinol at a dose of 300 mg once daily, which was increased in 100-mg increments monthly until the patient either had a serum urate level of less than 6.0 mg per deciliter or was receiving an allopurinol dose of 600 mg once daily. Patients who had an estimated creatinine clearance of at least 30 but less than 60 ml

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per minute initially received 200 mg of allopurinol; the dose was increased in 100-mg increments until the patient either had a serum urate level of less than 6.0 mg per deciliter or was receiving an allopurinol dose of 400 mg once daily.

Febuxostat doses were not modified according to kidney function. Patients who were randomly assigned to receive febuxostat initially received 40 mg once daily and continued to receive this dose if the serum urate level was less than 6.0 mg per deciliter after 2 weeks of therapy. If the serum urate level was higher than 6.0 mg per deciliter at the week 2 visit, the dose of febuxostat was increased to 80 mg once daily for the remainder of the trial.

The patients' serum urate levels were revealed to the site investigators only during a 10-week dose-adjustment period to facilitate dose increases that were based on urate response. During that period, the administration of double-blind, double-dummy trial medications was guided by an interactive voice-response system, a procedure that prevented unblinding for patients whose dose was not adjusted. After dose adjustments were completed, urate levels were concealed from investigators and the sponsor, and the interactive voice-response system was used to manage treatment throughout the trial.

At the screening visit, all urate-lowering therapy was discontinued and, unless the patient had a history of unacceptable side effects from colchicine, treatment with colchicine at a dose of 0.6 mg daily was started for gout flare prophylaxis. All the patients received prophylaxis for the first 6 months of randomly assigned treatment. If colchicine treatment resulted in unacceptable side effects and the estimated creatinine clearance was at least 50 ml per minute, patients received naproxen (250 mg twice daily) with lansoprazole (15 mg once daily). If patients could receive neither colchicine nor naproxen, other nonsteroidal antiinflammatory drugs (NSAIDs) or prednisone could be provided as prophylaxis, or the investigators could choose to manage gout flares as they occurred.

Outpatient visits were scheduled at screening and randomization and at 2, 4, 6, 8, 10, 12, and 24 weeks after randomization and every 6 months during subsequent years of the trial. Patients with reduced kidney function or who were older than 65 years of age at randomization also had visits at 9 months and 15 months to monitor serum chemical profiles. If patients agreed to be monitored but would not return for study visits, telephone contacts were completed, but this was not preferred or recommended to the sites.

END POINTS

The primary composite end point was the first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or urgent revascularization for unstable angina (definitions are provided in Table S2 in the Supplementary Appendix).[10] The secondary safety end points included a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke as well as the individual components of the primary end point. The consistency of effects on the primary end point was explored in a variety of subgroups (both prespecified and post hoc). Additional safety end points included death from any cause, urgent cerebrovascular revascularization, transient ischemic attack, hospitalization for heart failure, arrhythmias not associated with ischemia, and venous thromboembolic events. An independent central end-points committee, the members of which were unaware of the treatment assignments, adjudicated all suspected end-point events.

STATISTICAL ANALYSIS

Cox proportional-hazards models, stratified according to baseline kidney function, were used to analyze the time to first occurrence of primary and secondary end-point events for all patients who underwent randomization and received treatment. A determination of noninferiority of febuxostat to allopurinol required that the upper bound of the one-sided confidence interval of the hazard ratio for the primary end point be less than 1.3. The number and percentage of patients with a primary end-point event or cardiovascular death were tabulated for various subgroups. The relative risk (febuxostat vs. allopurinol) was calculated within each subgroup, with homogeneity among subgroup levels assessed with the use of the Cochran–Mantel–Haenszel test. Sensitivity analyses were performed by excluding events that occurred after treatment discontinuation and events that occurred more than 30 days after treatment discontinuation.

The trial was designed to accrue 624 primary events for assessing the noninferiority of febuxo-

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stat to allopurinol with regard to cardiovascular risk, under the assumption of a true hazard ratio of 1.0 and 90% power. Interim analyses were conducted when approximately 25%, 50%, and 75% of the events had occurred. For each group-sequential analysis, it was specified that the upper bound of the one-sided confidence interval for the hazard ratio (febuxostat vs. allopurinol) would be calculated with the use of the critical value from the Lan–DeMets–O'Brien–Fleming alpha-spending function, which preserves an overall one-sided alpha of 0.025.[11] No other adjustments for multiplicity were made. Each of these analyses was conducted by an independent statistician and reviewed by the data and safety monitoring board.

It was planned that, if the upper bound of the one-sided confidence interval of the hazard ratio was less than 1.3 at any interim analysis, the trial would be stopped, since noninferiority of febuxostat to allopurinol with regard to cardiovascular risk would be declared. In April 2016, at the time of the 75% interim analysis, the estimated hazard ratio and adjusted upper bound of the confidence interval for the hazard ratio were 0.99 and 1.23, respectively. However, because of a discrepancy between the hazard ratio for death from any cause in the intention-to-treat analysis and in the analysis of events that occurred during treatment, the data and safety monitoring board recommended continuing the trial until the prespecified 624 primary events had occurred.

RESULTS

PATIENTS

We enrolled 6198 patients from 320 North American sites from April 2010 through May 2017. Eight patients never received trial medication, which left 6190 patients in a modified intention-to-treat analysis (Fig. S1 in the Supplementary Appendix). The two treatment groups were well balanced with regard to all baseline characteristics (Table 1, and Table S3 in the Supplementary Appendix). In the febuxostat group, 61.0% of the patients received 40 mg and 39.0% received 80 mg daily as the final adjusted dose. In the allopurinol group, on the basis of the protocol-directed criteria for estimated creatinine clearance, 21.8% of the patients received 200 mg, 44.6% received 300 mg, 25.2% received 400 mg, 4.3% received 500 mg, and 4.1% received 600 mg.

Overall, 56.6% of patients discontinued trial treatment prematurely; the rates of premature discontinuation were similar in the febuxostat and allopurinol groups (57.3% and 55.9%, respectively). The percentage of patients who did not complete all trial visits was 45.0% overall — 45.0% in the febuxostat group and 44.9% in the allopurinol group. The median duration of exposure to febuxostat was 728 days, and the median duration of exposure to allopurinol was 719 days. The median duration of follow-up was 968 days in the febuxostat group and 942 days in the allopurinol group.

BIOCHEMICAL EFFECTS

The proportion of patients with a serum urate level of less than 6.0 mg per deciliter was higher in the febuxostat group than in the allopurinol group at week 2; thereafter, higher proportions of patients in the febuxostat group had maintenance of serum urate levels at less than 6.0 mg per deciliter at most time points, although the differences between the groups were not large (Table S4 in the Supplementary Appendix). In addition, a larger proportion of patients in the febuxostat group than in the allopurinol group had serum urate levels of less than 5.0 mg per deciliter (300 μmol per liter) for the entire trial. Overall, the rates of gout flares were similar in the two treatment groups (0.68 and 0.63 flares per patient-year in the febuxostat group and allopurinol group, respectively). There were no significant differences in serum levels of electrolytes, glucose, or lipids or in blood pressure between the groups during the trial (Table S5 in the Supplementary Appendix), nor were there differences in cardiovascular medication use (Table S6 in the Supplementary Appendix).

SAFETY

After the accrual of 624 events that initiated trial closeout and before database lock, 32 additional primary end-point events occurred. In the complete analysis, a primary end-point event occurred at similar rates in the febuxostat group and the allopurinol group (10.8% and 10.4% of patients, respectively, at a median period of 32 months; hazard ratio, 1.03; upper bound of the one-sided 98.5% confidence interval [CI], 1.23; P=0.002 for noninferiority) (Table 2 and Fig. 1). In the analysis of the nonfatal secondary end points, the

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Table 1. Baseline Characteristics of the Patients.*

Characteristic	Febuxostat (N=3098)	Allopurinol (N=3092)
Median age (interquartile range) — yr	64.0 (58–71)	65.0 (58–71)
Age ≥65 yr — no. (%)	1514 (48.9)	1586 (51.3)
Male sex — no. (%)	2604 (84.1)	2592 (83.8)
Duration of gout — yr	11.8±11.4	11.9±11.2
Baseline serum urate level — mg/dl	8.7±1.7	8.7±1.7
Presence of tophi — no. (%)	668 (21.6)	650 (21.0)
Median body weight (interquartile range) — kg	97.7 (84–113)	97.3 (84–113)
Body-mass index†	33.6±7.0	33.4±6.9
Race or ethnic group — no. (%)‡		
White	2160 (69.7)	2140 (69.2)
Black	552 (17.8)	593 (19.2)
Asian	92 (3.0)	96 (3.1)
American Indian or Alaska Native	262 (8.5)	234 (7.6)
Native Hawaiian or other Pacific Islander	13 (0.4)	14 (0.5)
Other	19 (0.6)	15 (0.5)
Cardiovascular risk factors and history — no. (%)		
Diabetes mellitus with small-vessel disease	1193 (38.5)	1213 (39.2)
Hypertension	2864 (92.4)	2851 (92.2)
Hyperlipidemia	2678 (86.4)	2702 (87.4)
Myocardial infarction	1197 (38.6)	1231 (39.8)
Hospitalization for unstable angina	855 (27.6)	869 (28.1)
Coronary revascularization	1129 (36.4)	1182 (38.2)
Cerebral revascularization	69 (2.2)	54 (1.7)
Congestive heart failure	622 (20.1)	631 (20.4)
Stroke	460 (14.8)	410 (13.3)
Peripheral vascular disease	412 (13.3)	375 (12.1)
Median estimated creatinine clearance — ml/min§		
Stage 1 or 2 chronic kidney disease	75.0	73.0
Stage 3 chronic kidney disease	46.0	46.0
Stage of chronic kidney disease — no./total no. (%)		
Stage 1 or 2	1456/3092 (47.1)	1459/3090 (47.2)
Stage 3	1636/3092 (52.9)	1631/3090 (52.8)

* Plus–minus values are means ±SD. There were no significant differences between the two groups with regard to any baseline characteristic. To convert the values for urate to micromoles per liter, multiply by 59.48.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Race or ethnic group was reported by the patient.
§ Estimated creatinine clearance was calculated with the use of the Cockcroft–Gault formula and was corrected for ideal body weight. A value of 60 ml per minute or more indicated stage 1 or 2 chronic kidney disease, and a value of at least 30 but less than 60 ml per minute indicated stage 3 chronic kidney disease.

hazard ratios were consistent with the overall result. However, the risk of death from any cause and the risk of cardiovascular death were higher in the febuxostat group than in the allopurinol group (Table 2). Among the causes of cardiovascular death, sudden cardiac death was the most

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Table 2. Major Safety End Points (Modified Intention-to-Treat Analysis).*

End Point	Febuxostat (N=3098)	Allopurinol (N=3092)	Hazard Ratio (95% CI)	P Value†
	no. of patients (%)			
Primary end point: composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or urgent revascularization due to unstable angina	335 (10.8)	321 (10.4)	1.03 (0.87–1.23)‡	0.66 (0.002)
Secondary end points				
Cardiovascular death	134 (4.3)	100 (3.2)	1.34 (1.03–1.73)	0.03
Nonfatal myocardial infarction	111 (3.6)	118 (3.8)	0.93 (0.72–1.21)	0.61
Nonfatal stroke	71 (2.3)	70 (2.3)	1.01 (0.73–1.41)	0.94
Urgent revascularization for unstable angina	49 (1.6)	56 (1.8)	0.86 (0.59–1.26)	0.44
Composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	296 (9.6)	271 (8.8)	1.09 (0.92–1.28)	0.33
Death from any cause	243 (7.8)	199 (6.4)	1.22 (1.01–1.47)	0.04

* The modified intention-to-treat analysis included all patients who underwent randomization with the exception of the 8 patients who never received febuxostat or allopurinol.
† The P value in parentheses is for test of the null hypothesis that the hazard ratio is at least 1.3 versus the one-sided alternative (noninferiority). All other P values are values for the test of superiority of febuxostat to allopurinol and were calculated with the use of a Cox regression analysis.
‡ The 97% confidence interval is provided here.

prevalent classification, occurring in 83 patients (2.7%) in the febuxostat group and 56 patients (1.8%) in the allopurinol group (Table S7 in the Supplementary Appendix). Rates of hospitalization for heart failure, hospital admissions for arrhythmias not associated with ischemia, venous thromboembolic events, and hospitalization for transient ischemic attacks were similar in the two groups (Table S8 in the Supplementary Appendix).

In an analysis according to subgroup, the results with regard to the primary end point showed no heterogeneity associated with any of the baseline factors (Fig. 2). For cardiovascular mortality, there was an interaction for NSAID use and the absence of use of low-dose aspirin (unadjusted P<0.05 for both comparisons) (Fig. S2 in the Supplementary Appendix).

ANALYSES OF EVENTS THAT OCCURRED DURING TREATMENT

In the prespecified analysis of events that occurred during receipt of the trial drug or within 30 days after discontinuation of treatment, a primary end-point event occurred in 7.8% of patients in the febuxostat group and 7.7% of patients in the allopurinol group (hazard ratio, 1.00; upper bound of the one-sided 98.5% CI, 1.22). In this analysis, the rate of cardiovascular death was higher in the febuxostat group than in the allopurinol group (hazard ratio, 1.49; 95% CI, 1.01 to 2.22) (Table 3). In a post hoc analysis of events that occurred during treatment, a primary end-point event was also found to occur at similar rates in the febuxostat group and the allopurinol group (6.2% and 6.4% of patients, respectively; hazard ratio, 0.94; upper bound of the one-sided 98.5% CI, 1.17) (Table S9 in the Supplementary Appendix). The risk of death from any cause and the risk of cardiovascular death were higher in the febuxostat group than in the allopurinol group.

OTHER ANALYSES

The baseline characteristics were balanced among the patients who did not complete all the trial visits and those who completed all the visits (Table S10 in the Supplementary Appendix). The proportions of patients who did not complete all the trial visits were larger in the United States than in Canada or Mexico (Table S11 in the Supplementary Appendix). There were 199 additional patients, identified by a search company (Omni-

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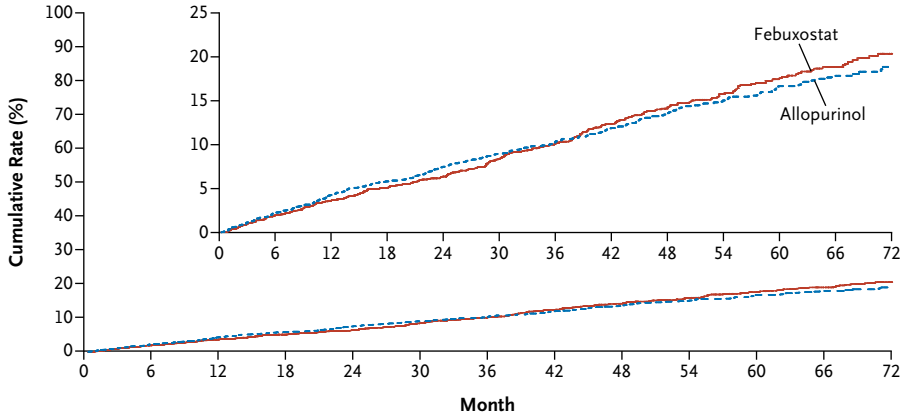
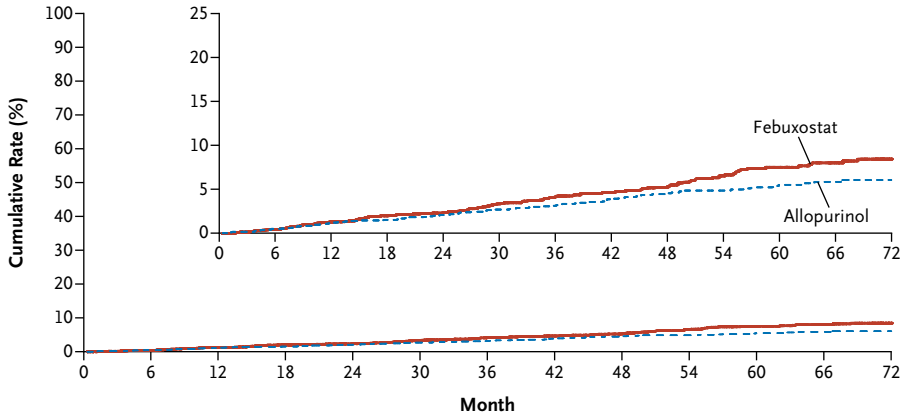
A Primary End Point



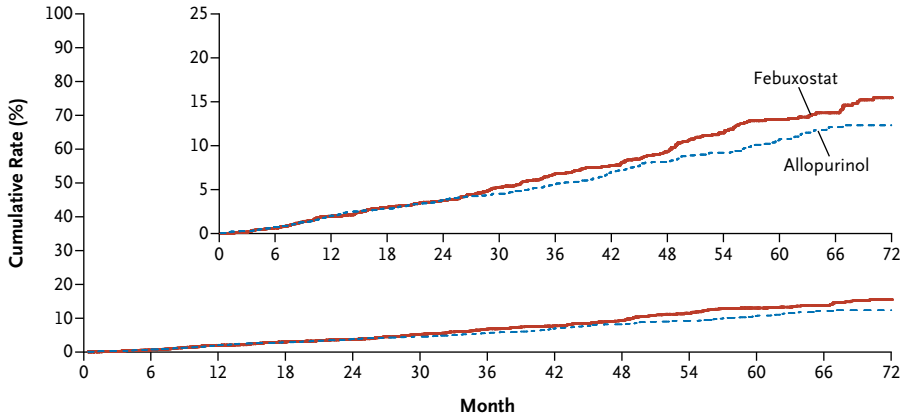
No. at Risk													
Febuxostat	3098	2784	2493	2111	1854	1589	1369	1165	955	778	573	441	264
Allopurinol	3092	2764	2465	2080	1815	1560	1361	1132	933	767	589	437	258

B Cardiovascular Mortality



No. at Risk													
Febuxostat	3098	2823	2550	2174	1922	1659	1440	1243	1033	838	627	482	288
Allopurinol	3092	2807	2530	2152	1898	1637	1433	1204	1008	838	646	489	287

C All-Cause Mortality



No. at Risk													
Febuxostat	3098	2828	2552	2179	1928	1666	1447	1251	1038	840	631	487	289
Allopurinol	3092	2812	2540	2161	1906	1648	1444	1215	1015	842	650	489	288

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Figure 1 (facing page). Cumulative Kaplan–Meier Estimates of the Time to the First Occurrence of an Adjudicated End-Point Event.

Panel A shows the time until the first occurrence of a primary end-point event — cardiovascular death, myocardial infarction, stroke, or urgent revascularization due to unstable angina — in the febuxostat group and the allopurinol group. A primary end-point event occurred in 10.8% of patients in the febuxostat group and 10.4% of patients in the allopurinol group after a median exposure of 32 months (hazard ratio, 1.03; upper bound of the one-sided 98.5% CI, 1.23). Panel B shows the time until death from a cardiovascular cause (hazard ratio, 1.34; 95% CI, 1.03 to 1.73), and Panel C the time until death from any cause (hazard ratio, 1.22; 95% CI, 1.01 to 1.47). The insets show the same data on an enlarged y axis.

Trace), who died (Table S12 in the Supplementary Appendix). The rates of death from any cause during treatment (incorporating the additional deaths) were consistent with those in the analyses of events that occurred during treatment described above. The rates of death from any cause after discontinuation of trial medication were similar in the two treatment groups.

DISCUSSION

In the CARES trial, treatment with febuxostat resulted in overall rates of major cardiovascular events that were similar to those associated with allopurinol treatment among patients with gout who had coexisting cardiovascular disease. However, cardiovascular death and deaths from any cause were more frequent in the febuxostat group than in the allopurinol group.

Although xanthine oxidase inhibitors are in widespread clinical use for the treatment of patients with gout,[12] data on the cardiovascular safety of these drugs from large, randomized clinical trials are limited. During a development program involving more than 5000 patients, the rate of cardiovascular events was higher among patients treated with febuxostat (0.74 per 100 patient-years; 95% CI, 0.36 to 1.37) than among those treated with allopurinol (0.60 per 100 patient-years; 95% CI, 0.16 to 1.53).[6-8] In contrast, observational evaluations have suggested beneficial cardiovascular outcomes after treatment with febuxostat or allopurinol in patients with gout and coexisting cardiorenal conditions.[13,14] The population in our trial included patients who were at considerably higher cardiovascular risk than those included in other assessments of the cardiovascular safety of various gout therapies,[15,16] with event rates during our trial of more than 10%. The safety outcomes in this trial were prespecified and adjudicated by members of a cardiovascular end-point committee who were unaware of the treatment assignments; therefore, our safety outcomes may be more reliable than data based on conventional adverse-event reporting.

Unexpectedly, all-cause mortality was higher in the febuxostat group than in the allopurinol group, because of an excess of cardiovascular deaths. Findings were similar in the modified intention-to-treat analysis and in the prespecified analysis that included events that occurred during treatment and within 30 days after treatment discontinuation. The mechanism underlying this risk of death is unclear. Preclinical cardiovascular studies of febuxostat have shown no toxic effects related to cardiac rhythm, function, or metabolism.[17-21] In addition, the rates of adjudicated nonfatal events, including myocardial infarction, coronary revascularization, arrhythmias, and hospitalization for heart failure, were similar in the febuxostat group and the allopurinol group.

The only heterogeneity in the analyses of cardiovascular mortality occurred in two subgroups — patients with concomitant administration of aspirin or NSAIDs. These drugs may be associated with more frequent gout flares, which, in turn, could lead to increases in cardiovascular events.[22] However, we did not find a large difference in the reduction in urate level between the treatment groups, nor did we detect differences in flare rates. Furthermore, the occurrence and intensity of gout flares are difficult to capture accurately in clinical trials. Finally, these findings may have been due to chance, given the large number of tests performed and the small numbers of events in each subgroup.

Important limitations of this trial are the large number of participants who discontinued the trial treatment and the large number of participants who did not complete follow-up. Discontinuation of treatment would be expected to bias the analyses toward the null hypothesis, which could have resulted in missing a significant difference between the groups in the primary or nonfatal secondary outcomes. The effect of the high rate of loss to follow-up is less easy to predict, since it may not have been random; however,

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Subgroup	Febuxostat	Allopurinol	Relative Risk (95% CI)	P Value for Interaction
	no. of patients with primary end point/total no. (%)			
Baseline renal function				0.40
Moderately reduced	207/1636 (12.7)	212/1631 (13.0)	0.97 (0.81–1.16)	
Mildly reduced	110/1217 (9.0)	92/1231 (7.5)	1.21 (0.93–1.58)	
Normal	17/239 (7.1)	17/228 (7.5)	0.95 (0.50–1.82)	
Age				0.38
<65 yr	133/1584 (8.4)	130/1506 (8.6)	0.97 (0.77–1.23)	
≥65 yr	202/1514 (13.3)	191/1586 (12.0)	1.11 (0.92–1.33)	
Sex				0.61
Female	42/494 (8.5)	45/500 (9.0)	0.94 (0.63–1.41)	
Male	293/2604 (11.3)	276/2592 (10.6)	1.06 (0.90–1.23)	
BMI				0.89
<30	110/1045 (10.5)	106/1063 (10.0)	1.06 (0.82–1.36)	
≥30	225/2053 (11.0)	215/2024 (10.6)	1.03 (0.86–1.23)	
NSAID use				0.10
Yes	112/856 (13.1)	95/908 (10.5)	1.25 (0.97–1.62)	
No	223/2242 (9.9)	226/2184 (10.3)	0.96 (0.81–1.15)	
Low-dose aspirin use				0.09
Yes	163/1496 (10.9)	175/1481 (11.8)	0.92 (0.75–1.13)	
No	172/1602 (10.7)	146/1611 (9.1)	1.18 (0.96–1.46)	
Smoking history				0.91
Current smoker	38/390 (9.7)	38/415 (9.2)	1.06 (0.69–1.63)	
Nonsmoker or former smoker	297/2708 (11.0)	283/2677 (10.6)	1.04 (0.89–1.21)	
Baseline serum urate (mg/dl)				0.78
<9.0	162/1778 (9.1)	166/1815 (9.1)	1.00 (0.81–1.22)	
9.0 to <10.0	83/666 (12.5)	71/646 (11.0)	1.13 (0.84–1.53)	
≥10.0	90/654 (13.8)	84/631 (13.3)	1.03 (0.78–1.36)	
History of diabetes				0.72
Yes	193/1710 (11.3)	180/1699 (10.6)	1.07 (0.88–1.29)	
No	142/1388 (10.2)	141/1393 (10.1)	1.01 (0.81–1.26)	
History of hypertension				0.73
Yes	318/2864 (11.1)	306/2851 (10.7)	1.03 (0.89–1.20)	
No	17/234 (7.3)	15/241 (6.2)	1.17 (0.60–2.28)	
History of nonfatal myocardial infarction				0.37
Yes	185/1197 (15.5)	171/1231 (13.9)	1.11 (0.92–1.35)	
No	150/1901 (7.9)	150/1861 (8.1)	0.98 (0.79–1.22)	
History of nonfatal stroke				0.15
Yes	63/460 (13.7)	67/410 (16.3)	0.84 (0.61–1.15)	
No	272/2638 (10.3)	254/2682 (9.5)	1.09 (0.93–1.28)	
Race				0.65
White	268/2160 (12.4)	260/2140 (12.1)	1.02 (0.87–1.20)	
Nonwhite	67/938 (7.1)	61/952 (6.4)	1.11 (0.80–1.56)	
Years since gout diagnosis				0.46
<5	130/1150 (11.3)	118/1091 (10.8)	1.05 (0.83–1.32)	
5–10	48/580 (8.3)	60/615 (9.8)	0.85 (0.59–1.22)	
>10	156/1367 (11.4)	143/1386 (10.3)	1.11 (0.89–1.37)	
History of cardiac revascularization				0.16
Yes	187/1129 (16.6)	169/1182 (14.3)	1.16 (0.96–1.40)	
No	148/1969 (7.5)	152/1910 (8.0)	0.94 (0.76–1.17)	
Initial gout flare prophylaxis				0.91
Colchicine	295/2604 (11.3)	283/2591 (10.9)	1.04 (0.89–1.21)	
Noncolchicine	40/494 (8.1)	38/501 (7.6)	1.07 (0.70–1.63)	
Colchicine use during trial				0.15
Yes	104/699 (14.9)	84/694 (12.1)	1.23 (0.94–1.61)	
No	231/2399 (9.6)	237/2398 (9.9)	0.97 (0.82–1.16)	
History of hyperlipidemia				0.33
Yes	297/2678 (11.1)	294/2702 (10.9)	1.02 (0.88–1.19)	
No	38/420 (9.0)	27/390 (6.9)	1.31 (0.81–2.10)	
At least one dose adjustment				0.97
Yes	153/1207 (12.7)	176/1485 (11.9)	1.07 (0.87–1.31)	
No	182/1891 (9.6)	145/1607(9.0)	1.07 (0.87–1.31)	
Insulin use during trial				0.91
Yes	116/620 (18.7)	111/607 (18.3)	1.02 (0.81–1.29)	
No	219/2478 (8.8)	210/2485 (8.5)	1.05 (0.87–1.25)	
History of congestive heart failure				0.86
Yes	115/622 (18.5)	114/631 (18.1)	1.02 (0.81–1.29)	
No	220/2476 (8.9)	207/2461 (8.4)	1.06 (0.88–1.27)	

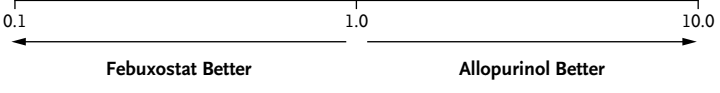

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Figure 2 (facing page). Risk Ratios for the Primary End Point According to Subgroup.

All subgroup analyses were prespecified with the exception of the analyses of race, years since gout diagnosis, history of cardiac revascularization, initial gout flare prophylaxis, colchicine use during the trial, history of hyperlipidemia, dose adjustment during the trial, insulin use during the trial, and history of congestive heart failure, which were post hoc.

approximately equal numbers of patients discontinued follow-up in the two treatment groups, and the baseline characteristics of these participants were similar to those of participants who completed follow-up.

In conclusion, among patients with gout and cardiovascular disease, treatment with febuxostat resulted in overall rates of major adverse cardiovascular events similar to those associated with allopurinol. Higher all-cause mortality, resulting from an imbalance in cardiovascular deaths, was observed with febuxostat than with allopurinol.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank all the patients who participated in the trial.

Table 3. Events That Occurred during Treatment or within 30 Days after Discontinuation of Treatment.*

End Point	Febuxostat (N=3098)	Allopurinol (N=3092)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
Primary end point: composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or urgent revascularization due to unstable angina	242 (7.8)	238 (7.7)	1.00 (0.82–1.22)†	0.99
Secondary end points				
Cardiovascular death	62 (2.0)	41 (1.3)	1.49 (1.01–2.22)	0.047
Nonfatal myocardial infarction	93 (3.0)	106 (3.4)	0.87 (0.66–1.15)	0.32
Nonfatal stroke	59 (1.9)	62 (2.0)	0.94 (0.66–1.34)	0.72
Urgent revascularization for unstable angina	45 (1.5)	44 (1.4)	1.00 (0.66–1.52)	0.98
Composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	205 (6.6)	200 (6.5)	1.01 (0.83–1.22)	0.93
Death from any cause	92 (3.0)	72 (2.3)	1.26 (0.93–1.72)	0.14

* This analysis was prespecified in the statistical analysis plan.
† The 97% confidence interval is provided here.

REFERENCES

1. Roddy E, Doherty M. Epidemiology of gout. Arthritis Res Ther 2010;12:223-34.
2. Choi HK, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. Circulation 2007; 116:894-900.
3. Krishnan E, Svendsen K, Neaton JD, Grandits G, Kuller LH. Long-term cardiovascular mortality among middle-aged men with gout. Arch Intern Med 2008;168: 1104-10.
4. FDA announces new recommendations on evaluating cardiovascular risk in drugs intended to treat type 2 diabetes. Pharmaceutical Online. December 18, 2008 (https://www.pharmaceuticalonline.com/doc/fda-announces-new-recommendations-on-0001).
5. Schumacher HR Jr, Becker MA, Wortmann RL, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. Arthritis Rheum 2008;59:1540-8.
6. Becker MA, Schumacher HR Jr, Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med 2005; 353:2450-61.
7. Schumacher HR Jr, Becker MA, Lloyd E, MacDonald PA, Lademacher C. Febuxostat in the treatment of gout: 5-yr findings of the FOCUS efficacy and safety study. Rheumatology (Oxford) 2009;48: 188-94.
8. White WB, Chohan S, Dabholkar A, Hunt B, Jackson R. Cardiovascular safety of febuxostat and allopurinol in patients with gout and cardiovascular comorbidities. Am Heart J 2012;164:14-20.
9. Wallace SL, Robinson H, Masi AT, Decker JL, McCarty DJ, Yü TF. Preliminary criteria for the classification of the acute arthritis of primary gout. Arthritis Rheum 1977;20:895-900.
10. Hicks KA, Tcheng JE, Bozkurt B, et al. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). Circulation 2015; 132:302-61.
11. Lan KKG, DeMets DL. Discrete se-

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quential boundaries for clinical trials. Biometrika 1983;70:659-63.
12. Khanna D, Khanna PP, Fitzgerald JD, et al. 2012 American College of Rheumatology guidelines for the management of gout. Part 2: therapy and anti-inflammatory prophylaxis of acute gouty arthritis. Arthritis Care Res 2012;63:1447-61.
13. Foody J, Turpin RS, Tidwell BA, Lawrence D, Schulman KL. Major cardiovascular events in patients with gout and associated cardiovascular disease or heart failure and chronic kidney disease initiating a xanthine oxidase inhibitor. Am Health Drug Benefits 2017;10:393-401.
14. Singh JA, Ramachandaran R, Yu S, Curtis JR. Allopurinol use and the risk of acute cardiovascular events in patients with gout and diabetes. BMC Cardiovasc Disord 2017;17:76.
15. Wei L, Mackenzie IS, Chen Y, Struthers AD, MacDonald TM. Impact of allopurinol use on urate concentration and cardiovascular outcome. Br J Clin Pharmacol 2011;71:600-7.
16. Bardin T, Keenan RT, Khanna PP, et al. Lesinurad in combination with allopurinol: a randomised, double-blind, placebo-controlled study in patients with gout with inadequate response to standard of care (the multinational CLEAR 2 study). Ann Rheum Dis 2017;76:811-20.
17. Grewal HK, Martinez JR, Espinoza LR. Febuxostat: drug review and update. Expert Opin Drug Metab Toxicol 2014;10:747-58.
18. Sanchez-Lozada LG, Tapia E, Bautista-García Pet al. Effects of febuxostat on metabolic and renal alterations in rats with fructose-induced metabolic syndrome. Am J Physiol Renal Physiol 2008;294:F710-718.
19. Zhao L, Roche BM, Wessale JL, et al. Chronic xanthine oxidase inhibition following myocardial infarction in rabbits: effects of early versus delayed treatment. Life Sci 2008;82:495-502.
20. Xu X, Hu X, Lu Z, et al. Xanthine oxidase inhibition with febuxostat attenuates systolic overload-induced left ventricular hypertrophy and dysfunction in mice. J Card Fail 2008;14:746-53.
21. Hou M, Hu Q, Chen Y, Zhao L, Zhang J, Bache RJ. Acute effects of febuxostat, a nonpurine selective inhibitor of xanthine oxidase, in pacing induced heart failure. J Cardiovasc Pharmacol 2006;48:255-63.
22. Krishnan E. Inflammation, oxidative stress and lipids: the risk triad for atherosclerosis in gout. Rheumatology (Oxford) 2010;49:1229-38.
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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.

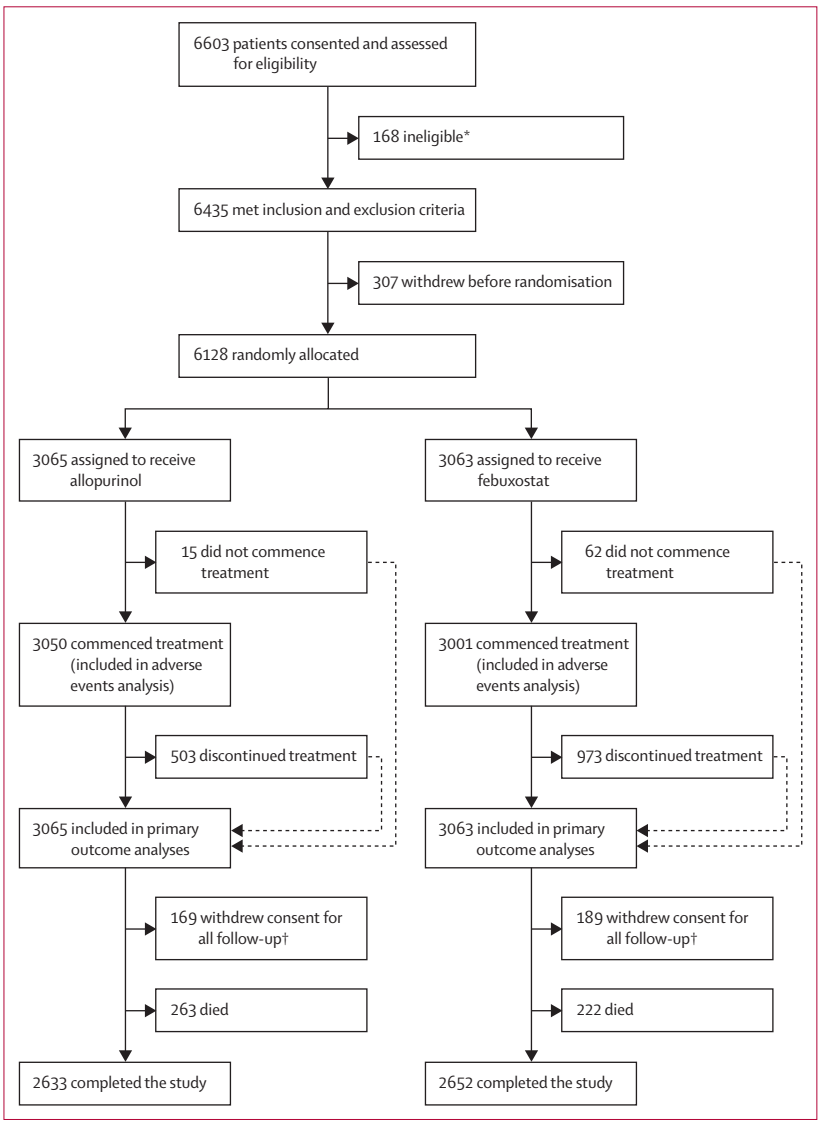

Figure 1: **Trial profile**
14 randomised patients and one non-randomised patient recruited from a single UK site are not included in these numbers because their data were deleted following instruction from the sponsor due to concerns about the validity of their consent and inclusion of their data following 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

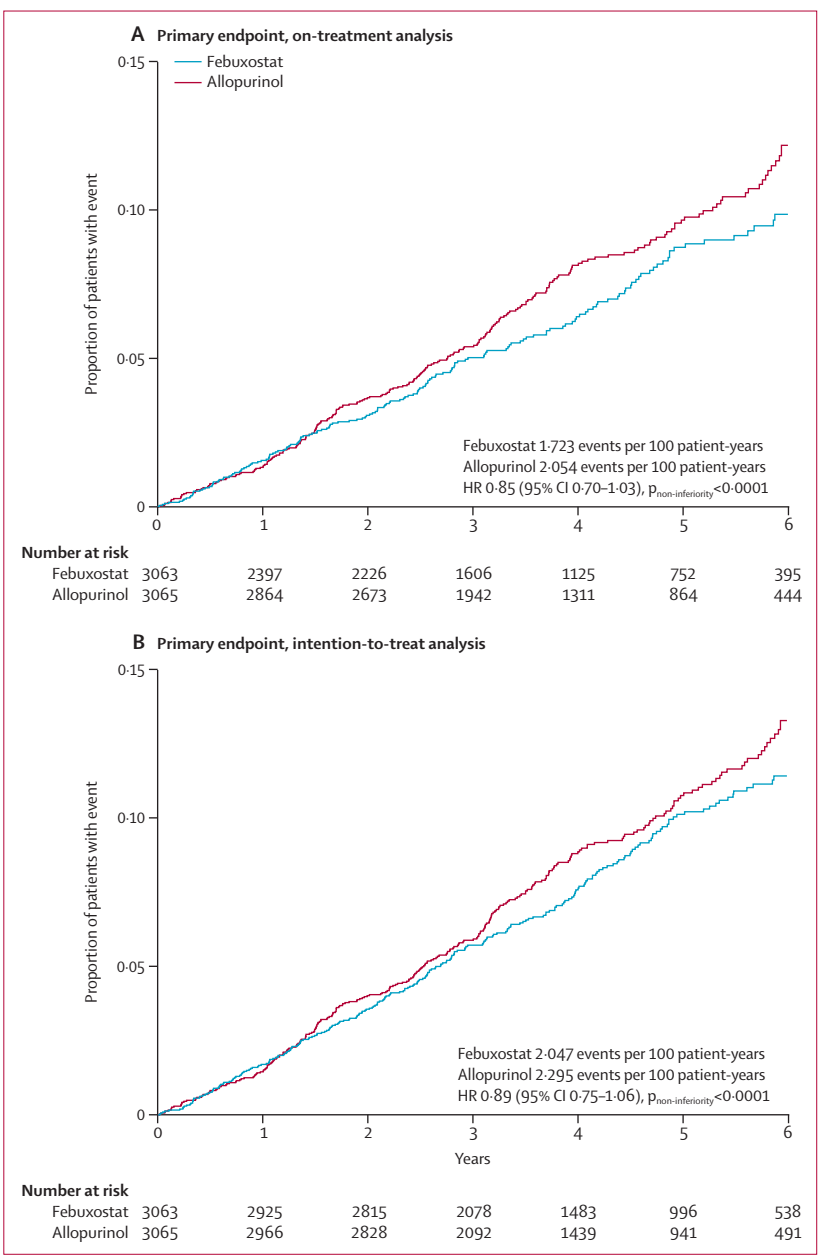

Figure 2: **Cumulative incidence functions for the primary composite endpoint (n=6128)**
The primary composite endpoint consisted of cardiovascular death; hospitalisation for non-fatal myocardial infarction or biomarker-positive acute coronary syndrome; or non-fatal stroke. Analyses were adjusted for 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).

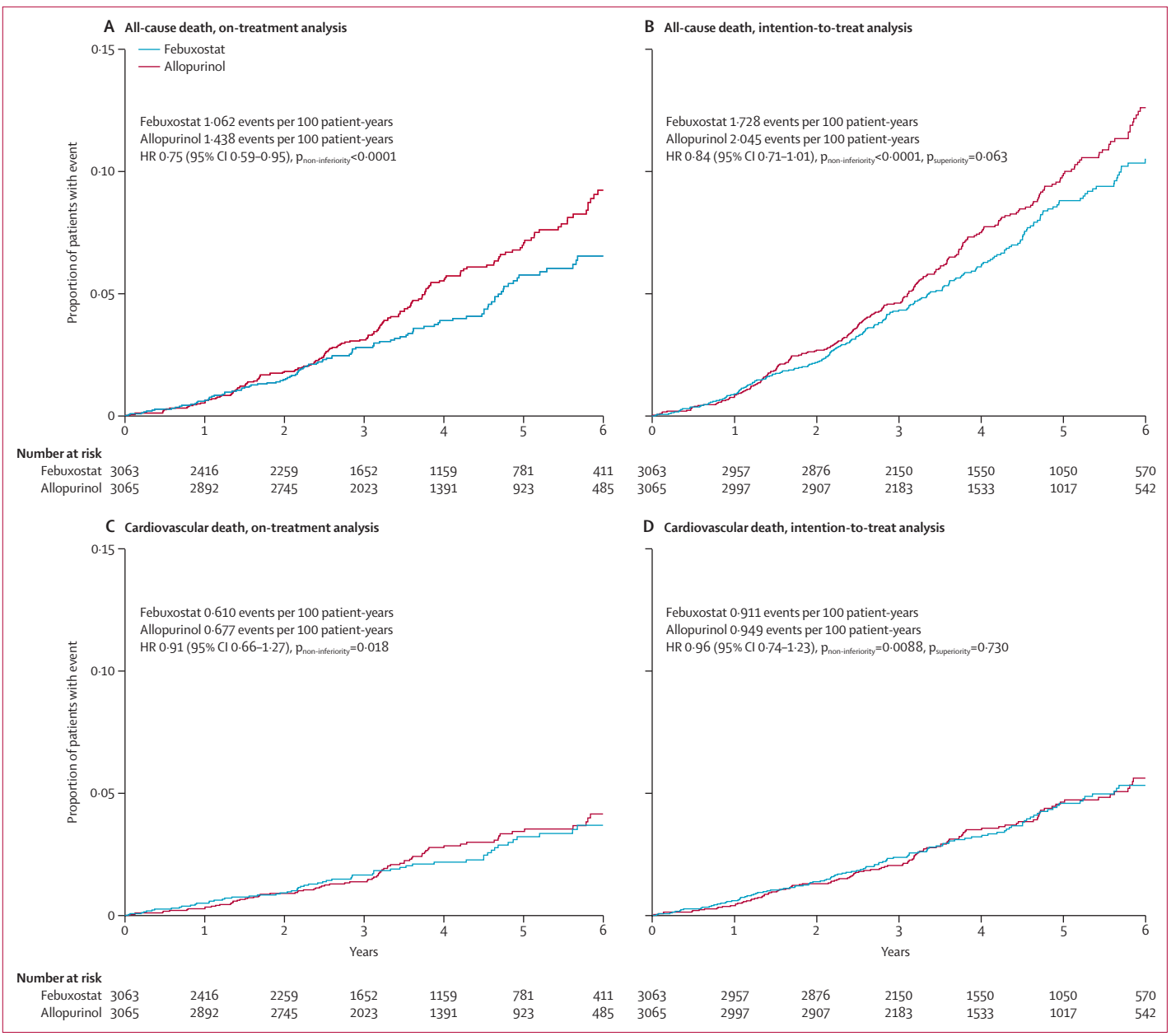

Figure 3: **Cumulative incidence functions for selected secondary endpoints (n=6128)**
(A) All-cause death in the on-treatment analysis. (B) All-cause death in the intention-to-treat analysis. (C) Cardiovascular death in the on-treatment analysis, adjusting for the competing risk of deaths not included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

1 Hansildaar R, Vedder D, Baniaamam M, Tausche AK, Gerritsen M, Nurmohamed MT. Cardiovascular risk in inflammatory arthritis: rheumatoid arthritis and gout. *Lancet Rheumatol* 2020; published online Sept 1. https://doi.org/10.1016/S2665-9913(20)30221-6.

2 Zhu Y, Pandya BJ, Choi HK. Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007–2008. *Am J Med* 2012; **125:** 679–687.e1.

3 Richette P, Clerson P, Périssin L, Flipo RM, Bardin T. Revisiting comorbidities in gout: a cluster analysis. *Ann Rheum Dis* 2015; **74:** 142–47.

4 Hui M, Carr A, Cameron S, et al. The British Society for Rheumatology guideline for the management of gout. *Rheumatology (Oxford)* 2017; **56:** 1056–59.

5 Becker MA, Schumacher HR Jr, Wortmann RL, et al. Febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase: a twenty-eight-day, multicenter, phase II, randomized, double-blind, placebo-controlled, dose-response clinical trial examining safety and efficacy in patients with gout. *Arthritis Rheum* 2005; **52:** 916–23.

6 Schumacher HR Jr, Becker MA, Wortmann RL, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. *Arthritis Rheum* 2008; **59:** 1540–48.

7 Schumacher HR Jr, Becker MA, Lloyd E, MacDonald PA, Lademacher C. Febuxostat in the treatment of gout: 5-yr findings of the FOCUS efficacy and safety study. *Rheumatology (Oxford)* 2009; **48:** 188–94.

8 Becker MA, Schumacher HR, MacDonald PA, Lloyd E, Lademacher C. Clinical efficacy and safety of successful longterm urate lowering with febuxostat or allopurinol in subjects with gout. *J Rheumatol* 2009; **36:** 1273–82.

9 Becker MA, Schumacher HR, Espinoza LR, et al. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial. *Arthritis Res Ther* 2010; **12:** R63.

10 MacDonald TM, Ford I, Nuki G, et al. Protocol of the Febuxostat versus Allopurinol Streamlined Trial (FAST): a large prospective, randomised, open, blinded endpoint study comparing the cardiovascular safety of allopurinol and febuxostat in the management of symptomatic hyperuricaemia. *BMJ Open* 2014; **4:** e005354.

11 Taylor WJ, Fransen J, Jansen TL, et al. Study for updated gout classification criteria: identification of features to classify gout. *Arthritis Care Res (Hoboken)* 2015; **67:** 1304–15.

12 Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. *Ann Rheum Dis* 2017; **76:** 29–42.

13 Cefalu WT, Kaul S, Gerstein HC, et al. Cardiovascular outcomes trials in type 2 diabetes: where do we go from here? Reflections from a *Diabetes Care* editors' expert forum. *Diabetes Care* 2018; **41:** 14–31.

14 FibroGen. FibroGen announces positive phase 3 pooled roxadustat safety and efficacy results for treatment of anemia in chronic kidney disease. Nov 8, 2019. https://investor.fibrogen.com/news-releases/news-release-details/fibrogen-announces-positive-phase-3-pooled-roxadustat-safety-and (accessed Oct 16, 2020).

15 Bohula EA, Wiviott SD, McGuire DK, et al. Cardiovascular safety of lorcaserin in overweight or obese patients. *N Engl J Med* 2018; **379:** 1107–17.

16 Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. *N Engl J Med* 2016; **375:** 2519–29.

17 White WB, Saag KG, Becker MA, et al. Cardiovascular safety of febuxostat or allopurinol in patients with gout. *N Engl J Med* 2018; **378:** 1200–10.

18 Li X, Meng X, Timofeeva M, et al. Serum uric acid levels and multiple health outcomes: umbrella review of evidence from observational studies, randomised controlled trials, and Mendelian randomisation studies. *BMJ* 2017; **357:** j2376.

19 White J, Sofat R, Hemani G, et al. Plasma urate concentration and risk of coronary heart disease: a Mendelian randomisation analysis. *Lancet Diabetes Endocrinol* 2016; **4:** 327–36.

20 Bouabdallaoui N, Tardif J-C, Waters DD, et al. Time-to-treatment initiation of colchicine and cardiovascular outcomes after myocardial infarction in the Colchicine Cardiovascular Outcomes Trial (COLCOT). *Eur Heart J* 2020; published online Aug 29. https://doi.org/10.1093/eurheartj/ehaa659.

21 Al-Abdouh A, Barbarawi M, Khan SU, et al. Colchicine therapy in patients with coronary artery disease: a systematic review and meta-analysis of randomized controlled trials. *Coron Artery Dis* 2020; published online July 23. https://doi.org/10.1097/MCA.0000000000000931.

22 Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in patients with chronic coronary disease. *N Engl J Med* 2020; published online Aug 31. https://doi.org/10.1056/nejmoa2021372.

23 Tardif J-C, Kouz S, Waters DD, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med* 2019; **381:** 2497–505.

24 Mackenzie IS, Ford I, Walker A, et al. Multicentre, prospective, randomised, open-label, blinded end point trial of the efficacy of allopurinol therapy in improving cardiovascular outcomes in patients with ischaemic heart disease: protocol of the ALL-HEART study. *BMJ Open* 2016; **6:** e013774.

MAYO CLINIC

ORIGINAL ARTICLE

Comparing Cardiovascular Safety of Febuxostat and Allopurinol in the Real World: A Population-Based Cohort Study

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Abstract

Objective: To determine and compare the risk of cardiovascular events and mortality of febuxostat and allopurinol use.

Patients and Methods: We conducted a cohort study using the Taiwan National Health Insurance Research Database. New users of febuxostat and allopurinol between April 1, 2012 and December 31, 2015 were identified, and the two groups were 1:1 matched by propensity score, benzbromarone use history, renal impairment, and time of drug initiation. The risk of major adverse cardiovascular events (MACEs), venous thromboembolism (VTE), heart failure (HF) hospitalization, atrial fibrillation hospitalization, cardiovascular (CV) death, and all-cause mortality was assessed using Cox proportional hazards models. The dose-response relationship between xanthine oxidase inhibitor use and adverse CV outcomes were also determined.

Results: A total of 44,111 patients were included for each group, and all baseline covariates were well matched. Febuxostat users were at a significantly higher risk for HF hospitalization (hazard ratio [HR], 1.22; 95% CI, 1.13-1.33), atrial fibrillation hospitalization (HR, 1.19; 95% CI, 1.05-1.36), and CV death (HR, 1.19; 95% CI, 1.03-1.36) than allopurinol users, whereas no difference was found for the major adverse cardiac events composite endpoint, venous thromboembolism, myocardial infarction, ischemic stroke, and all-cause mortality. The elevated risk of HF hospitalization was consistent throughout the primary and sensitivity analyses. In addition, febuxostat increased the risk of adverse CV outcomes in a dose-dependent manner.

Conclusion: The use of febuxostat, compared with allopurinol, was associated with a significantly increased risk of adverse CV events. Higher febuxostat doses had a greater impact. Further studies are needed to investigate the mechanisms linking febuxostat to adverse CV outcomes.

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Gout is the most common type of inflammatory arthritis with a global prevalence of 0.076% in 2010[1]; however, it affects 6.24% of individuals in Taiwan.[2] Hyperuricemia, often defined as a serum uric acid level greater than 6.8 or 7.0 mg/dL, can lead to the accumulation of urate crystals and the flare of gout. Febuxostat and allopurinol, two xanthine oxidase inhibitors (XOIs), can inhibit uric acid synthesis and are recommended as first-line pharmacologic therapy for patients with hyperuricemia or gout.[3] The use of allopurinol is limited by the elevated risk of severe cutaneous adverse reactions, especially in ethnic groups with a high frequency of the HLA-B*5801 allele (eg, Han Chinese or Thai descent).[4,5] For patients intolerant to allopurinol, febuxostat treatment is considered a safer alternative.[3] In addition, febuxostat requires no dose adjustment in patients with mild to moderate renal/liver insufficiency or advanced age. Febuxostat has also been shown to be more effective than allopurinol in reducing serum urate level at doses (ie, febuxostat 40-120 mg vs allopurinol 100-300 mg) examined in clinical trials.[6-10]

For editorial comment, see page 1128

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Despite the clinical advantages of febuxostat, a series of recent clinical trials have reported more cardiovascular (CV) events among febuxostat users.[6-10] A pharmacovigilance study using the US Food and Drug Administration (FDA) Adverse Event Reporting System database also indicated potential signals of febuxostat-associated CV thromboembolic events.[11] Recently, the Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial suggested a higher rate of all-cause and CV mortality with febuxostat than with allopurinol.[12] However, very few studies have examined the outcomes of febuxostat in the real-world setting, and the current evidence is conflicting.[13] Thus, the present study aimed to determine if febuxostat use was associated with increased risks of CV events and mortality. Additionally, the dose-response relationship between febuxostat and the CV outcomes were analyzed.

PATIENTS AND METHODS

An expanded version of the study methods is provided in the Supplemental Methods (available online at http://www.mayoclinicproceedings.org).

Data Source

We conducted a retrospective cohort study using the 2011-2015 National Health Insurance Research Database in Taiwan (provided by the Health and Welfare Data Center, Taiwan's Ministry of Health and Welfare). This study was approved by the Institutional Review Board of the National Taiwan University Hospital.

Study Population

We identified patients who were first prescribed febuxostat or allopurinol between April 1, 2012, and December 31, 2015. Several patient exclusion criteria (details provided in the Supplemental Methods [available online at http://www.mayoclinicproceedings.org]) were applied.

Exposure Definition

All eligible participants were new XOI users and were classified as new febuxostat and allopurinol users (new user design). Allopurinol was used as an active comparator to enhance the study validity by increasing overlap in measured characteristics and reducing potential unmeasured confounding between the study groups.[14]

The mean daily dose of the febuxostat users was calculated every month after the index date and categorized into low ($\leq$0.5 of the defined daily dose [DDD]), medium (>0.5 DDD, $\leq$1 DDD), and high doses (>1 DDD).[15]

Outcome Definition

A number of CV and mortality outcomes were examined, including major adverse cardiovascular events (MACEs; consisting of myocardial infarction [MI] hospitalization,[16] ischemic stroke hospitalization,[17] and CV death[18,19]), venous thromboembolism (VTE) hospitalization,[20,21] heart failure (HF) hospitalization,[22] atrial fibrillation (AF) hospitalization, and all-cause mortality (detailed diagnosis codes provided in Supplemental Table 1 [available online at http://www.mayoclinicproceedings.org]). The individual components in MACE were also analyzed separately. All of the hospitalization outcomes were defined using the primary and secondary diagnoses from the inpatient data, and sensitivity analysis using only the inpatient primary diagnosis for event definition was performed subsequently. Mortality and causes of death were determined based on the National Death Registry in Taiwan.

Covariates

Currently, no urate-lowering therapy is recommended as first-line for the management of gout and hyperuricemia in Taiwan's treatment guideline.[23] According to the original National Health Insurance reimbursement scheme (before March 1, 2013), febuxostat can only be prescribed to patients who have failed to achieve target serum urate levels using allopurinol and benzbromarone.[24] The reimbursement criteria were revised on March 1, 2013; now, febuxostat can also be prescribed for patients who have failed benzbromarone treatment or been diagnosed with chronic kidney disease or liver cirrhosis. Considering the changes in the drug reimbursement policy over

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time, the two groups (new febuxostat and allopurinol users) were 1:1 matched by the propensity score (PS) as well as history of benzbromarone use, history of renal impairment, and time of index date (before or after March 1, 2013). Details of the PS estimation and matching were provided in the Supplemental Methods material.[25] The complete lists of comorbidities and comedications is provided in Supplemental Table 2 and 3 (available online at http://www.mayoclinicproceedings.org).

Statistical Analysis

Standardized differences in each covariate were computed to compare the distribution of baseline characteristics between the two groups before and after matching.[26] Cox proportional hazards regression models were used to assess the associations between use of XOIs and risks of the study outcomes, and hazard ratios (HRs) with 95% CIs were presented. In the primary as-treated analysis, each individual was followed from the index date till event occurrence or censored on the earliest date of drug discontinuation, switching to the other study medication, death (if not the analysis outcome), or end of the study period (December 31, 2015). Patients who discontinued medication were censored at the end of the latest dispensing (exhaustion of the day supply) plus a 30-day lag period to account for possible persistent effects of the medication. Patients who switched to the other study medication were censored on the date when the other study drug was prescribed.

All data management and analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC). Two-sided *P* values less than 0.05 were considered statistically significant.

Dose-Response Analyses

Dose-response relationship was studied separately in febuxostat and allopurinol users. Because renal function is a factor that influences the febuxostat dosage, only patients without a renal impairment history were included in the analysis. The mean daily dose categories were analyzed as time-dependent variables in the Cox regression models.

Sensitivity and Subgroup Analyses

A series of sensitivity analyses and subgroup analyses were performed. Details of these analyses can be found in the Supplemental Methods.

RESULTS

Study Cohort and Baseline Characteristics

We identified 270,423 new XOI users between April 1, 2012, and December 31, 2015. After 1:1 matching, 44,111 patients were included in each group for the outcome assessment (Supplemental Figure [available online at http://www.mayoclinicproceedings.org]).

The baseline characteristics of both groups before and after matching are presented in Table 1. Before matching, febuxostat users (n=56,262) were on average older and had more comorbidities and comedications at baseline than allopurinol users (n=214,161). After matching (n=44,111 in each group), all covariates were balanced between the two groups with a standardized difference of less than 0.1:[26] the mean age was approximately 65 years, 74.3% (n=65,557 of 88,222) were male, and ischemic heart disease was the most common CV disease. In addition, hypertension (overall 68.9%; n=60,765 of 88,222), gout (57.9%; 51,037), diabetes mellitus (36.7%; 32,355), and hyperlipidemia (37.5%; n=33,063) were frequent comorbidities, and associated medications were balanced between groups at baseline.

Comparison of Outcomes

Using the as-treated analytic approach, the mean (median) follow-up duration for the study endpoints was approximately 200 (120) days in the febuxostat group and 160 (85) days in the allopurinol group. Follow-up censoring due to drug discontinuation was found in 50.2% to 52.9% (n=22,138 to 23,355 of 44,111) of febuxostat users and 65.8% to 68.2% (n=29,047 to 30,082) of allopurinol users, and 1.5% to 1.6% (n=666 to 691) of febuxostat users and 6.2% to 6.5% (n=2,750 to 2,856) of allopurinol users had their follow-up censored because of switching to the other study treatment.

The Cox regression models showed that the use of febuxostat, compared with

TABLE 1. Baseline Characteristics Before and After Matching

	Before matching			After 1:1 matching		
	Febuxostat	Allopurinol	Std diff	Febuxostat	Allopurinol	Std diff
No. of subjects	56,262	214,161		44,111	44,111	
Age, mean (SD)	65.9 (15.5)	58.3 (16.4)	0.48	65.0 (15.7)	64.1 (15.0)	0.06
Sex, n (%)			0.16			0.01
Female	15,509 (27.6)	45,035 (21.0)		11,335 (25.7)	11,159 (25.3)	
Male	40,655 (72.3)	168,180 (78.5)		32,694 (74.1)	32,863 (74.5)	
Missing	98 (0.2)	946 (0.4)		82 (0.2)	89 (0.2)	
Index date, n (%)			1.28			0.00
Before March 1, 2013	7735 (13.8)	142,443 (66.5)		7735 (17.5)	7735 (17.5)	
March 1, 2013, or after	48,527 (86.3)	71,718 (33.5)		36,376 (82.5)	36,376 (82.5)	
Comorbidity before index date, n (%)						
Myocardial infarction	1884 (3.4)	3761 (1.8)	0.10	1388 (3.2)	1235 (2.8)	0.02
Other ischemic heart disease	12,372 (22.0)	30,199 (14.1)	0.21	9390 (21.3)	8582 (19.5)	0.05
Heart failure	8776 (15.6)	17,071 (8.0)	0.24	6264 (14.2)	5405 (12.3)	0.06
Cardiomyopathy	505 (0.9)	1242 (0.6)	0.04	380 (0.9)	347 (0.8)	0.01
Cardiac arrhythmia	5641 (10.0)	14,345 (6.7)	0.12	4249 (9.6)	4,014 (9.1)	0.02
Valvular heart disease	2995 (5.3)	7133 (3.3)	0.10	2259 (5.1)	2067 (4.7)	0.02
Transient ischemic attack	1083 (1.9)	2972 (1.4)	0.04	800 (1.8)	833 (1.9)	-0.01
Ischemic stroke	3812 (6.8)	9104 (4.3)	0.11	2847 (6.5)	2649 (6.0)	0.02
Hemorrhagic stroke	584 (1.0)	1844 (0.9)	0.02	439 (1.0)	463 (1.1)	-0.01
Pulmonary embolism	102 (0.2)	246 (0.1)	0.02	76 (0.2)	75 (0.2)	0.00
Deep vein thrombosis	516 (0.9)	1045 (0.5)	0.05	370 (0.8)	317 (0.7)	0.01
Peripheral vascular disease	2297 (4.1)	6685 (3.1)	0.05	1681 (3.8)	1732 (3.9)	-0.01
Hypertension	40,320 (71.7)	114,798 (53.6)	0.38	30,433 (69.0)	30,332 (68.8)	0.00
Gout	29,368 (52.2)	152,472 (71.2)	-0.40	24,597 (55.8)	26,440 (59.9)	-0.08
Diabetes mellitus	23,080 (41.0)	51,308 (24.0)	0.37	16,875 (38.3)	15,480 (35.1)	0.07
Hyperlipidemia	21,037 (37.4)	61,091 (28.5)	0.19	16,566 (37.6)	16,497 (37.4)	0.00
Disorders of thyroid gland	1485 (2.6)	3758 (1.8)	0.06	1128 (2.6)	1028 (2.3)	0.01
Renal impairment	22,210 (39.5)	27,029 (12.6)	0.64	10,266 (23.3)	10,266 (23.3)	0.00
Liver disease	6514 (11.6)	25,089 (11.7)	0.00	5241 (11.9)	5515 (12.5)	-0.02
Solid malignancy	4582 (8.1)	11,963 (5.6)	0.10	3400 (7.7)	3259 (7.4)	0.01
Chronic obstructive pulmonary disease	4281 (7.6)	12,617 (5.9)	0.07	3237 (7.3)	3135 (7.1)	0.01
Peptic ulcer disease	10,379 (18.5)	35,237 (16.5)	0.05	7877 (17.9)	8030 (18.2)	-0.01
Comedication before index date, n (%)						
NSAIDs	35,672 (63.4)	166,829 (77.9)	-0.32	28,960 (65.7)	30,484 (69.1)	-0.07
Colchicine	24,013 (42.7)	117,906 (55.1)	-0.25	19,920 (45.2)	20,783 (47.1)	-0.04
Corticosteroids	21,071 (37.5)	72,971 (34.1)	0.07	16,168 (36.7)	16,382 (37.1)	-0.01
Benzbromarone	23,781 (42.3)	60,760 (28.4)	0.29	19,089 (43.3)	19,089 (43.3)	0.00
Probenecid	38 (0.1)	252 (0.1)	-0.02	36 (0.1)	33 (0.1)	0.00
Sulfinpyrazone	2782 (4.9)	5253 (2.5)	0.13	2333 (5.3)	1783 (4.0)	0.06
α-Blockers	8812 (15.7)	17,334 (8.1)	0.24	6072 (13.8)	5236 (11.9)	0.06
β-Blockers	26,547 (47.2)	70,439 (32.9)	0.29	19,865 (45.0)	18,922 (42.9)	0.04
Calcium channel blockers	36,872 (65.5)	100,608 (47.0)	0.38	27,577 (62.5)	26,877 (60.9)	0.03
ACEIs/ARBs/aliskiren	38,435 (68.3)	100,362 (46.9)	0.44	29,148 (66.1)	28,273 (64.1)	0.04
Diuretics	31,914 (56.7)	81,230 (37.9)	0.38	23,460 (53.2)	22,334 (50.6)	0.05
Class I/III antiarrhythmic agents	4176 (7.4)	10,048 (4.7)	0.11	3098 (7.0)	2836 (6.4)	0.02
Digoxin	2216 (3.9)	6142 (2.9)	0.06	1717 (3.9)	1633 (3.7)	0.01
Nitrate	12,645 (22.5)	27,099 (12.7)	0.26	9101 (20.6)	8080 (18.3)	0.06
Anticoagulants	6337 (11.3)	13,334 (6.2)	0.18	4637 (10.5)	4202 (9.5)	0.03
Aspirin	19,658 (34.9)	58,532 (27.3)	0.16	14,937 (33.9)	14,769 (33.5)	0.01
Antiplatelets other than aspirin	14,540 (25.8)	32,362 (15.1)	0.27	10,430 (23.6)	9758 (22.1)	0.04

Continued on next page

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TABLE 1. Continued

	Before matching			After 1:1 matching		
	Febuxostat	Allopurinol	Std diff	Febuxostat	Allopurinol	Std diff
Comedication before index date, n (%), continued						
Statins	26,621 (47.3)	61,732 (28.8)	0.39	20,143 (45.7)	19,112 (43.3)	0.05
Fibrates	6001 (10.7)	22,339 (10.4)	0.01	4719 (10.7)	4949 (11.2)	-0.02
Antihyperglycemic agents	20,879 (37.1)	47,176 (22.0)	0.34	15,508 (35.2)	14,242 (32.3)	0.06
Insulins	11,748 (20.9)	18,627 (8.7)	0.35	7974 (18.1)	6494 (14.7)	0.09

ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor blockers; NSAIDs = nonsteroidal anti-inflammatory drugs; Std diff = standardized difference.

allopurinol, was associated with a significantly higher risk of HF hospitalization (incidence density, 60.1 vs 51.0 per 1000 person-years; HR, 1.22; 95% CI, 1.13-1.33), AF hospitalization (incidence density, 23.7 vs 20.7 per 1000 person-years; HR, 1.19; 95% CI, 1.05-1.36), and CV death (incidence density, 19.2 vs 17.2 per 1000 person-years; HR, 1.19; 95% CI, 1.03 to 1.36) (Table 2). However, no elevated risk was found for the MACE composite endpoint, hospitalized VTE events, MI, ischemic stroke, or all-cause mortality.

Sensitivity and Subgroup Analyses

The sensitivity analysis results are summarized in Figure 1. Consistent trends in the CV risk were found when using the alternative intention-to-treat analytic approach (Supplemental Table 4 [available online at http://www.mayoclinicproceedings.org]). The significantly higher risk of HF hospitalization associated with febuxostat use was consistent throughout the primary and sensitivity analyses. Febuxostat users also had a consistently higher risk of AF hospitalization except that the difference did not reach statistical significance when defining the outcome based only on the primary diagnosis. The lack of sufficient statistical power is conceivable because AF can hardly be the main reason for hospital admission. In addition, the increased risk of CV death with febuxostat use was consistently observed across the sensitivity analyses except when requiring the index drug to be initiated in the outpatient setting.

In general, the subgroup analysis yielded findings similar to those obtained for the overall cohort. Febuxostat users had an increased risk of HF hospitalization in each subgroup, with adjusted HRs ranging from 1.10 to 1.33 (Figure 2). However, the significantly greater risk of AF hospitalization and CV death associated with febuxostat was not observed in many of the subgroups, probably due to the much lower event numbers for these outcomes. In particular, the increased risks of HF hospitalization and CV death associated with febuxostat were higher in patients without, compared with those with, a history of renal impairment (P value for interaction <0.05). The subgroup analyses for the other study endpoints are presented in Supplemental Tables 5 to 10 (available online at http://www.mayoclinicproceedings.org) except for that for VTE because the incidence rate of this endpoint was too low for the analysis.

Dose-Response Analyses

The mean daily dose of febuxostat users in the first month after drug initiation (ie, index date) was 53.1 mg (0.66 DDD), and the doses in the first, second, and third quartiles were 0.5, 0.5, and 1 DDD, respectively. The mean daily dose of allopurinol users in the first month after initiation was 133.3 mg (0.33 DDD), and the doses in the first, second, and third quartiles were 0.25, 0.25, and 0.375 DDD, respectively.

Use of medium- and high-dose febuxostat was associated with a hierarchically increased risk of adverse CV outcomes, including MACE and hospitalization related to ischemic stroke, HF, and AF (Table 3). With allopurinol, no dose-response relationship regarding CV outcomes was observed

TABLE 2. Comparison of Outcomes Between Matched Treatment Groups (Using an As-Treated Analytic Approach)

	Febuxostat users (n=44,111)				Allopurinol users (n=44,111)				
	No. of events	Mean time to event (days)	Mean/median follow-up days	Incidence density rate[a]	No. of events	Mean time to event (days)	Mean/median follow-up days	Incidence density rate[a]	HR (95% CI)
MACEs (composite)	968	152.2	199.8/120	40.1	741	162.8	158.0/85	38.8	1.07 (0.97-1.18)
VTE	87	147.4	201.8/121	3.6	65	137.5	160.1/85	3.4	1.10 (0.80-1.51)
CV-related hospitalization									
Myocardial infarction	272	154.2	201.3/121	11.2	193	186.5	159.4/85	10.0	1.14 (0.95-1.37)
Ischemic stroke	344	167.7	200.7/121	14.2	298	164.1	158.9/85	15.5	0.93 (0.80-1.09)
Heart failure	1423	138.5	195.9/118	60.1	963	142.5	156.1/85	51.0	1.22 (1.13-1.33)
Atrial fibrillation	573	140.5	199.8/120	23.7	396	141.3	158.7/85	20.7	1.19 (1.05-1.36)
CV death	468	137.1	202.2/122	19.2	334	148.9	160.3/85	17.2	1.19 (1.03-1.36)
All-cause mortality	1630	125.6	202.2/122	66.7	1301	126.1	160.3/85	67.1	1.07 (0.99-1.15)

[a]Presented as events per 1000 person-years.

CV = cardiovascular; HR = hazard ratio; MACEs = major adverse cardiovascular events; VTE = venous thromboembolism.

(Supplemental Table 11 [available online at http://www.mayoclinicproceedings.org]). The CIs were noticeably wider because allopurinol tended to be prescribed at a lower DDD.

DISCUSSION

Using a new user and active comparator design, this study revealed that the use of febuxostat was associated with a significantly higher risk of HF, AF, and CV death than the use of allopurinol. No elevated risk was found for MACEs (as a composite endpoint), VTE, MI, ischemic stroke, and all-cause mortality.

Since early trials suggested a modestly higher rate of CV events with febuxostat,[6,7,9] the CARES trial was required by the US FDA to determine the comparative CV safety of febuxostat and allopurinol in patients with gout and CV disease.[12] The US FDA also issued the Drug Safety Communication on November 15, 2017, to warn about the preliminary results from the trial, which showed an increased risk of heart-related death with febuxostat,[27] and recently on February 21, 2019, a boxed warning was added to the prescribing information for febuxostat.[28] Although the CARES trial showed that febuxostat was noninferior to allopurinol with respect to the primary composite endpoint of CV outcomes (nonfatal MI, nonfatal stroke, unstable angina with urgent revascularization, or CV death), rates of CV deaths and all-cause mortality were higher with febuxostat than with allopurinol in patients with gout and CV comorbidities.[12] Similar to the CARES trial, our study showed an increased risk of CV death in the febuxostat group with both as-treated and intention-to-treat analytic approaches, although we did not find evidence for an increased risk of all-cause mortality. However, in the sensitivity analysis that only included patients who were prescribed their first XOI at the outpatient encounter, the risk of CV death was slightly reduced and became statistically insignificant. The probable reason was that patients identified from only outpatient settings tend to be clinically stable with a better health status; this was supported by the substantially lower incidence rates of CV death (19.2 vs 17.2 per 1000 person-years in the primary analysis and 11.9 vs 10.9 per 1000 person-years among outpatients).

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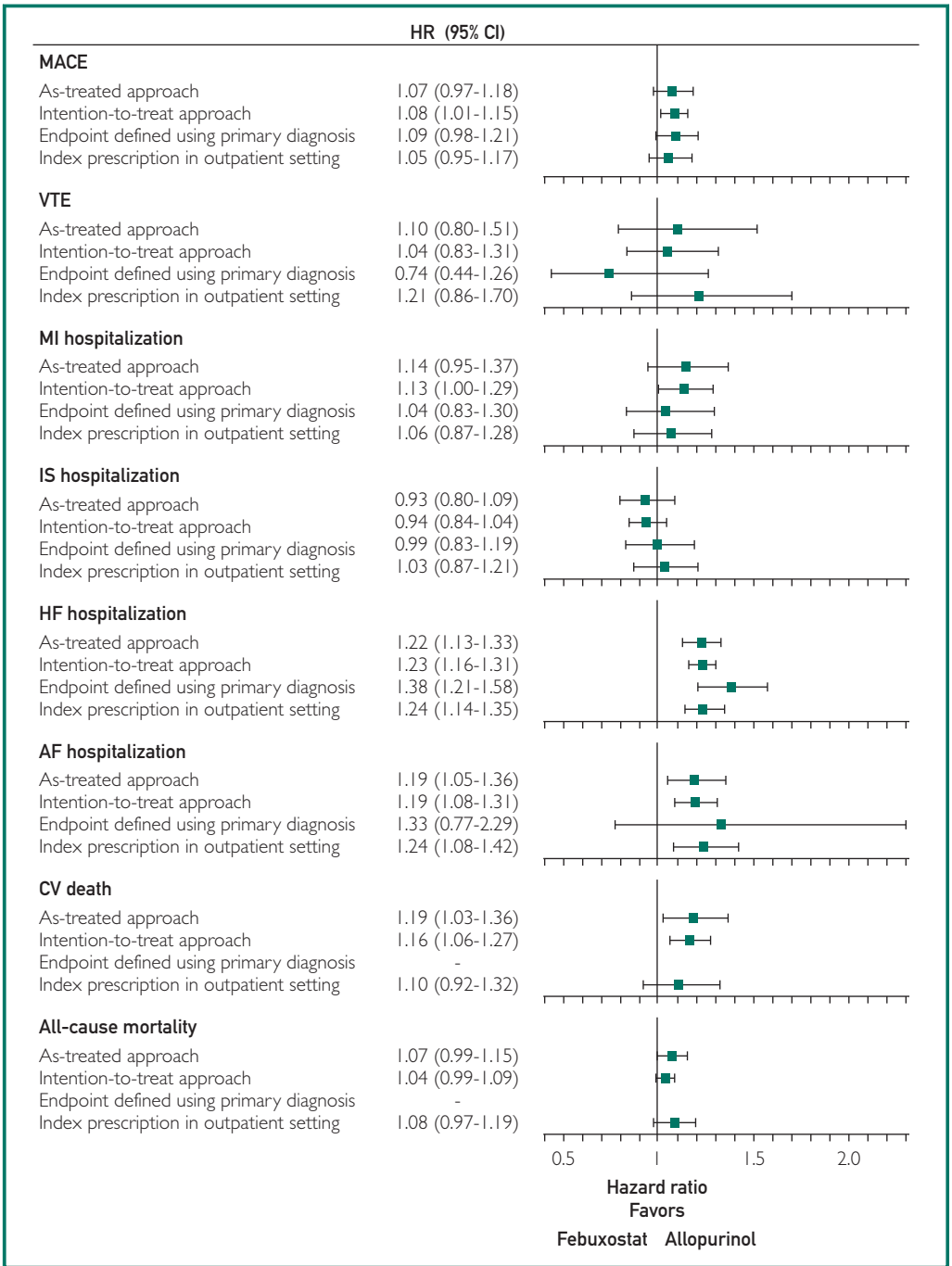

FIGURE 1. Forest plots of the primary results and sensitivity analyses. AF = atrial fibrillation; CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; MACE = major adverse cardiovascular event; MI = myocardial infarction; IS = ischemic stroke; VTE = venous thromboembolism.

In the present study, the increased risk of HF hospitalization with febuxostat was consistently observed throughout the primary and sensitivity analyses. Febuxostat use was associated with a 22% (HR, 1.22; 95% CI, 1.13 to 1.33) increased risk of HF hospitalization in our primary analysis. In the CARES trial, the event rate of hospitalization for HF was also slightly higher in the febuxostat group (4.3%, n=134 of

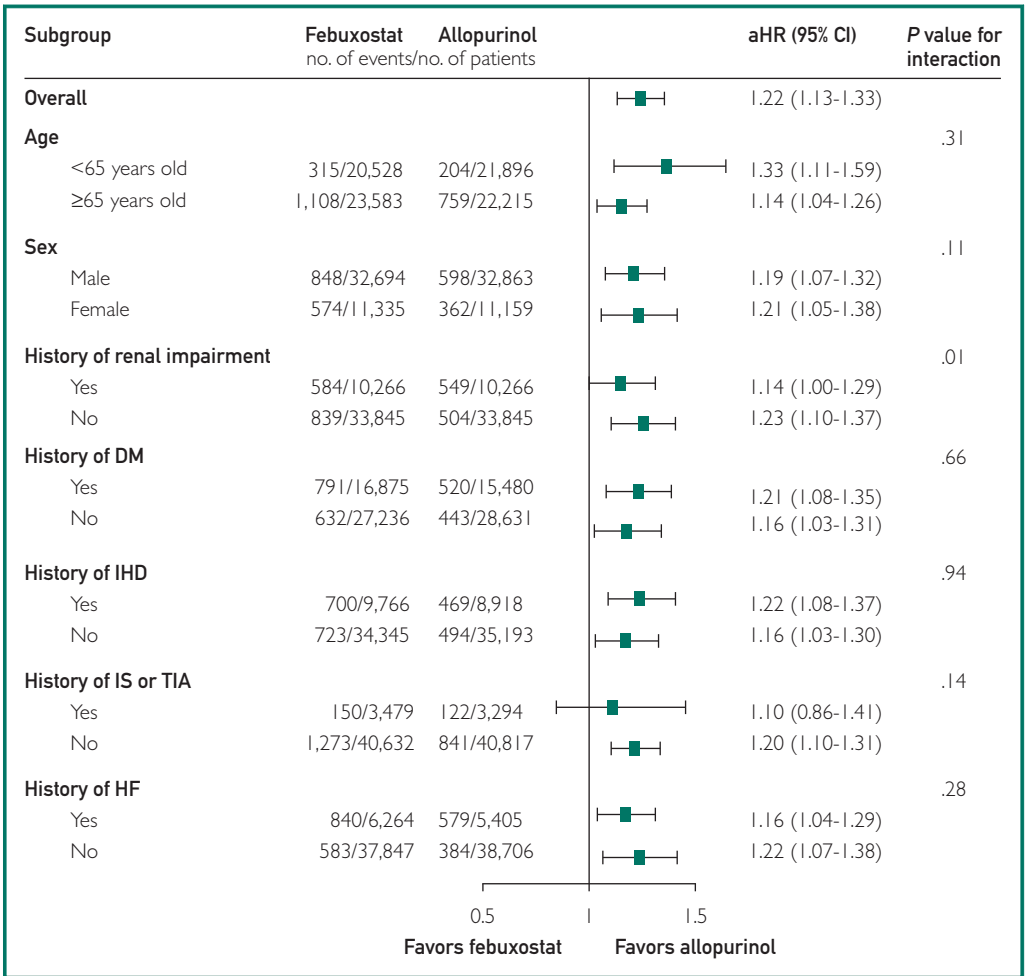

FIGURE 2. Subgroup analyses of heart failure hospitalization. aHR = adjusted hazard ratio; CI = confidence interval; DM = diabetes mellitus; HF = heart failure; IHD = ischemic heart disease; IS = ischemic stroke; TIA = transient ischemic attack.

3098) than in the allopurinol group (3.9%, n=121 of 3092), although the difference did not reach statistical significance (HR, 1.10; 95% CI, 0.86-1.40).[12] In addition, 20 (0.6%) patients in the febuxostat group and 13 (0.4%) in the allopurinol group died from HF. Although more studies are needed to confirm the observed higher rate of HF hospitalization and mortality associated with febuxostat use, our study suggested the importance of monitoring clinical HF symptoms and cardiac functions after initiating febuxostat.

A recent population-based cohort study using longitudinal claims data from US Medicare examined the risk of CV events in gout patients aged 65 years and older who started febuxostat or allopurinol.[13] In this study, a total of 24,936 febuxostat initiators were 1:3 PS-matched to 74,808 allopurinol initiators; the mean (SD) follow-up times were 1.1 (1.1) and 1.2 (1.2) years among the febuxostat and allopurinol initiators, respectively. Unlike the CARES trial and the present study, no risk difference was found between those initiating febuxostat versus allopurinol in the primary outcome, which was a composite endpoint of hospitalization for MI or stroke (HR, 1.01; 95% CI, 0.94-1.08), nor in the individual endpoints of hospitalization for MI, stroke, new-onset HF, coronary

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TABLE 3. Dose-Response Analyses in Febuxostat Users

	Crude hazard ratio (95% CI)			Adjusted hazard ratio (95% CI)[a]		
	≤0.5 DDD	>0.5, ≤1 DDD	>1 DDD	≤0.5 DDD	>0.5 DDD, ≤1 DDD	>1 DDD
MACE composite	reference	1.01 (0.85-1.19)	1.25 (0.98-1.61)	reference	1.22 (1.03-1.46)	1.51 (1.17-1.94)
VTE	reference	1.77 (0.97-3.24)	1.75 (0.72-4.22)	reference	2.15 (1.16-3.99)	1.81 (0.74-4.45)
CV-related hospitalization						
Myocardial infarction	reference	1.00 (0.71-1.40)	0.93 (0.53-1.63)	reference	1.14 (0.80-1.62)	1.10 (0.62-1.93)
Ischemic stroke	reference	1.36 (1.03-1.80)	1.68 (1.13-2.49)	reference	1.70 (1.28-2.26)	2.10 (1.41-3.14)
Heart failure	reference	1.37 (1.19-1.59)	1.55 (1.25-1.93)	reference	1.83 (1.57-2.13)	1.98 (1.59-2.46)
Atrial fibrillation	reference	1.53 (1.22-1.91)	2.00 (1.47-2.71)	reference	1.92 (1.53-2.42)	2.36 (1.73-3.22)

[a]Adjusted for all baseline and matching variables.

CV = cardiovascular; DDD = defined daily dose; MACEs = major adverse cardiovascular events; VTE = venous thromboembolism.

revascularization, and all-cause mortality.[13] Importantly, in this US Medicare study, the average age of the matched allopurinol cohort was 76 years old, and 30.67% of allopurinol initiators had a daily dose of 300 mg or higher. The cohorts in the present study, by contrast, were much younger (mean age 65 years, similar to that in the CARES trial) and the daily dose of the allopurinol users was much lower (mean, 133.3 mg), with very few patients taking a daily dose of 300 mg or higher. It is possible that the differences in age and allopurinol dosing may account for, at least partially, the distinct results between the US Medicare study and our study. Nevertheless, our findings signify the importance of real-world data and the needs for further understanding the safety profile of XOIs in various settings.

The US FDA Adverse Event Reporting System received 21 reports of febuxostat-associated CV thromboembolic events from February 2009 to the fourth quarter of 2011. These reported events included MI, stroke, pulmonary embolism, deep vein thrombosis, and others. The pharmacovigilance analysis using Bayesian statistics within the neural network architecture (Bayesian confidence propagation neural network) indicated potential signals of febuxostat-associated CV thromboembolic events.[11] However, a causal link between febuxostat and febuxostat-associated CV thromboembolic events has not been established. In our study, however, no elevated risk of VTE, MI, or ischemic stroke was found to be associated with febuxostat use.

The underlying mechanism of febuxostat-related adverse CV outcomes remains undetermined. Observational studies have shown that both hyperuricemia and hypouricemia are associated with an increased risk of adverse CV outcomes (J-curve phenomenon).[29-31] Although high serum uric acid level is an independent risk factor for hypertension and arteriosclerosis, low serum levels of uric acid, an important physiologic antioxidant and radical scavenger, could lead to increased oxidative stress and predisposes to CV dysfunction.[32,33] Previous studies have shown that 80 mg (1 DDD) of febuxostat daily can lower the serum urate by 41.4% to 44.7%, whereas 300 mg (0.75 DDD) of allopurinol daily can lower the serum uric acid by 28.7% to 33.0%.[6,34] In our study, the mean daily doses of the febuxostat and allopurinol users were 53.1 mg (0.66 DDD) and 133.3 mg (0.33 DDD), respectively. Therefore, it is likely that the higher mean daily dose of febuxostat had lowered the serum urate level to a greater extent[6,35] and resulted in an increased risk of adverse CV events. However, owing to the lack of serum uric acid information in the database, we could not confirm the proposed hypothesis or examine the risk of CV events in relation to the serum urate level.

The present study had several important strengths. First, a series of CV outcomes were examined with a rigorous new user and active comparator design. Use of the national insurance claims database also provided us with a large sample size and

higher generalizability for answering the study question. Second, sensitivity analyses conducted with different analytic methods, outcome definitions, and selection of the eligible population showed consistent results, suggesting the robustness of the study findings. Subgroup and dose-response analyses also helped elucidate the drug effects in different subpopulations and patients with different doses. Moreover, the study groups were well balanced through PS methods and additional matching criteria, with careful consideration of the unique reimbursement policy in Taiwan.

Despite these strengths, this study has several limitations. Unlike randomized controlled trials, observational studies can suffer from confounding and selection bias due to lack of a randomization process. Although we controlled for covariates by matching and regression adjustment, residual confounding due to unmeasured covariates (eg, serum uric acid and creatinine levels), data inaccuracy or diagnosis undercoding (eg, gout) remains possible. In our study, the outcomes and baseline comorbidities were defined using diagnostic codes, most of which have been validated.[16-18,20,21] Even though we conducted a sensitivity analysis with outcomes identified based on the primary diagnosis only and the results were generally consistent, coding problems might not be completely excluded. Finally, similar to many other retrospective studies, we could only define medication exposure based on pharmacy dispensing records, and true medication adherence was unknown.

CONCLUSION

In the real-world setting, febuxostat was associated with an increased risk of HF hospitalization, AF hospitalization, and CV death, compared with allopurinol. The elevated risk of HF was found to be robust throughout the analyses. Additionally, a dose-response relationship between febuxostat use and adverse CV outcomes was observed. These data strongly suggest that CV symptoms and cardiac function should be frequently assessed in patients receiving febuxostat. Further studies are needed to investigate the underlying mechanism of the adverse CV outcomes linked to febuxostat.

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Ms Ching-Yen Su and Dr Li-Jiuan Shen contributed equally to this work.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **AF** = atrial fibrillation; **CV** = cardiovascular; **DDD** = defined daily dose; **HF** = heart failure; **MACE** = major adverse cardiovascular event; **MI** = myocardial infarction; **PS** = propensity score; **VTE** = venous thromboembolism; **XOI** = xanthine oxidase inhibitor

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REFERENCES

1. Smith E, Hoy D, Cross M, et al. The global burden of gout: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis*. 2014;73(8):1470-1476.
2. Kuo CF, Grainge MJ, See LC, et al. Epidemiology and management of gout in Taiwan: a nationwide population study. *Arthritis Res Ther*. 2015;17:13.
3. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res (Hoboken)*. 2012;64(10):1431-1446.

4. Hung SI, Chung WH, Liou LB, et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proc Natl Acad Sci U S A*. 2005; 102(11):4134-4139.
5. Hershfield MS, Callaghan JT, Tassaneeyakul W, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for human leukocyte antigen-B genotype and allopurinol dosing. *Clin Pharmacol Ther*. 2013;93(2):153-158.
6. Becker MA, Schumacher HR Jr, Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med*. 2005;353(23):2450-2461.
7. Schumacher HR Jr, Becker MA, Wortmann RL, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. *Arthritis Rheum*. 2008;59(11):1540-1548.
8. Becker MA, Schumacher HR, MacDonald PA, Lloyd E, Lademacher C. Clinical efficacy and safety of successful long-term urate lowering with febuxostat or allopurinol in subjects with gout. *J Rheumatol*. 2009;36(6):1273-1282.
9. Schumacher HR Jr, Becker MA, Lloyd E, MacDonald PA, Lademacher C. Febuxostat in the treatment of gout: 5-yr findings of the FOCUS efficacy and safety study. *Rheumatology (Oxford)*. 2009;48(2):188-194.
10. Becker MA, Schumacher HR, Espinoza LR, et al. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial. *Arthritis Res Ther*. 2010;12(2):R63.
11. Gandhi PK, Gentry WM, Bottorff MB. Cardiovascular thromboembolic events associated with febuxostat: investigation of cases from the FDA adverse event reporting system database. *Semin Arthritis Rheum*. 2013;42(6):562-566.
12. White WB, Saag KG, Becker MA, et al. Cardiovascular safety of febuxostat or allopurinol in patients with gout. *N Engl J Med*. 2018;378(13):1200-1210.
13. Zhang M, Solomon DH, Desai RJ, et al. Assessment of cardiovascular risk in older patients with gout initiating febuxostat versus allopurinol. *Circulation*. 2018;138(11):1116-1126.
14. Yoshida K, Solomon DH, Kim SC. Active-comparator design and new-user design in observational studies. *Nat Rev Rheumatol*. 2015;11(7):437-441.
15. WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2018. https://www.whocc.no/atc_ddd_index/. Accessed April 25, 2018.
16. Cheng CL, Lee CH, Chen PS, Li YH, Lin SJ, Yang YHK. Validation of acute myocardial infarction cases in the National Health Insurance Research Database in Taiwan. *J Epidemiol*. 2014; 24(6):500-507.
17. Cheng CL, Kao YH, Lin SJ, Lee CH, Lai ML. Validation of the National Health Insurance Research Database with ischemic stroke cases in Taiwan. *Pharmacoepidemiol Drug Saf*. 2011; 20(3):236-242.
18. Harriss LR, Ajani AE, Hunt D, et al. Accuracy of national mortality codes in identifying adjudicated cardiovascular deaths. *Aust N Z J Public Health*. 2011;35(5):466-476.
19. Chen JH, Lan JL, Cheng CF, et al. Effect of urate-lowering therapy on the risk of cardiovascular disease and all-cause mortality in patients with gout: a case-matched cohort study. *J Rheumatol*. 2015;42(9):1694-1701.
20. Birman-Deych E, Waterman AD, Yan Y, Nilasena DS, Radford MJ, Gage BF. Accuracy of ICD-9-CM codes for identifying cardiovascular and stroke risk factors. *Med Care*. 2005; 43(5):480-485.
21. Cushman M, Tsai AW, White RH, et al. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. *Am J Med*. 2004; 117(1):19-25.
22. Saczynski JS, Andrade SE, Harrold LR, et al. A systematic review of validated methods for identifying heart failure using administrative data. *Pharmacoepidemiol Drug Saf*. 2012;21(suppl 1):129-140.
23. Yu KH, Chen DY, Chen JH, et al. Management of gout and hyperuricemia: multidisciplinary consensus in Taiwan. *Int J Rheum Dis*. 2018;21(4):772-787.
24. Lee MH, Graham GG, Williams KM, Day RO. A benefit-risk assessment of benzbromarone in the treatment of gout. Was its withdrawal from the market in the best interest of patients? *Drug Saf*. 2008;31(8):643-665.
25. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat*. 2011;10(2): 150-161.
26. Austin PC. Using the Standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Commun Stat Simul Comput*. 2009;38(6): 1228-1234.
27. Uloric (febuxostat): Drug safety communication - FDA to evaluate increased risk of heart-related death. U.S. Food and Drug Administration. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-evaluate-increased-risk-heart-related-death-and-death-all-causes. Accessed April 6, 2018.
28. FDA adds Boxed Warning for increased risk of death with gout medicine Uloric (febuxostat). US Food and Drug Administration. https://www.fda.gov/drugs/drug-safety-and-availability/fda-adds-boxed-warning-increased-risk-death-gout-medicine-uloric-febuxostat. Published February 21, 2019. Accessed February 25, 2019.
29. Odden MC, Amadu AR, Smit E, Lo L, Peralta CA. Uric acid levels, kidney function, and cardiovascular mortality in US adults: National Health and Nutrition Examination Survey (NHANES) 1988-1994 and 1999-2002. *Am J Kidney Dis*. 2014;64(4):550-557.
30. Essex MN, Hopps M, Bienen EJ, Udall M, Mardekian J, Makinson GT. Evaluation of the relationship between serum uric acid levels and cardiovascular events in patients with gout: a retrospective analysis using electronic medical record data. *J Clin Rheumatol*. 2017;23(3):160-166.
31. Kang E, Hwang SS, Kim DK, et al. Sex-specific relationship of serum uric acid with all-cause mortality in adults with normal kidney function: an observational study. *J Rheumatol*. 2017; 44(3):380-387.
32. Becker BF. Towards the physiological function of uric acid. *Free Radic Biol Med*. 1993;14(6):615-631.
33. Kuwabara M. Hyperuricemia, cardiovascular disease, and hypertension. *Pulse (Basel)*. 2016;3(3-4):242-252.
34. Yu KH, Lai JH, Hsu PN, Chen DY, Chen CJ, Lin HY. Safety and efficacy of oral febuxostat for treatment of HLA-B*5801-negative gout: a randomized, open-label, multicentre, allopurinol-controlled study. *Scand J Rheumatol*. 2016;45(4): 304-311.
35. Becker MA, Schumacher HR Jr, Wortmann RL, et al. Febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase: a twenty-eight-day, multicenter, phase II, randomized, double-blind, placebo-controlled, dose-response clinical trial examining safety and efficacy in patients with gout. *Arthritis Rheum*. 2005; 52(3):916-923.

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Original article

Comparative cardiovascular risk of allopurinol *versus* febuxostat in patients with gout: a nation-wide cohort study

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Abstract

Objective. To compare cardiovascular (CV) risk among gout patients initiating allopurinol *vs* febuxostat.

Methods. Using 2002–2015 Korean National Health Insurance Service data for the entire Korean population, we conducted a cohort study on gout patients initiating allopurinol or febuxostat. The primary outcome was a composite CV end point of myocardial infarction, stroke/transient ischaemic attack, or coronary revascularization. Secondary outcomes were individual components of the primary outcome, and all-cause mortality. We used propensity score-matching with a 4:1 ratio for allopurinol and febuxostat initiators to control for confounding. Competing risk analyses were done for non-fatal outcomes accounting for deaths.

Results. We included 39 640 allopurinol initiators propensity score-matched on 9910 febuxostat initiators. The mean age was 59.1 years and 78.4% were male. The incidence rate per 100 person-years for the primary outcome was 1.89 for allopurinol and 1.84 for febuxostat initiators. The corresponding hazard ratio comparing allopurinol *vs* febuxostat initiators was 1.09 (95% CI: 0.90, 1.32). No significant difference was found for the secondary outcomes, including all-cause mortality (hazard ratio 0.96; 95% CI: 0.79, 1.16). Subgroup analyses limited to those at high CV risk and to equipotent-dose initiators (i.e. allopurinol $\geqslant$300 mg/day *vs* febuxostat $\geqslant$40 mg/day) showed similar results.

Conclusion. Overall, this large Korean population-based study suggests no difference in the risk of non-fatal CV events and all-cause mortality between allopurinol and febuxostat initiators. These findings are consistent with the recent US Medicare population study, although the current study population consisted of younger Asians.

Key words: gout, cardiovascular disease, allopurinol, febuxostat

CLINICAL SCIENCE

Rheumatology key messages

- Non-fatal cardiovascular and mortality risk was similar between febuxostat and allopurinol in gout patients.
- Similar results were found among high cardiovascular risk patients and equipotent index dose users.
- This real-world setting study adds generalizability to comparable cardiovascular risk between allopurinol and febuxostat.

Introduction

Gout is a chronic inflammatory arthritis characterized by an inflammatory response against monosodium urate crystals deposited in the joints as a result of hyperuricaemia. It is the most common inflammatory arthritis in men and post-menopausal women [1, 2], affecting 3.9% of the US adult population [3]. The prevalence and incidence of gout are increasing [3, 4], probably due to lifestyle changes, population ageing and related comorbidities, and medications [4]. Beyond gouty arthritis, hyperuricaemia and gout have been associated with the risk of various cardiovascular (CV) outcomes, including ischaemic heart disease [5–9] and stroke [8–10], peripheral vascular disease [11], heart failure [12, 13], as well as with renal impairment [14] and premature mortality [7, 8, 10].

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Allopurinol is an xanthine oxidase inhibitor (XOI) that has been in use to treat gout for decades while febuxostat, another XOI, was approved by the FDA in 2009. So far, the comparative CV risk between allopurinol and febuxostat treatment has been controversial. In clinical trials comparing allopurinol *vs* febuxostat on gout treatment, a numerically higher CV incidence was noted in patients receiving febuxostat without statistical difference [15]. Subsequent observational studies have been conflicting on this issue [16–19]. Recently, the Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial ($n = 6190$) found a similar risk for the primary composite end point of major adverse CV events between febuxostat and allopurinol users, whereas the risk for CV and all-cause mortality was higher with febuxostat compared to allopurinol treatment [20]. However, a recent large population study based on elderly US Medicare patients found no such difference in the risk of all-cause mortality or non-fatal CV events between the two XOIs [21]. These inconsistencies among the limited available evidence call for further information on this important topic.

Thus, we conducted a large population-based study to provide more comprehensive and generalizable information on a comparative CV risk between allopurinol and febuxostat treatment among Korean gout patients.

Methods

Data sources

Using the Korean National Health Insurance Service (KNHIS) database, which covers the entire Korean population, we conducted a population-based cohort study among gout patients who initiated allopurinol or febuxostat between 2002 and 2015. The database contains longitudinal patient data including demographics, diagnosis codes according to the International Classification of Diseases Tenth Revision (ICD-10), procedures, prescription records (brand name, generic name, prescription date, number of days of supply, dose and route of administration), and type of medical utilization (outpatient, inpatient or emergency department) of all Korean citizens [22]. The Institutional Review Board of the Seoul National University Bundang Hospital approved the study protocol and privacy precautions (X-1704-393-903).

Study population

Eligible patients were initiators of either allopurinol or febuxostat with ICD-10 diagnosis codes of gout (M10.xx). The initiators were defined as those who had no prior dispensing of any urate-lowering therapy for at least 12 months before the first dispensing date (i.e. index date) of either allopurinol or febuxostat. We excluded patients with a diagnosis of cancer and those who had ever undergone dialysis during the 12-month pre-index period. We also excluded patients with a diagnosis of chronic kidney disease (CKD): based on the sensitivity of CKD diagnosis codes (i.e. $<20\%$ in case of estimated glomerular filtration rate <60 ml/min/1.73 m^2; $<65\%$ in case of <30 ml/min/1.73 m^2) [23], we intended to preferentially exclude severe CKD patients in whom confounding by indication is a greater concern while preserving a majority of mild-to-moderate CKD patients in the study cohort.

The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation good clinical practices. The protocols were reviewed and approved by the institutional review board of Seoul National University Bundang Hospital. All patients provided written informed consent before undergoing the survey.

Outcome definition

The primary outcome was a composite CV end point of hospitalized myocardial infarction (MI), stroke/transient ischaemic attack (TIA), or coronary revascularization. Secondary outcomes consisted of individual components of the primary outcome, and death of any cause. MI and stroke/TIA were identified using inpatient ICD-10 diagnosis codes (MI: I21.xx; stroke/TIA: I60.xx, I61.xx, I63.xx, I64.xx and G45.x). Coronary revascularization was identified using inpatient procedure codes. In prior studies, the positive predictive values of these algorithms to identify the corresponding CV outcome were $\geqslant 80\%$ [24–26].

Covariate assessment

We assessed variables potentially associated with all CV outcomes during the 1-year pre-index period. These variables were demographics, baseline CV conditions (MI, angina, stroke/TIA and heart failure), traditional CV risk factors (i.e. hypertension, dyslipidaemia, diabetes, peripheral vascular disease, smoking and obesity), other comorbidities, gout medications (i.e. colchicine, naproxen and other NSAIDs, cox-2 inhibitors, and steroids), other medications (i.e. angiotensin converting enzyme inhibitors, angiotensin receptor blockers and diuretics), markers of health care use intensity including hospitalization, emergency department visits, or the use of laboratory or other diagnostic tests including those for serum creatinine and uric acid levels (Supplementary Table S1, available at *Rheumatology* online). To assess the level of comorbidities, we used the Charlson and Deyo comorbidity score [27].

Statistical analysis

To adjust for $\geqslant 50$ potential confounders listed above, we used propensity score (PS) matching. We estimated PS using a multivariable logistic regression model that included all the baseline variables listed in Table 1 plus index year; since febuxostat was available beginning in 2012 in Korea, only index years from 2012 were included. Nearest neighbour matching for allopurinol *vs* febuxostat initiators was done with a 4:1 ratio using a calliper of 0.2 of the standard deviation of PS. The achieved PS balance was inspected by tabulating baseline patient

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Table 1 Baseline characteristics of the 4:1 propensity score-matched cohort[a]

	Allopurinol initiators (n = 39 640)	Febuxostat initiators (n = 9910)
Demographics		
Age, mean (S.D.), years	59.1 (12.5)	59.4 (12.9)
Male (%)	78.9	78.3
Index year (%)		
2012	19.8	19.4
2013	33.7	33.4
2014	21.1	21.3
2015	25.5	25.9
Cardiovascular comorbidities		
Angina pectoris (%)	12.2	12.4
Atrial fibrillation (%)	4.3	4.4
Myocardial infarction (%)	1.6	1.6
Stroke/transient ischaemic attack (%)	7.6	8.0
Heart failure (%)	7.3	7.5
Hypertension (%)	54.0	55.4
Venous thromboembolism (%)	1.4	1.5
Peripheral vascular disease (%)	12.7	13.0
Other comorbidities		
Hyperlipidaemia (%)	44.8	45.5
Liver disease (%)	28.3	28.8
Chronic obstructive pulmonary disease (%)	18.7	19.1
Asthma (%)	11.5	11.8
Diabetes (%)	28.6	29.5
Renal stone (%)	2.6	2.6
Obesity (%)	0.1	0.1
Sleep apnoea (%)	0.2	0.1
Smoking (%)	0.1	0.1
Alcoholism (%)	4.4	4.4
Comorbidity score (%)	1.63±1.75	1.67±1.78
Gout-related medications		
Colchicine (%)	28.0	27.1
Any NSAIDs (%)	72.8	72.4
Naproxen (%)	9.8	9.5
COXIBs (%)	7.1	7.0
Opioids (%)	18.3	18.5
Oral steroids (%)	59.6	59.4
Other medications		
ACE inhibitors or ARBs (%)	28.8	29.5
Beta blockers (%)	22.3	22.9
Calcium channel blockers (%)	34.8	35.7
Any diuretics (%)	33.1	34.2
Loop diuretics (%)	11.3	13.6
Insulin (%)	6.2	6.4
Non-insulin hypoglycaemic drugs (%)	16.8	17.3
Anticoagulants (%)	6.2	6.3
Antiplatelets (%)	25.7	26.2
Thrombolytic agents (%)	0.1	0.1
Statins (%)	28.3	29.0
Other lipid lowering agents (%)	5.9	6.0
Health care utilization pattern		
Hospitalization (%)	25.2	25.8
ER visits (%)	13.8	14.2
ECG ordered (%)	37.3	38.0
Echocardiogram ordered (%)	0.9	0.9
HbA1C ordered (%)	27.8	28.5
Lipid/cholesterol test ordered (%)	61.9	62.8
Serum creatinine test ordered (%)	67.0	67.8
Uric acid test ordered (%)	77.0	76.8

[a]All the covariates shown in the table have standard differences of <0.1. ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; COXIB: Cox-2 inhibitor; ER: emergency room; HbA1C: haemoglobin A1C.

characteristics according to treatment status and by examining the standardized differences.

For the primary as-treated analysis, the follow-up time started the day after the index date and continued through to the earliest date among the following events: discontinuation of the index drug, outcome occurrence, insurance disenrollment, end of study follow-up or death. Study drug discontinuation was defined similarly to the previous Medicare population study [21] as occurring either after a grace period of 30 days from the last date of drug availability estimated from the last dispensing date plus days' supply or at the drug switching date to other urate lowering agents, whichever comes first. Only a single entry into the study cohort was allowed per patient. For the secondary 365-day intention-to-treat analysis, follow-up time was truncated on the 366th day after the index date unless patients were censored based on the previously mentioned criteria, except for drug discontinuation.

We estimated the hazard ratio (HR) with 95% CI for each outcome associated with allopurinol use *vs* febuxostat by Cox proportional hazards models. For non-fatal CV outcomes, we accounted for the competing risk of death by Fine–Gray sub-distribution hazards models [28]. We tested the interaction between the exposure and follow-up time to ensure that the proportional hazards assumption was met and observed no violation [29]. All analyses were completed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA).

Subgroup analysis

We performed two specific subgroup analyses to compare the CV effect of the two XOIs: high risk patients defined similarly to CARES participants (i.e. men aged $\geqslant$50 years or women aged $\geqslant$55 years who had any diagnosis of angina, MI, stroke/TIA, peripheral vascular disease or diabetes during the 1-year pre-index period) [20]; and, among equipotent dose initiators with a daily index dose of $\geqslant$300 mg of allopurinol *vs* $\geqslant$40 mg of

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febuxostat [21]. Independent PS-matching based on a separate multivariable logistic regression model was done for each subgroup to account for the same baseline covariates as in the main analysis.

Sensitivity analysis

To examine whether patients developed CV end points or died after treatment discontinuation, we conducted sensitivity analyses with a 90-day grace period after the last date of drug availability and performed as-treated analyses for all of non-fatal CV and mortality outcomes.

Results

Patient characteristics

We identified a total of 452 909 gout patients who initiated allopurinol or febuxostat in the KNHIS database during the study period (Supplementary Fig. S1, available at *Rheumatology* online). Before PS-matching, febuxostat initiators showed more comorbidities than allopurinol initiators (Supplementary Table S1, available at *Rheumatology* online): hypertension (55.4 *vs* 49.3%), diabetes (29.5 *vs* 22.0%), hyperlipidaemia (45.5 *vs* 31.6%) and previous CV events (12.4 *vs* 9.6% for angina, 1.6 *vs* 1.3% for MI, and 8.0 *vs* 6.4% for stroke/TIA). After PS-matching, 39 640 allopurinol and 9910 febuxostat initiators were identified. The mean age was 59.1 years and 78.4% were male. All baseline covariates including CV risk factors and the index year were well balanced with a standardized difference of prevalence <0.1 after PS-matching (Table 1) [30]. The mean (S.D.) follow-up time for the primary outcome was 303 (358) days, with 316 (369) days for allopurinol and 251 (308) days for febuxostat initiators.

Allopurinol and febuxostat usage pattern

Supplementary Table S2, available at *Rheumatology* online, shows the distribution of the daily index dosage of the study drugs and their maximum daily dose dispensed during the follow-up among the PS-matched cohort. At the index date, the most common daily dose of allopurinol was 300 mg, as taken by 36.8% of allopurinol initiators, whereas 72.0% of febuxostat initiators took 80 mg. During the follow-up, ~38.8% of allopurinol initiators used a daily dose of 300 mg at the maximum while 74.5% of febuxostat initiators used 80 mg at the maximum.

Risk of CV outcomes between allopurinol *vs* febuxostat initiators

In our primary as-treated analysis, the incidence rate for the composite CV end point was 1.89 per 100 person-years in allopurinol initiators and 1.84 in febuxostat initiators. After a competing risk analysis accounting for deaths, the PS-matched HR (95% CI) of the composite end point comparing allopurinol *vs* febuxostat initiators was 1.09 (0.90, 1.32) (Table 2). The results for the secondary outcomes did not significantly differ between the two treatments. Of note, the PS-matched HR (95% CI) for all-cause mortality was non-significant (HR 0.96; 95% CI: 0.79, 1.16) (Table 2).

In the sensitivity analyses with a 90-day grace period added to the last date of drug availability, we found no material difference from the primary analysis for the non-fatal CV outcomes as well as all-cause mortality (for the composite CV endpoint, HR 1.07; 95% CI: 0.90, 1.28; for all-cause mortality, HR 0.98; 95% CI: 0.83, 1.16) (Supplementary Table S3, available at *Rheumatology* online). Similarly, in our secondary 365-day intention-to-treat analysis, the results remain similar to the primary analysis (for the composite CV endpoint, HR 1.08; 95% CI: 0.90, 1.29; for all-cause mortality, HR 0.98; 95% CI: 0.84, 1.14) (Supplementary Table S4, available at *Rheumatology* online).

Subgroup analyses for the high CV risk group and equipotent dose initiators

We performed a subgroup analysis on 12 936 allopurinol initiators 4:1 PS-matched on 3234 febuxostat initiators who are at high CV risk. The mean age was 68.8 years and 68% of the participants were male (Supplementary Table S5, available at *Rheumatology* online). There was no difference between the two treatment initiators in the primary (HR 1.10; 95% CI: 0.88, 1.37) and secondary CV outcomes, including all-cause mortality (HR 0.99; 95% CI: 0.79, 1.24) (Table 3).

In our subgroup analysis comparing CV risk in 4:1 PS-matched equipotent dose initiators with a daily index dose of allopurinol $\geqslant$300 mg/day ($n=38$ 224) *vs* febuxostat $\geqslant$40 mg/day ($n=9556$) (Supplementary Table S6, available at *Rheumatology* online), the HR (95% CI) for the primary outcome was 0.92 (0.74, 1.14) and that for all-cause mortality was 0.83 (0.66, 1.04) (Table 4).

Discussion

In this large population cohort of Korean patients with gout who initiated allopurinol or febuxostat, we found no difference in the risk of non-fatal CV outcomes and all-cause mortality between allopurinol and febuxostat treatment. These results persisted in sensitivity analyses with a larger grace period for discontinuation of the medications, as well as in an intention-to-treat analysis. Furthermore, our subgroup analyses among high CV risk patients as well as on equipotent dose users of allopurinol and febuxostat, reflecting the CARES trial population [20], also showed no significant difference in CV risk or all-cause mortality. These findings replicate the recent US Medicare population study [21], although the current study population was composed of younger Asians.

This study is the first large-scale Asian population study on the comparative CV risk between allopurinol and febuxostat treatment among gout patients. In the recent large study of elderly Medicare enrollees (median 76 years of age), Zhang and colleagues found no difference in the risk of non-fatal CV events and all-cause mortality after rigorous adjustment for baseline confounders [21]. Of note, similar to our study, they found no difference in the risk of all-cause mortality even in the high-risk

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Table 2 Comparative cardiovascular risk between allopurinol and febuxostat initiators

	Allopurinol initiators ($n = 39\,640$)			Febuxostat initiators (Ref) ($n = 9910$)				
	Events	PY	IR[a] (95% CI)	Events	PY	IR[a] (95% CI)	HR[b] (95% CI)	HR[c] (95% CI)
Composite endpoint	648	34 382	1.89 (1.74, 2.03)	125	6809	1.84 (1.51, 2.16)	1.15 (0.95, 1.40)	1.09 (0.90, 1.32)
MI	88	34 879	0.25 (0.20, 0.31)	20	6872	0.29 (0.16, 0.42)	0.98 (0.60, 1.60)	0.91 (0.56, 1.47)
Coronary revascularization	267	34 705	0.77 (0.68, 0.86)	44	6849	0.64 (0.45, 0.83)	1.33 (0.97, 1.83)	1.25 (0.91, 1.71)
Stroke or TIA	382	34 623	1.10 (0.99, 1.21)	78	6847	1.14 (0.89, 1.39)	1.09 (0.85, 1.39)	1.03 (0.81, 1.32)
Death	545	34 944	1.56 (1.43, 1.69)	135	6884	1.96 (1.63, 2.29)	0.96 (0.79, 1.16)	

[a]IR is per 100 person-years. [b]HR by Cox proportional hazard models. [c]HR by Fine–Gray models for non-fatal CV events. HR: hazard ratio; IR: incidence rate; MI: myocardial infarction; PY: person-years; TIA: transient ischaemic attack.

Table 3 Comparative cardiovascular risk between allopurinol and febuxostat initiators at high risk for cardiovascular disease

	Allopurinol initiators ($n = 12\,396$)			Febuxostat initiators (Ref) ($n = 3234$)				
	Events	PY	IR[a] (95% CI)	Events	PY	IR[a] (95% CI)	HR[b] (95% CI)	HR[c] (95% CI)
Composite endpoints	469	11 415	4.11 (3.74, 4.48)	98	2484	3.95 (3.16, 4.73)	1.09 (0.88, 1.36)	1.10 (0.88, 1.37)
MI	67	11 772	0.57 (0.43, 0.71)	15	2533	0.59 (0.29, 0.89)	1.03 (0.58, 1.80)	1.01 (0.58, 1.76)
Coronary revascularization	191	11 651	1.64 (1.41, 1.87)	35	2515	1.39 (0.93, 1.85)	1.26 (0.88, 1.81)	1.23 (0.86, 1.77)
Stroke or TIA	275	11 594	2.37 (2.09, 2.65)	61	2513	2.43 (1.82, 3.04)	1.01 (0.77, 1.34)	1.03 (0.78, 1.37)
Death	409	11 817	3.46 (3.13, 3.80)	95	2542	3.74 (2.99, 4.49)	0.99 (0.79, 1.24)	

[a]IR is per 100 person-years. [b]HR by Cox proportional hazard models. [c]HR by Fine–Gray models for non-fatal CV events. HR: hazard ratio; IR: incidence rate; MI: myocardial infarction; PY: person-years; TIA: transient ischaemic attack.

Table 4 Comparative cardiovascular risk between equipotent-dose allopurinol ($\geqslant$300 mg/day) and febuxostat ($\geqslant$40 mg/day) initiators

	Allopurinol initiators ($n = 38\,224$)			Febuxostat initiators (Ref) ($n = 9556$)				
	Events	PY	IR[a] (95% CI)	Events	PY	IR[a] (95% CI)	HR[b] (95% CI)	HR[c] (95% CI)
Composite endpoint	452	31 426	1.44 (1.31, 1.57)	105	6420	1.64 (1.32, 1.95)	1.13 (0.91, 1.40)	0.92 (0.74, 1.14)
MI	64	31 776	0.20 (0.15, 0.25)	19	6471	0.29 (0.16, 0.43)	0.90 (0.53, 1.52)	0.74 (0.44, 1.22)
Coronary revascularization	180	31 662	0.57 (0.49, 0.65)	38	6452	0.59 (0.40, 0.78)	1.21 (0.85, 1.73)	0.99 (0.70, 1.40)
Stroke or TIA	268	31 599	0.85 (0.75, 0.95)	64	6452	0.99 (0.75, 1.23)	1.09 (0.83, 1.44)	0.90 (0.69, 1.18)
Death	307	31 833	0.96 (0.86, 1.07)	109	6481	1.68 (1.37, 2.00)	0.83 (0.66, 1.04)	

[a]IR is per 100 person-years. [b]HR by Cox proportional hazard models. [c]HR by Fine-Gray models for non-fatal CV events. HR: hazard ratio; IR: incidence rate; MI: myocardial infarction; PY: person-years; TIA: transient ischaemic attack.

subgroup defined similarly to the CARES participants in terms of underlying CV risk [20, 21]. As our study cohort represents a much younger population of Asians who have a considerably lower prevalence of underlying CV conditions and risk factors than Medicare patients [21], our study adds to the generalizability of these findings.

Our null findings for the non-fatal CV end points are consistent with the CARES trial (a randomized double-

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blinded trial) [20], whereas those for all-cause mortality did not agree with the trial's main findings that showed an increased risk in association with febuxostat treatment. The CARES trial required a history of CV disease and the median follow-up (32 months) was longer than the current study and Medicare study [20, 21]. These differences may explain the discrepancies; however, the inconsistency between non-fatal and fatal CV outcomes as reported in the CARES trial is unusual. Furthermore, while the CARES trial had the clear advantage of randomization for balancing comparison groups at baseline, 57% of participants prematurely discontinued treatment and 45% were lost to follow-up, leaving a concern for the association between patient drop-out and study outcomes (i.e. selection bias) [31]. Indeed, when the *post hoc* ascertainment process added 199 deaths to the original 442 deaths, 21 more deaths were added to allopurinol than febuxostat (110 *vs* 89), nullifying the HR [31]. These findings suggest that the mortality risk found in the CARES trial may be vulnerable to such a potential selection bias due to a large loss to follow-up.

The relationship between serum uric acid and CV events has consistently been shown as J-shaped, with the lowest quartile having a higher risk than the middle quartiles and the curve inflection occurring at serum uric acid level around 4–5 mg/dl [32–35]. These finding have suggested that excessive decrease of serum uric acid might increase CV risk, possibly due to deprivation of antioxidant activity of uric acids [32]. The drug use pattern in our PS-matched cohort showed that >95% of febuxostat initiators used a daily dose of ⩾40 mg while 61% of allopurinol initiators used a daily dose of ⩾200 mg (Supplementary Table S2, available at *Rheumatology* online). Therefore, there might be a proportion of febuxostat initiators who experienced hazardously low serum uric acid levels, attenuating the beneficial effect of the drug if any. Similarly, the proportion of patients whose serum uric acid levels reached below 5 mg/dl was higher in users of febuxostat than of allopurinol throughout the CARES study period. However, there has been no data or guide on the optimal lower bound for a target serum uric acid level for urate lowering treatment, which should be addressed in future studies.

Several important strengths of this study deserve comment. First, rigorous pharmacoepidemiological methods were used including the new user and active comparator design to minimize biases due to the depletion of susceptibles and confounding by indication [36]. Since the active comparator design ensures that the clinical circumstances for the two treatments to be used are very similar, it has been considered as a power tool to minimize bias by disease severity [36]. Both allopurinol and febuxostat are XOIs to lower serum uric acid levels, recommended equivalently as a first-line urate lowering agent by the 2012 ACR guidelines for gout management [37] and we ensured that the study medications were used as a fist-line urate lowering agent by including only new users of allopurinol or febuxostat. In addition, we performed extensive PS-matching for ⩾50 variables related to gout severity and associated comorbidities. To further account for renal status of CKD patients potentially included in our study, we balanced the use of loop and other diuretics, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, and other medications at baseline. Second, death is an important competing risk and our study appropriately accounted for this. Third, this study provides high generalizability based on a large general population. Fourth, our highly relevant subgroup analyses showed consistent results as noted in the primary analysis. Finally, we utilized previously validated claims-based algorithms to define CV outcomes to minimize misclassification bias [24–26].

There are limitations to this study. First, as is inherent to any observational study, our study is subject to residual or unmeasured confounding, despite our rigorous efforts for confounding adjustment. Febuxostat initiators showed a higher prevalence of CV risk factors and greater comorbidity index at baseline before PS-matching (Supplementary Table S1, available at *Rheumatology* online). It is possible that febuxostat initiators had a higher gout severity than allopurinol initiators even after our extensive PS-matching. Such residual or unmeasured confounding would have made our results conservative against beneficial effects of febuxostat if any. Second, similar to the Medicare study [21], our follow-up time was shorter than that of the CARES trial [20]. While these observational data directly reflect the low persistence of urate-lowering therapy in the real world setting [38], caution is need in interpreting the long term CV effect of the two treatment groups. Future studies with a longer-term follow-up would be valuable to clarify this issue. Third, although excluding patients based on the CKD diagnosis codes would help ensure the validity of our study, it may harm the generalizability of the study results. However, as seen in Supplementary Fig. S1, available at *Rheumatology* online, the prevalence of CKD diagnoses was very low among our gout patients, reflecting a poor sensitivity of the diagnosis codes [23] and a younger population age. Consequently, it is unlikely that this measure altered the overall study population characteristics or study results. Finally, cause of death was not available from the database. Nevertheless, we expect that CV deaths would likely agree with all-cause deaths as in many CV studies, including the CARES trial, as CV death continues to be the major contributor for all-cause mortality.

In conclusion, in this large Korean population-based cohort study, we found no difference in the risk for MI, stroke/TIA, coronary revascularization or all-cause mortality. These findings replicate the recent US Medicare population study [21]. As the study population was composed of younger Asians, these findings add to the generalizability of these findings.

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All authors interpreted the data, critically revised the manuscript for important intellectual content, and approved the final version of the manuscript. S.C.K. and E.H.K. conceived and designed the study. E.H.K., A.S., H.K.C. and S.C.K. participated in the statistical analysis.

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A.S. conducted the programming. E.H.K. acquired the data and drafted the manuscript and all authors contributed to critical revision of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1 Lawrence RC, Helmick CG, Arnett FC *et al*. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthritis Rheum 1998;41:778–99.

2 VanItallie TB. Gout: epitome of painful arthritis. Metabolism 2010;59(Suppl 1):S32–6.

3 Chen-Xu M, Yokose C, Rai SK *et al*. Contemporary prevalence of gout and hyperuricemia in the United States and decadal trends: The National Health and Nutrition Examination Survey 2007–2016. Arthritis Rheumatol 2019, doi:10.1002/art.40807.

4 Roddy E, Doherty M. Epidemiology of gout. Arthritis Res Ther 2010;12:223.

5 Choi HK, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. Circulation 2007;116:894–900.

6 Krishnan E, Svendsen K, Neaton JD *et al*.; MRFIT Research Group. Long-term cardiovascular mortality among middle-aged men with gout. Arch Intern Med 2008;168:1104.

7 Li M, Hu X, Fan Y *et al*. Hyperuricemia and the risk for coronary heart disease morbidity and mortality a systematic review and dose-response meta-analysis. Sci Rep 2016;6:19520.

8 Chen JH, Chuang SY, Chen HJ *et al*. Serum uric acid level as an independent risk factor for all-cause, cardiovascular, and ischemic stroke mortality: a Chinese cohort study. Arthritis Rheum 2009;61:225–32.

9 Seminog OO, Goldacre MJ. Gout as a risk factor for myocardial infarction and stroke in England: evidence from record linkage studies. Rheumatology (Oxford) 2013;52:2251–9.

10 Storhaug HM, Norvik JV, Toft I *et al*. Uric acid is a risk factor for ischemic stroke and all-cause mortality in the general population: a gender specific analysis from The Tromsø Study. BMC Cardiovasc Disord 2013;13:115.

11 Baker JF, Schumacher HR, Krishnan E. Serum uric acid level and risk for peripheral arterial disease: analysis of data from the multiple risk factor intervention trial. Angiology 2007;58:450–7.

12 Krishnan E. Gout and the risk for incident heart failure and systolic dysfunction. BMJ Open 2012;2:e000282.

13 Huang H, Huang B, Li Y *et al*. Uric acid and risk of heart failure: a systematic review and meta-analysis. Eur J Heart Fail 2014;16:15–24.

14 Richette P, Perez-Ruiz F, Doherty M *et al*. Improving cardiovascular and renal outcomes in gout: what should we target? Nat Rev Rheumatol 2014;10:654–61.

15 Zhang T, Pope JE. Cardiovascular effects of urate-lowering therapies in patients with chronic gout: a systematic review and meta-analysis. Rheumatology (Oxford) 2017;56:1144–53.

16 Tausche AK, Christoph M, Forkmann M *et al*. As compared to allopurinol, urate-lowering therapy with febuxostat has superior effects on oxidative stress and pulse wave velocity in patients with severe chronic tophaceous gout. Rheumatol Int 2014;34:101–9.

17 Sezai A, Soma M, Nakata K *et al*. Comparison of febuxostat and allopurinol for hyperuricemia in cardiac surgery patients with chronic kidney disease (NU-FLASH trial for CKD). J Cardiol 2015;66:298–303.

18 Foody J, Turpin RS, Tidwell BA, Lawrence D, Schulman KL. Major cardiovascular events in patients with gout and associated cardiovascular disease or heart failure and chronic kidney disease initiating a xanthine oxidase inhibitor. Am Health Drug Benefits 2017;10:393–401.

19 Singh JA, Cleveland JD. Comparative effectiveness of allopurinol versus febuxostat for preventing incident renal disease in older adults: an analysis of Medicare claims data. Ann Rheum Dis 2017;76:1669–78.

20 White WB, Saag KG, Becker MA *et al*.; CARES Investigators. Cardiovascular safety of febuxostat or allopurinol in patients with gout. N Engl J Med 2018;378:1200–10.

21 Zhang M, Solomon DH, Desai RJ *et al*. Assessment of cardiovascular risk in older patients with gout initiating febuxostat versus allopurinol: a population-based cohort study. Circulation 2019;139:1348–9.

22 Son JS, Choi S, Kim K *et al*. Association of blood pressure classification in Korean young adults according to the 2017 American College of Cardiology/American Heart Association guidelines with subsequent cardiovascular disease events. JAMA 2018;320:1783–92.

23 Ronksley PE, Tonelli M, Quan H *et al*.; Alberta Kidney Disease Network. Validating a case definition for chronic kidney disease using administrative data. Nephrol Dial Transplant 2012;27:1826–31.

24 Kiyota Y, Schneeweiss S, Glynn RJ *et al*. Accuracy of Medicare claims-based diagnosis of acute myocardial infarction: estimating positive predictive value on the basis of review of hospital records. Am Heart J 2004;148:99–104.

25 Choma NN, Griffin MR, Huang RL *et al*. An algorithm to identify incident myocardial infarction using Medicaid data. Pharmacoepidemiol Drug Saf 2009;18:1064–71.

26 Andrade SE, Harrold LR, Tjia J *et al*. A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data. Pharmacoepidemiol Drug Saf 2012;21(Suppl 1):100–28.

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27 Sundararajan V, Henderson T, Perry C *et al*. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. J Clin Epidemiol 2004;57:1288–94.

28 Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. Circulation 2016;133:601–9.

29 Kleinbaum DG, Klein M. Evaluating the proportional hazards assumption. In: Survival Analysis: A Self-Learning Text, 3rd edn. New York: Springer, 2012: 161–200.

30 Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat 2011;10:150–61.

31 Choi H, Neogi T, Stamp L *et al*. Implications of the cardiovascular safety of febuxostat and allopurinol in patients with gout and cardiovascular morbidities (CARES) trial and associated FDA public safety alert. Arthritis Rheumatol 2018;70:1702–9.

32 Johnson RJ, Kang DH, Feig D *et al*. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension 2003;41:1183–90.

33 Suliman ME, Johnson RJ, García-López E *et al*. J-shaped mortality relationship for uric acid in CKD. Am J Kidney Dis 2006;48:761–71.

34 Odden MC, Amadu AR, Smit E, Lo L, Peralta CA. Uric acid levels, kidney function, and cardiovascular mortality in US adults: National Health and Nutrition Examination Survey (NHANES) 1988-1994 and 1999-2002. Am J Kidney Dis 2014;64:550–7.

35 Tseng WC, Chen YT, Ou SM, Shih CJ, Tarng DC; Taiwan Geriatric Kidney Disease (TGKD) Research Group. U-shaped association between serum uric acid levels with cardiovascular and all-cause mortality in the elderly: the role of malnourishment. J Am Heart Assoc 2018;7:e007523.

36 Yoshida K, Solomon DH, Kim SC. Active-comparator design and new-user design in observational studies. Nat Rev Rheumatol 2015;11:437–41.

37 Khanna D, Fitzgerald JD, Khanna PP *et al*.; American College of Rheumatology. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken) 2012;64:1431–46.

38 Janssen CA, Oude Voshaar MAH, Vonkeman HE *et al*. A retrospective analysis of medication prescription records for determining the levels of compliance and persistence to urate-lowering therapy for the treatment of gout and hyperuricemia in The Netherlands. Clin Rheumatol 2018;37:2291–6.

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Circulation

ORIGINAL RESEARCH ARTICLE

Assessment of Cardiovascular Risk in Older Patients With Gout Initiating Febuxostat Versus Allopurinol

Population-Based Cohort Study

Editorial, see p 1127

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BACKGROUND: Hyperuricemia and gout are associated with an increased risk of cardiovascular disease. Xanthine oxidase inhibitors, allopurinol and febuxostat, are the mainstay of urate-lowering treatment for gout and may have different effects on cardiovascular risk in patients with gout.

METHODS: Using US Medicare claims data (2008–2013), we conducted a cohort study for comparative cardiovascular safety of initiating febuxostat versus allopurinol among patients with gout ≥65 years of age. The primary outcome was a composite end point of hospitalization for myocardial infarction or stroke. Secondary outcomes were individual end points of hospitalization for myocardial infarction, stroke, coronary revascularization, new and recurrent heart failure, and all-cause mortality. We used propensity score matching with a ratio of 1:3 to control for confounding. We estimated incidence rates and hazard ratios for primary and secondary outcomes in the propensity score–matched cohorts of febuxostat and allopurinol initiators.

RESULTS: We included 24 936 febuxostat initiators propensity score–matched to 74 808 allopurinol initiators. The median age was 76 years, 52% were male, and 12% had cardiovascular disease at baseline. The incidence rate per 100 person-years for the primary outcome was 3.43 in febuxostat and 3.36 in allopurinol initiators. The hazard ratio for the primary outcome was 1.01 (95% CI, 0.94–1.08) in the febuxostat group compared with the allopurinol group. Risk of secondary outcomes including all-cause mortality was similar in both groups, except for a modestly decreased risk of heart failure exacerbation (hazard ratio, 0.94; 95% CI, 0.91–0.99) in febuxostat initiators. The hazard ratio for all-cause mortality associated with long-term use of febuxostat (>3 years) was 1.25 (95% CI, 0.56–2.80) versus allopurinol. Subgroup and sensitivity analyses consistently showed similar cardiovascular risk in both groups.

CONCLUSIONS: Among a cohort of 99 744 older Medicare patients with gout, overall there was no difference in the risk of myocardial infarction, stroke, new-onset heart failure, coronary revascularization, or all-cause mortality between patients initiating febuxostat compared with allopurinol. However, there seemed to be a trend toward an increased, albeit not statistically significant, risk for all-cause mortality in patients who used febuxostat for >3 years versus allopurinol for >3 years. The risk of heart failure exacerbation was slightly lower in febuxostat initiators.

Key Words: adverse events ■ complication ■ cardiovascular outcomes ■ gout ■ treatment

Sources of Funding, see page 1125

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Clinical Perspective

What Is New?

- In the CARES trial, febuxostat was noninferior to allopurinol with respect to rates of adverse cardiovascular events, but febuxostat users had a greater risk of cardiovascular mortality and all-cause mortality.
- In this cohort study of 99 744 older patients with gout enrolled in Medicare, overall we found no difference in cardiovascular risk, including myocardial infarction, stroke, coronary revascularization, new heart failure, or all-cause mortality between febuxostat and allopurinol initiators.

What Are the Clinical Implications?

- Among older patients with gout with and without cardiovascular comorbidities, the risk of cardiovascular events and all-cause mortality was similar between febuxostat and allopurinol initiators.
- However, there is a suggestion for an increased risk of all-cause mortality associated with long-term use of febuxostat versus allopurinol.

Gout, a disorder characterized by monosodium urate crystal deposition in the joints, is 1 of the most common inflammatory arthropathies, affecting ≈8.3 million individuals in the United States.[1,2] Although the association between gout and cardiovascular disease (CVD) has been well documented, the evidence for a causal relationship between xanthine oxidase inhibitors (XOI) and CVD remains equivocal.[3–6] Although some studies have demonstrated a protective effect of allopurinol against myocardial infarction (MI), cardiovascular outcomes, and all-cause mortality, other studies have shown no benefit on heart failure (HF).[7–11] A recent cohort study comparing patients with gout on XOI with nonusers who have hyperuricemia showed that XOI initiation had no effect on cardiovascular risk.[12] The current literature for XOI-mediated CVD risk reduction remains inconsistent.[13–16]

Indeed, the concern for an XOI-related increased CVD risk has even been raised. In the original 2 phase III randomized controlled trials of febuxostat, APEX and FACT, febuxostat (at 80 and 120 mg/d) was more effective at lowering serum uric acid levels compared with allopurinol (at 300 mg/d) over 1 year.[17,18] Despite the more potent urate-lowering effect of febuxostat, the incidence of major adverse cardiovascular events, including nonfatal MI, nonfatal stroke, and cardiovascular death in both trials, was numerically, although not statistically significantly, higher with febuxostat than allopurinol, and rates of cardiovascular events did not correlate with febuxostat dose.[17–19] These initial findings prompted the US Food and Drug Administration to mandate additional safety evaluations. Subsequently, the phase IIIB randomized controlled CARES trial was conducted to further investigate the cardiovascular safety of febuxostat compared with allopurinol in patients with gout with known cardiovascular comorbidities.[20] The CARES trial ultimately showed no difference in the combined risk of cardiovascular death, nonfatal MI, nonfatal stroke, and unstable angina with urgent coronary revascularization for febuxostat compared with allopurinol. However, the individual risks of cardiovascular mortality and all-cause mortality were 1.2 to 1.3 times higher in febuxostat initiators. A similar randomized controlled trial titled FAST is also underway in Europe.[21] Given the relatively limited evidence and overall high prevalence of CVD in patients with gout, we sought to examine the risk of cardiovascular events in patients with gout with and without baseline CVD who started febuxostat or allopurinol (both at typical and equipotent dosing) using longitudinal comprehensive medical and pharmacy dispensing claims data from US Medicare.

METHODS

The data and study materials cannot be made available to other researchers because of the data use agreement with the Centers for Medicare and Medicaid Services.

Data Source

We conducted a cohort study among patients with gout initiating febuxostat versus allopurinol using longitudinal claims data from Medicare Parts A/B/D from January 1, 2008, to December 31, 2013. Medicare, a federal health insurance program in the United States, provides coverage for legal residents ≥65 years of age, patients <65 years of age with certain disabilities, and those with end-stage renal disease requiring dialysis or transplant. Medicare Part A covers inpatient care. Part B coverage encompasses physician services, including outpatient visits, laboratory testing, and imaging. Finally, Part D provides outpatient prescription drug coverage.[22] As a result, the study database includes patient information on demographics, diagnosis, and procedure codes from outpatient visits; emergency room visits and acute care hospitalizations; and dispensing records of prescription drugs. The study protocol and waiver for patient-informed consent were approved by the Institutional Review Board of the Brigham and Women's Hospital.

Study Cohort

Patients ≥65 years of age with a diagnosis of gout based on the *International Classification of Diseases, 9th Revision, Clinical Modification* codes 274.00, 274.01, 274.02, 274.03, 274.81, 274.82, 274.89, or 274.9 were eligible for the study. Patients with uric acid nephrolithiasis were not included. We identified initiators of febuxostat or allopurinol using the national drug codes in Part D claims. The index date was the drug initiation date. Drug initiation was defined as having ≥365 days free of a given drug. In other words, allopurinol initiators were allowed to use febuxostat in the 365 days before the first prescription of allopurinol and vice versa. This restriction was to

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reflect typical prescription practices for febuxostat initiation. Naivety to both drugs before the index date was examined in subsequent sensitivity analyses (see Statistical Analysis).

Exclusion criteria included <65 years of age on the index date, <365 days of insurance eligibility in Parts A/B/D before the index date, no active claim in the 365 days before the index date, use of pegloticase or rasburicase in the 365 days before the index date, and end-stage renal disease/dialysis in the 365 days before the index date.

Outcome Definition

The primary outcome was defined as a composite end point of hospitalization for MI or stroke (excluding transient ischemic attacks). Secondary outcomes included hospitalization for MI, stroke, coronary revascularization, HF subdivided into new-onset HF or HF exacerbation, and all-cause mortality. Cause-specific mortality was not available in the Medicare database. New-onset HF was defined as hospitalization for HF among patients with no baseline history of HF based on the primary inpatient diagnosis. HF exacerbation was defined as hospitalization for HF in patients with a baseline history of HF based on the primary inpatient diagnosis. These outcomes were identified with previously validated claims-based algorithms with the positive predictive value >80%.[23–25]

Covariates Assessment

To adjust for potential confounders between the 2 XOI groups, we assessed 81 prespecified baseline variables in the 365 days before the index date or on the index date (see Table 1 for partial list of covariates). Covariates included demographic data (age, sex, place of residence), index year, cardiovascular comorbidities (ie, MI, stroke, coronary revascularization), other medical comorbidities (ie, any stage of chronic kidney disease, diabetes mellitus, mellitus, hyperlipidemia), gout-related medications (ie, probenecid, colchicine, nonsteroidal antiinflammatory drugs, steroids), other medications (ie, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics), and healthcare utilization patterns (ie, number of emergency room visits, outpatient visits, various tests ordered). To better account for potential confounding by various comorbidities, we also used a comorbidity score that incorporated 20 different medical conditions, including HF, renal failure, respiratory disease, cirrhosis, and malignancy.[26]

Statistical Analysis

Main Analysis (Propensity Score Matching, Primary and Secondary Outcomes)

For confounding adjustment, we used propensity score (PS) matching, in which all the baseline covariates were simultaneously adjusted for. The PS was defined as the probability of receiving febuxostat versus allopurinol given patients' baseline characteristics and calculated based on multivariable logistic regression models that incorporated baseline variables such as demographic information, medical comorbidities, medications, and healthcare utilization patterns listed in Table 1. Using nearest-neighbor matching within a caliper of 0.05 on the PS scale, febuxostat initiators were matched to allopurinol initiators with a fixed ratio of 1:3 to optimize the size of the febuxostat group and overall study cohort. The fixed ratio of 1:3 was maintained throughout all subsequent main, subgroup, and sensitivity analyses. We compared baseline characteristics of febuxostat and allopurinol initiators before and after PS matching. Variables with standardized differences <10% between the 2 groups were considered well balanced after PS matching.[27,28]

For the primary as-treated analysis, follow-up started on the day after the index date and ended on the earliest date of the following censoring events: drug discontinuation, last day of study database, insurance disenrollment (Part A/B/D), and occurrence of outcome, death, or nursing home admission. The last drug available date was defined as the last dispensing date plus days of supply with a 30-day grace period. Treatment adherence was calculated using a proportion of days covered, where proportion of days covered (%) was equal to the number of days covered by prescriptions multiplied by 100, divided by the total number of days of follow-up.

For the secondary intention-to-treat 365-day analysis, follow-up time was truncated on the 366th day after the index date unless patients were censored based on the previously mentioned criteria except drug discontinuation. This analysis was conducted to address the potential for lower adherence over long term follow-up.

Incidence rates (IRs) and 95% CIs were calculated for the previously mentioned primary and secondary outcomes among the PS-matched groups separately. Cox proportional hazards regression compared the risk of primary and secondary outcomes in the PS-matched cohorts of febuxostat and allopurinol initiators. Cumulative incidence plots between treatment groups were compared. We assessed the proportional hazards assumption by testing the significance of the interaction term between exposure and follow-up time and found that the assumption was violated for the all-cause mortality analysis (P=0.02 for the interaction term). Therefore, we conducted Cox regression stratified by follow-up time for all-cause mortality. In addition, we ran follow-up time-stratified Cox regression for the primary outcome.

Subgroup Analyses

We conducted two subgroup analyses. The first analysis was an a priori defined PS-matched subgroup analysis by the presence or absence of baseline CVD (defined as history of MI, hospitalized unstable angina, coronary or cerebral revascularization, stroke, or hospitalized transient ischemic attack). IR and hazard ratio (HR) were calculated for both primary and secondary outcomes. In the second subgroup analysis, we identified patients with high cardiovascular risk, similar to the CARES inclusion criteria (ie, peripheral vascular disease or diabetes mellitus in addition to the previously defined CVD).

Sensitivity Analyses

We also performed two sensitivity analyses. The first analysis was limited to patients who initiated equipotent dosing of febuxostat (≥40 mg daily) versus allopurinol (≥300 mg daily) on the index date. The second analysis was limited to patients who initiated equipotent dosing of febuxostat (≥40 mg daily) versus allopurinol (≥300 mg daily) on the index date and were naïve to both drugs prior to index date.

All analyses were done using SAS 9.4 statistical software (SAS Institute, Cary, NC).

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Table 1. Baseline Characteristics of the 1:3 PS-Matched Cohort

	Febuxostat	Allopurinol	Standardized Difference, %
N	24936	74808	—
Demographics			
Age, y median (IQR)	76 (70–82)	76 (71–82)	0
Male, %	52.3	52.3	0.1
White race, %	76.4	76.2	0.4
US region			
Midwest, %	19.3	19.1	0.6
Northeast, %	18.7	19.0	–0.6
South, %	42.5	42.4	0.3
West, %	19.4	19.5	–0.4
Cardiovascular comorbidities			
Myocardial infarction	3.5	3.6	–0.2
Stroke	7.2	7.3	–0.2
Coronary revascularization	2.3	2.3	0.1
Heart failure, %	35.7	35.8	–0.2
Recent heart failure, 60 d, %	5.1	5.1	–0.1
Venous thromboembolism, %	7.7	7.6	0.4
Hypertension, %	95.4	95.4	–0.1
Peripheral vascular disease, %	19.7	19.7	–0.1
Cardiovascular disease, %	12.2	12.2	–0.2
Other comorbidities			
Hyperlipidemia, %	82.8	82.9	–0.2
Chronic kidney disease, %	57.1	58.0	–1.7
Chronic obstructive pulmonary disease, %	32.5	32.5	–0.1
Diabetes mellitus, %	55.0	55.2	–0.6
Malignancy, %	21.7	21.5	0.4
Renal stone, %	5.6	5.7	–0.3
Liver disease, %	7.1	7.1	0.2
Obesity, %	17.5	17.3	0.6
Sleep apnea, %	9.5	9.3	0.5
Smoking, %	6.0	5.9	0.3
Comorbidity score, median (IQR)	3 (1–6)	3 (1–6)	0
Gout-related medications			
Colchicine, %	42.8	43.1	–0.7
NSAIDs/COXIB, %	41.0	41.0	0.1
Opioids, %	49.4	49.0	0.6
365-d Cumulative prednisone equivalent dose, mg, median (IQR)	0 (0–240)	0 (0–210)	0
Any steroid use, 365 d, %	41.4	41.2	0.3
Recent steroid use, 90 d, %	29.4	29.2	0.4
Other medications			
ACE inhibitors/angiotensin receptor blockers, %	68.2	68.3	–0.2
ß-Blockers, %	47.1	47.1	–0.1
Calcium channel blockers, %	42.8	43.1	–0.5
Diuretics, %	76.5	76.6	–0.4
Nitrates, %	17.3	17.4	–0.2
Noninsulin antidiabetic drugs, %	30.1	30.3	–0.4
Insulin, %	14.9	15.1	–0.5
Anticoagulants, %	21.2	21.1	0.4
Antiplatelets, %	17.8	18.0	–0.5
Statins, %	61.4	61.5	–0.1
Other lipid-lowering drugs, %	17.2	17.3	–0.2
Healthcare utilization pattern			
No. of emergency room visits, median (IQR)	0 (0–1)	0 (0–1)	0
No. of all outpatient visits, median (IQR)	14 (8–21)	13 (8–21)	0
No. of prescription drugs, median (IQR)	15 (11–20)	15 (11–20)	0
Hospitalization, %	33.7	33.7	0
No. of cardiology visits, median (IQR)	0 (0–2)	0 (0–2)	0
No. of rheumatology visits, median (IQR)	0 (0–0)	0 (0–0)	0.1
CRP test ordered, %	22.1	22.0	0.2
ECG ordered, %	63.7	64.0	–0.5
Echocardiogram ordered, %	2.1	2.2	–0.3
Cardiac stress test ordered, %	16.3	16.6	–0.8
Hemoglobin A1c ordered, %	54.4	54.7	–0.6
Lipid/cholesterol test ordered, %	80.8	80.9	–0.3
Uric acid test ordered, %	86.5	87.1	–1.7
Serum creatinine test ordered, %	97.9	98.1	–1.3

Recent history of MI (60 d), stroke (60 d), alcoholism, and phosphate binders was present in <1% of patients. For all covariates, standardized differences were less than 10%.

ACE indicates angiotensin converting enzyme; COXIB, Cox-2 inhibitor; CRP, C-reactive protein; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; and PS, propensity score.

RESULTS

Cohort Selection

Application of inclusion and exclusion criteria resulted in a total of 331 134 patients with gout aged 65 years or older continuously enrolled in Medicare Parts A, B and D for at least 365 days prior to initiation of febuxostat (n=26 233) and allopurinol (n=304 901) (Figure in the online-only Data Supplement). Following 1:3 PS matching, 95% of febuxostat initiators (n=24 936) and 25% of allopurinol initiators (n=74 808) were included in the study.

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Patient Characteristics

Baseline demographics and clinical characteristics of each group after 1:3 PS matching are summarized in Table 1 (see Table in the online-only Data Supplement for baseline characteristics before PS matching). Among febuxostat users, the median (interquartile range) age was 76 (70–82) years and 52% were male. Among allopurinol users, the median (interquartile range) age was 76 (71–82) years and 52% were male. In both groups, 12% had CVD at baseline. Hypertension (95%), chronic kidney disease (58%), diabetes (55%), and heart failure (36%) were common comorbidities in both groups. Use of gout-related medications including colchicine (43%), nonsteroidal anti-inflammatory drugs (41%), and steroids (41%) was also common among all users. All the baseline covariates were well balanced between the PS-matched groups with a standardized difference <10%.[27]

The mean (SD) follow-up time was 1.1 (1.1) years among febuxostat initiators and 1.2 (1.2) years among allopurinol initiators. There were 5013 (20.1%) febuxostat and 18235 (24.4%) allopurinol initiators, who had over 730 days of follow-up time. Of the febuxostat initiators, 30.4% had been on allopurinol at some point during the 365 days prior to febuxostat initiation. Among allopurinol initiators, 0.4% had been on febuxostat during the 365 days prior to allopurinol initiation.

Patterns of Febuxostat and Allopurinol Treatment

In the febuxostat group, the median (interquartile range) proportion of days covered was 93.85% (51.96–100) up to 180 days and 89.34% (48.15–100) up to 365 days. In the allopurinol group, the median (interquartile range) proportion of days covered was 85.08% (50.28–100) up to 180 days and 79.78% (33.33–98.92) up to 365 days. Among febuxostat initiators, 98.89% were on a dosage of 40 mg or higher per day. For allopurinol initiators, 30.67% were on a daily dosage of 300 mg of higher. Of febuxostat initiators, 13.2% had a dose increase during follow-up compared to 22.8% of allopurinol initiators.

Risk of Cardiovascular Events

In the primary as-treated analysis, the IR per 100 person-years for the primary outcome (ie, hospitalization for MI or stroke) was 3.43 (95% CI, 3.22–3.66) in febuxostat and 3.36 (95% CI, 3.25–3.49) in allopurinol initiators (Table 2). In the intention-to-treat 365-day analysis, the IR for the primary outcome was also similar in the two groups: IR per 100 person-years of 3.72 (95% CI, 3.45–4.00) for febuxostat and 3.83 (95% CI, 3.67–4.00) for allopurinol initiators. The HR for the primary outcome was 1.01 (95% CI, 0.94–1.08) in the febuxostat compared with allopurinol initiators (Table 2). Cumulative incidence plots also showed null results for the primary outcome with the log-rank test *P* value of 0.83 (Figure [A]). In the Cox regression analysis stratified by follow-up time (ie, treatment duration) for the primary outcome, the HR (95% CI) associated with febuxostat versus allopurinol was 0.84 (0.73–0.98) for 0 to 1 year of follow-up, 0.88 (0.61–1.25) for 1 to 2 years, 0.76 (0.42–1.39) for 2 to 3 years, and 1.17 (0.45–3.05) for >3 years.

The risk of developing secondary outcomes was also similar between the 2 groups. In the as-treated analysis, the HR in febuxostat initiators was 1.03 (95% CI, 0.94–1.13) for MI, 0.98 (95% CI, 0.87–1.10) for stroke, 0.95 (95% CI, 0.87–1.03) for coronary revascularization, and 0.95 (95% CI, 0.89–1.02) for all-cause mortality (Table 2). Cumulative incidence plots for all-cause mortality was also consistent with the log-rank test *P* value of 0.15 (Figure [B]). In the Cox regression analysis stratified by follow-up time for all-cause mortality, the HR (95% CI) associated with febuxostat was 0.75 (0.66–0.86) for 0 to 1 year of follow-up, 0.85 (0.63–1.15) for 1 to 2 years, 0.72 (0.53–1.54) for 2 to 3 years, and 1.25 (0.56–2.80) for >3 years.

The intention-to-treat 365-day analyses showed consistent results as well for the secondary outcomes.

Risk of Heart Failure

For new-onset HF hospitalizations, the IR per 100 person-years was 5.71 (95% CI, 5.37–6.06) for febuxostat initiators compared to 5.41 (95% CI, 5.23–5.60) for allopurinol initiators in the as-treated analysis (Table 3). The HR for new-onset HF in the as-treated analysis was 1.05 (95% CI, 0.98–1.12). For HF exacerbations, the IR per 100 person-years was 42.70 (95% CI, 41.16–44.29) for febuxostat initiators compared to 44.06 (95% CI, 43.18–44.96) for allopurinol initiators in the as-treated analysis. The HR for HF exacerbation in the as-treated analysis was 0.94 (95% CI, 0.91–0.99). Although this last HR was statistically significantly lower than 1.0, the degree of risk reduction appeared modest. Intention-to-treat 365-day analysis yielded similar results, with no difference between the 2 groups for new-onset HF and borderline risk reduction for HF exacerbation.

Subgroup Analyses

In the first subgroup analysis by baseline CVD, we noted no significant difference in the primary outcome between febuxostat and allopurinol initiators (Table 4). For the secondary outcome of all-cause mortality, the HR for febuxostat versus allopurinol was 0.97 (95% CI, 0.90–1.04) in those without baseline CVD and 0.85 (95% CI, 0.72–0.99) among those with baseline CVD.

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Table 2. Risk of Cardiovascular Events in Febuxostat vs Allopurinol Initiators: 1:3 PS-Matched Analysis

Outcome	Febuxostat (n=24 936)				Allopurinol (n=74 808)			
	Event (n)	Person-Years	IR* (95% CI)	HR (95% CI)	Event (n)	Person-Years	IR* (95% CI)	HR (95% CI)
As-treated analysis								
Primary outcome								
MI or stroke	935	27 251	3.43 (3.22–3.66)	1.01 (0.94–1.08)	3105	92 264	3.36 (3.25–3.49)	Ref
Secondary outcomes								
MI	596	27 440	2.17 (2.00–2.35)	1.03 (0.94–1.13)	1935	92 962	2.08 (1.99–2.18)	Ref
Stroke	372	27 609	1.35 (1.22–1.49)	0.98 (0.87–1.10)	1272	93 487	1.36 (1.29–1.44)	Ref
Coronary revascularization	719	27 209	2.64 (2.46–2.84)	0.95 (0.87–1.03)	2525	91 815	2.75 (2.65–2.86)	Ref
All-cause mortality	1144	27 809	4.11 (3.88–4.36)	0.95 (0.89–1.02)	4022	94 219	4.27 (4.14–4.40)	Ref
$ITT_{365\text{-}d}$ analysis								
Primary outcome								
MI or stroke	711	19 132	3.72 (3.45–4.00)	0.97 (0.89–1.06)	2146	55 986	3.83 (3.67–4.00)	Ref
Secondary outcomes								
MI	442	19 192	2.30 (2.10–2.53)	0.97 (0.87–1.08)	1334	56 190	2.37 (2.25–2.51)	Ref
Stroke	285	19 254	1.48 (1.32–1.66)	0.95 (0.83–1.09)	876	56 357	1.55 (1.45–1.66)	Ref
Coronary revascularization	570	19 133	2.98 (2.74–3.23)	0.93 (0.84–1.02)	1804	55 946	3.23 (3.08–3.38)	Ref
All-cause mortality	995	19 317	5.15 (4.84–5.48)	0.94 (0.88–1.01)	3092	56 571	5.47 (5.28–5.66)	Ref

HR indicates hazard ratio; IR, incidence rate; $ITT_{365\text{-}d}$, intention-to-treat analysis up to the 365th day of follow-up; MI, myocardial infarction; PS, propensity score; and Ref, reference.

*IR is per 100 person-years.

In the second subgroup analysis for high cardiovascular risk defined similar to the CARES's inclusion criteria, we also found no difference in both primary and secondary outcomes, including all-cause mortality (Table 5).

Sensitivity Analyses

For the sensitivity analysis limited to patients who initiated febuxostat ≥40 mg daily versus allopurinol ≥300 mg daily on the index date, the risk for the primary outcome

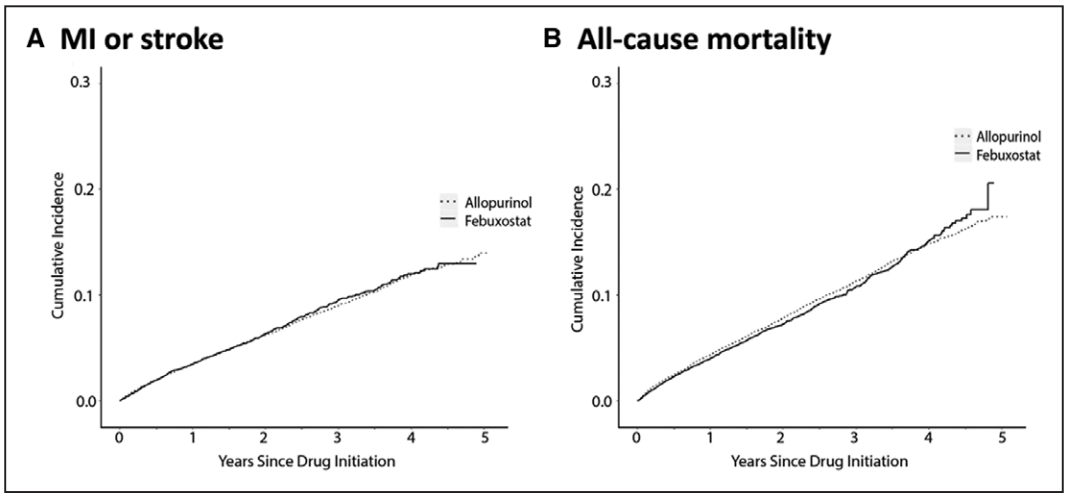

Figure. Cumulative incidences of the composite end point of MI or stroke and all-cause mortality.
Among the 1:3 propensity score-matched cohort of febuxostat and allopurinol initiators, the cumulative incidences of the composite end point of MI or stroke (**A**) and all-cause mortality (**B**) were compared with the log-rank test (P=0.8 for MI or stroke and P=0.15 for all-cause mortality). MI indicates myocardial infarction.

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Table 3. Risk of Heart Failure (HF) in Febuxostat Initiators vs Allopurinol Initiators: 1:3 PS-Matched Analysis

	Febuxostat					Allopurinol				
Outcome	N	Event (n)	Person-Years	IR* (95% CI)	HR (95% CI)	N	Event (n)	Person-Years	IR* (95% CI)	HR (95% CI)
As-treated analysis										
New-onset HF†	15929	1056	18500	5.71 (5.37–6.06)	1.05 (0.98–1.12)	47787	3437	63507	5.41 (5.23–5.60)	Ref
HF exacerbation‡	8977	2855	6687	42.70 (41.16–44.29)	0.94 (0.91–0.99)	26931	9426	21394	44.06 (43.18–44.96)	Ref
ITT_{365-d} analysis										
New-onset HF†	15929	760	12892	5.90 (5.49–6.33)	0.99 (0.91–1.07)	47787	2250	37723	5.97 (5.72–6.22)	Ref
HF exacerbation‡	8977	2646	5300	49.92 (48.06–51.86)	0.93 (0.89–0.98)	26931	8127	15137	53.69 (52.53–54.87)	Ref

HF indicates heart failure; HR, hazard ratio; IR, incidence rate; ITT_{365-d}, intention-to-treat analysis up to the 365th day of follow-up; PS, propensity score; and Ref, reference.
*IR is per 100 person-years.
†Among the subgroup of patients with no baseline history of HF.
‡Among the subgroup of patients with baseline history of HF, only counting the first exacerbation after the index date.

(hospitalization for MI or stroke) was similar between the PS-matched febuxostat and allopurinol groups with an HR of 1.05 (95% CI, 0.94–1.18) (Table 6). Results for the secondary outcomes, including MI, stroke, coronary revascularization, new-onset HF, HF recurrence, and all-cause mortality, were all consistent with the main analyses.

When we further restricted the cohort to those who initiated equipotent dosing (ie, ≥40 mg/d febuxostat or 300 mg/d allopurinol) and had no prior use of either febuxostat or allopurinol before the index date, there was no difference in risk between the 2 groups for the primary outcome (HR, 0.96; 95% CI, 0.85–1.08) (Table 7) as well as all secondary outcomes.

DISCUSSION

In our study of US Medicare patients with gout, initiation of febuxostat compared with allopurinol was not

Table 4. Subgroup Analysis by Baseline CVD: 1:3 PS-Matched As-Treated Analysis

	Febuxostat					Allopurinol				
Outcome	N	Event (n)	Person-Years	IR* (95% CI)	HR (95% CI)	N	Event (n)	Person-Years	IR* (95% CI)	HR (95% CI)
Without baseline CVD										
MI or stroke	21821	726	24526	2.96 (2.75–3.18)	0.99 (0.91–1.08)	65463	2471	83379	2.96 (2.85–3.08)	Ref
MI	21821	457	24683	1.85 (1.69–2.03)	0.98 (0.88–1.08)	65463	1579	83911	1.88 (1.79–1.98)	Ref
Stroke	21821	291	24813	1.17 (1.05–1.32)	1.00 (0.88–1.15)	65463	977	84420	1.16 (1.09–1.23)	Ref
Coronary revascularization	21821	577	24501	2.36 (2.17–2.56)	0.92 (0.84–1.01)	65463	2098	82859	2.53 (2.43–2.64)	Ref
All-cause mortality	21821	946	24972	3.79 (3.55–4.04)	0.97 (0.90–1.04)	65463	3309	84984	3.89 (3.76–4.03)	Ref
With baseline CVD										
MI or stroke	3067	207	2655	7.80 (6.80–8.93)	0.97 (0.83–1.13)	9201	693	8803	7.87 (7.31–8.48)	Ref
MI	3067	139	2686	5.18 (4.38–6.11)	0.98 (0.81–1.19)	9201	461	8938	5.16 (4.71–5.65)	Ref
Stroke	3067	79	2726	2.90 (2.32–3.61)	1.03 (0.80–1.32)	9201	252	9093	2.77 (2.45–3.14)	Ref
Coronary revascularization	3067	146	2634	5.55 (4.72–6.52)	1.10 (0.91–1.33)	9201	435	8820	4.93 (4.49–5.42)	Ref
All-cause mortality	3067	195	2765	7.05 (6.13–8.12)	0.85 (0.72–0.99)	9201	756	9235	8.19 (7.62–8.79)	Ref

CVD indicates cardiovascular disease; HR, hazard ratio; IR, incidence rate; MI, myocardial infarction; PS, propensity score; and Ref, reference.
*IR is per 100 person-years.

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Table 5. Subgroup Analysis by High CV Risk: 1:3 PS-Matched As-Treated Analysis

Outcome	Febuxostat					Allopurinol				
	N	Event (n)	Person-Years	IR* (95% CI)	HR (95% CI)	N	Event (n)	Person-Years	IR* (95% CI)	HR (95% CI)
Without high CV risk										
MI or stroke	16 174	674	16 943	3.98 (3.69–4.29)	0.97 (0.89–1.06)	48 522	2280	56 347	4.05 (3.88–4.22)	Ref
MI	16 174	448	17 062	2.63 (2.39–2.88)	1.00 (0.90–1.11)	48 522	1479	56 814	2.60 (2.47–2.74)	Ref
Stroke	16 174	252	17 208	1.46 (1.29–1.66)	0.96 (0.84–1.11)	48 522	866	57 335	1.51 (1.41–1.61)	Ref
Coronary revascularization	16 174	509	16 920	3.01 (2.76–3.28)	0.91 (0.82–1.00)	48 522	1840	56 089	3.28 (3.13–3.43)	Ref
All-cause mortality	16 174	801	17 337	4.62 (4.31–4.95)	0.93 (0.86–1.00)	48 522	2,847	57 821	4.92 (4.75–5.11)	Ref
With high CV risk										
MI or stroke	8645	253	10 212	2.48 (2.19–2.80)	1.03 (0.90–1.19)	25 935	832	34 790	2.39 (2.23–2.56)	Ref
MI	8645	143	10 279	1.39 (1.18–1.64)	1.01 (0.84–1.22)	25 935	479	35 029	1.37 (1.25–1.50)	Ref
Stroke	8645	116	10 303	1.13 (0.94–1.35)	1.04 (0.85–1.28)	25 935	378	35 123	1.08 (0.97–1.19)	Ref
Coronary revascularization	8645	202	10 198	1.98 (1.73–2.27)	1.02 (0.87–1.19)	25 935	668	34 725	1.92 (1.78–2.08)	Ref
All-cause mortality	8645	332	10 371	3.20 (2.88–3.57)	0.97 (0.86–1.10)	25 935	1162	35 366	3.29 (3.10–3.48)	Ref

CV indicates cardiovascular; HR, hazard ratio; IR, incidence rate; MI, myocardial infarction; PS, propensity score; and Ref, reference.
*IR is per 100 person-years.

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associated with a change in risk of cardiovascular events for MI, stroke, new-onset HF, coronary revascularization, or all-cause mortality. This finding was observed in the main as-treated as well as intention-to-treat analyses truncated at 1 year of follow-up. However, in a follow-up time-stratified analysis, we observed a trend toward a greater risk of all-cause mortality in the febuxostat group with >3 years of follow-up versus the allopurinol

Table 6. Sensitivity Analysis: Risk of Cardiovascular Events in Febuxostat (≥40 mg/d) vs Allopurinol (≥300 mg/d) Initiators: 1:3 PS-Matched As-Treated Analysis

Outcome	Febuxostat					Allopurinol				
	N	Event (n)	Person-Years	IR* (95% CI)	HR (95% CI)	N	Event (n)	Person-Years	IR* (95% CI)	HR (95% CI)
Primary outcome										
MI or stroke	12 252	404	13 848	2.92 (2.65–3.22)	1.05 (0.94–1.18)	36 756	1359	49 755	2.73 (2.59–2.88)	Ref
Secondary outcomes										
MI	12 252	242	13 938	1.74 (1.53–1.97)	1.08 (0.93–1.24)	36 756	796	50 144	1.59 (1.48–1.70)	Ref
Stroke	12 252	178	13 993	1.27 (1.10–1.47)	1.05 (0.89–1.24)	36 756	605	50 314	1.20 (1.11–1.30)	Ref
Coronary revascularization	12 252	358	13 779	2.60 (2.34–2.88)	1.01 (0.90–1.14)	36 756	1247	49 379	2.53 (2.39–2.67)	Ref
New-onset HF	9021	471	10 461	4.50 (4.11–4.93)	1.00 (0.91–1.11)	27 063	1687	37 948	4.45 (4.24–4.66)	Ref
HF exacerbation	3261	948	2556	37.09 (34.80–39.53)	0.97 (0.90–1.04)	9783	3274	8866	36.93 (35.68–38.22)	Ref
All-cause mortality	12 252	426	14 091	3.02 (2.75–3.32)	0.93 (0.84–1.04)	36 756	1620	50 720	3.19 (3.04–3.35)	Ref

HF indicates heart failure; HR, hazard ratio; IR, incidence rate; MI, myocardial infarction; PS, propensity score; and Ref, reference.
*IR is per 100 person-years.

Table 7. Sensitivity Analysis: Risk of Cardiovascular Events in Febuxostat (≥40 mg/d) vs Allopurinol (≥300 mg/d) Initiators Naïve to Both Drugs: 1:3 PS-Matched As-Treated Analysis

	Febuxostat					Allopurinol				
Outcome	N	Event (n)	Person-Years	IR* (95% CI)	HR (95% CI)	N	Event (n)	Person-Years	IR* (95% CI)	HR (95% CI)
Primary outcome										
MI or stroke	11220	368	12080	3.05 (2.75–3.37)	0.96 (0.85–1.08)	33660	1346	42943	3.13 (2.97–3.31)	Ref
Secondary outcomes										
MI	11220	224	12151	1.84 (1.62–2.10)	0.97 (0.84–1.13)	33660	811	43284	1.87 (1.75–2.01)	Ref
Stroke	11220	158	12219	1.29 (1.11–1.51)	0.97 (0.81–1.15)	33660	575	43489	1.32 (1.22–1.44)	Ref
Coronary revascularization	11220	308	12047	2.56 (2.29–2.86)	0.97 (0.86–1.10)	33660	1100	42691	2.58 (2.43–2.73)	Ref
New-onset HF	7785	454	8667	5.24 (4.78–5.74)	1.05 (0.95–1.17)	23355	1541	31460	4.90 (4.66–5.15)	Ref
HF exacerbation	3412	1,022	2561	39.91 (37.54–42.44)	1.00 (0.93–1.07)	10236	3393	8891	38.16 (36.90–39.47)	Ref
All-cause mortality	11220	420	12295	3.42 (3.10–3.76)	0.93 (0.83–1.03)	33660	1597	43848	3.64 (3.47–3.83)	Ref

HF indicates heart failure; HR, hazard ratio; IR, incidence rate; MI, myocardial infarction; PS, propensity score; and Ref, reference.
*IR is per 100 person-years.

group with >3 years of follow-up. We also found a modestly decreased risk for HF exacerbation associated with febuxostat versus allopurinol in the primary as-treated (HR, 0.94; 95% CI, 0.91–0.99) and intention-to treat analyses (HR, 0.93; 95% CI, 0.89–0.98).

In the subgroup analysis, there was no difference in the risk of cardiovascular events between the 2 groups with and without baseline CVD, except for a modestly decreased risk of all-cause mortality in febuxostat users with baseline CVD (HR, 0.85; 95% CI, 0.72–0.99). Among patients with high cardiovascular risk at baseline, we noted no difference in the risk of cardiovascular events or all-cause mortality between the 2 drugs. Finally, in the 2 sensitivity analyses where we compared (1) equipotent index dosages (febuxostat ≥40 mg versus allopurinol ≥300 mg daily) without naivety to both drugs before the index date and (2) equipotent index dosages (febuxostat ≥40 mg versus allopurinol ≥300 mg daily) with naivety to both drugs before the index date, we found no difference in cardiovascular risk between febuxostat and allopurinol users.

Although the original phase III randomized controlled trials for febuxostat (APEX and FACT) revealed a numerically higher but statistically nonsignificant risk for adverse cardiovascular events in febuxostat initiators compared with allopurinol initiators, the rates of cardiovascular events did not correlate with febuxostat dosage, and the number of cardiovascular events did not increase over the duration of the study.[17,18] In APEX, the number of adverse cardiovascular events ranged from 1 to 5 (<1% to 2%) in each of the febuxostat groups (80, 120, and 240 mg) versus 1 (<1%) in the allopurinol group.[17] In FACT, the number of adverse cardiovascular events was 1 (<1%) in each of the febuxostat groups (80 mg and 120 mg) versus 0 (0%) in the allopurinol group.[18] In both trials, the adverse cardiovascular events were considered to be unlikely related to the study drug. Nonetheless, the US Food and Drug Administration required the sponsor to collect additional safety data.

The recent CARES trial on cardiovascular risk of febuxostat versus allopurinol showed that the individual risk of cardiovascular mortality and all-cause mortality was higher in both febuxostat initiators.[20] There was no difference in risk of the composite end point of cardiovascular death, nonfatal MI, nonfatal stroke, and unstable angina with urgent coronary revascularization between the 2 drug groups. Similar to CARES, we found no difference in individual risk for MI, stroke, or coronary revascularization between the 2 groups. However, we also found no difference in the risk of all-cause mortality in the primary analysis, as well as subgroup analyses limited to those with baseline CVD or baseline high cardiovascular risk (ie, CVD, including peripheral vascular disease or diabetes mellitus as seen in CARES).

The discrepancy in results for mortality between CARES and our study may be related to differences in the underlying populations. CARES was restricted to patients with high cardiovascular risk defined as those with a history of major cardiovascular or cerebrovascular disease, including MI, hospitalized unstable angina, coronary or cerebral vascularization procedure, stroke, hospitalized transient ischemic attack, peripheral vascular disease, or diabetes mellitus with micro- and macrovascular complications. Our main analysis included

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patients with and without CVD. Our Medicare study population was also older, with a more equal sex distribution compared with CARES (52% male with a median age of 76 years in our trial versus 84% male with a median age of 64 years in CARES). However, in our follow-up time-stratified analysis, the risk for all-cause mortality appeared to be increased, albeit not statistically significantly, among patients who used febuxostat over 3 years compared with those who used allopurinol over 3 years. We were unable to assess cause-specific deaths, including cardiovascular mortality, because of limitations with the Medicare database.

There are several strengths to our study. By using an active comparator design (febuxostat versus allopurinol rather than febuxostat versus placebo), we increased the overlapping characteristics of the 2 groups and minimized unmeasured confounding.[29] We increased generalizability with a large sample size, performed a comprehensive covariate adjustment via PS matching, and used validated algorithms for outcome measurement. In addition, unlike the CARES study, we included patients who are representative of Medicare enrollees regardless of baseline cardiovascular comorbidities.

Limitations included misclassification bias because participant eligibility was largely dependent on diagnosis code, although this was likely minimized by the additional inclusion criteria of being prescribed ≥1 urate-lowering drug. Second, Medicare claims data did not provide information on cause-specific mortality, family history of CVD, severity of gout, and use of over-the-counter medications such as nonsteroidal antiinflammatory drugs or aspirin, which could have led to residual confounding. Third, with regard to generalizability, our gout cohort was roughly 52% male, which may appear low; however, this prevalence is comparable to other US Medicare gout studies and may reflect the older age of the cohort.[11,30] Fourth, mean follow-up time was ≈1.2 years, which led to less precise estimates for the long-term effects of febuxostat on cardiovascular as well as all-cause mortality, although our study still included many patients (n=23 317) with >2 years of follow-up. Fifth, because the aim of our study was to determine comparative cardiovascular safety of febuxostat and allopurinol, we did not examine the risk of cardiovascular events associated with XOIs compared with untreated patients with gout. Finally, our study did not include participant serum urate levels, so it is possible that participants were underdosed and inadequately treated. Any instances of suboptimal gout treatment, however, likely reflect real-life patterns of urate-lowering treatment allocation in the United States because prior studies on medication use and serum uric acid monitoring in patients with gout on urate-lowering therapy demonstrate widespread suboptimal dosing.[3]

CONCLUSIONS

In this retrospective cohort study of 99 744 patients with gout >65 years of age enrolled in Medicare, we noted no overall difference in the risk for MI, stroke, coronary revascularization, new HF, or all-cause mortality between febuxostat and allopurinol initiators. However, we noted a trend toward an increased risk, not statistically significant, for all-cause mortality in long-term users of febuxostat (>3 years) versus long-term users of allopurinol. The risk of HF exacerbation was slightly lower among febuxostat initiators versus allopurinol. Subgroup and sensitivity analyses showed consistent results.

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REFERENCES

1. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. *Arthritis Rheum*. 2011;63:3136–3141. doi: 10.1002/art.30520
2. Neogi T. Clinical practice: gout. *N Engl J Med*. 2011;364:443–452. doi: 10.1056/NEJMcp1001124
3. Kim SC, Schmidt BM, Franklin JM, Liu J, Solomon DH, Schneeweiss S. Clinical and health care use characteristics of patients newly starting allopurinol, febuxostat, and colchicine for the treatment of gout. *Arthritis Care Res (Hoboken)*. 2013;65:2008–2014. doi: 10.1002/acr.22067
4. Singh JA, Strand V. Gout is associated with more comorbidities, poorer health-related quality of life and higher healthcare utilisation in US veterans. *Ann Rheum Dis*. 2008;67:1310–1316. doi: 10.1136/ard.2007.081604
5. Annemans L, Spaepen E, Gaskin M, Bonnemaire M, Malier V, Gilbert T, Nuki G. Gout in the UK and Germany: prevalence, comorbidities and management in general practice 2000-2005. *Ann Rheum Dis*. 2008;67:960–966. doi: 10.1136/ard.2007.076232

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6. Zhu Y, Pandya BJ, Choi HK. Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007–2008. *Am J Med*. 2012;125:679.e671–687.e671. doi: 10.1016/j.amjmed.2011.09.033
7. Wei L, Mackenzie IS, Chen Y, Struthers AD, MacDonald TM. Impact of allopurinol use on urate concentration and cardiovascular outcome. *Br J Clin Pharmacol*. 2011;71:600–607. doi: 10.1111/j.1365-2125.2010.03887.x
8. Grimaldi-Bensouda L, Alpérovitch A, Aubrun E, Danchin N, Rossignol M, Abenhaim L, Richette P; PGRx MI Group. Impact of allopurinol on risk of myocardial infarction. *Ann Rheum Dis*. 2015;74:836–842. doi: 10.1136/annrheumdis-2012-202972
9. Givertz MM, Mann DL, Lee KL, Ibarra JC, Velazquez EJ, Hernandez AF, Mascette AM, Braunwald E. Xanthine oxidase inhibition for hyperuricemic heart failure patients: design and rationale of the EXACT-HF study. *Circ Heart Fail*. 2013;6:862–868. doi: 10.1161/CIRCHEARTFAILURE.113.000394
10. Thanassoulis G, Brophy JM, Richard H, Pilote L. Gout, allopurinol use, and heart failure outcomes. *Arch Intern Med*. 2010;170:1358–1364. doi: 10.1001/archinternmed.2010.198
11. Singh JA, Ramachandaran R, Yu S, Curtis JR. Allopurinol use and the risk of acute cardiovascular events in patients with gout and diabetes. *BMC Cardiovasc Disord*. 2017;17:76. doi: 10.1186/s12872-017-0513-6
12. Kim SC, Schneeweiss S, Choudhry N, Liu J, Glynn RJ, Solomon DH. Effects of xanthine oxidase inhibitors on cardiovascular disease in patients with gout: a cohort study. *Am J Med*. 2015;128:653.e657–653.e616. doi: 10.1016/j.amjmed.2015.01.013
13. Strasak A, Ruttmann E, Brant L, Kelleher C, Klenk J, Concin H, Diem G, Pfeiffer K, Ulmer H; VHM&PP Study Group. Serum uric acid and risk of cardiovascular mortality: a prospective long-term study of 83,683 Austrian men. *Clin Chem*. 2008;54:273–284. doi: 10.1373/clinchem.2007.094425
14. Strasak AM, Kelleher CC, Brant LJ, Rapp K, Ruttmann E, Concin H, Diem G, Pfeiffer KP, Ulmer H; VHM&PP Study Group. Serum uric acid is an independent predictor for all major forms of cardiovascular death in 28,613 elderly women: a prospective 21-year follow-up study. *Int J Cardiol*. 2008;125:232–239. doi: 10.1016/j.ijcard.2007.11.094
15. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. *N Engl J Med*. 2008;359:1811–1821. doi: 10.1056/NEJMra0800885
16. Ioachimescu AG, Brennan DM, Hoar BM, Hazen SL, Hoogwerf BJ. Serum uric acid is an independent predictor of all-cause mortality in patients at high risk of cardiovascular disease: a preventive cardiology information system (PreCIS) database cohort study. *Arthritis Rheum*. 2008;58:623–630. doi: 10.1002/art.23121
17. Schumacher HR Jr, Becker MA, Wortmann RL, Macdonald PA, Hunt B, Streit J, Lademacher C, Joseph-Ridge N. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. *Arthritis Rheum*. 2008;59:1540–1548. doi: 10.1002/art.24209
18. Becker MA, Schumacher HR Jr, Wortmann RL, MacDonald PA, Eustace D, Palo WA, Streit J, Joseph-Ridge N. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med*. 2005;353:2450–2461. doi: 10.1056/NEJMoa050373
19. Schumacher HR Jr, Becker MA, Lloyd E, MacDonald PA, Lademacher C. Febuxostat in the treatment of gout: 5-yr findings of the FOCUS efficacy and safety study. *Rheumatology (Oxford)*. 2009;48:188–194. doi: 10.1093/rheumatology/ken457
20. White WB, Saag KG, Becker MA, Borer JS, Gorelick PB, Whelton A, Hunt B, Castillo M, Gunawardhana L; CARES Investigators. Cardiovascular safety of febuxostat or allopurinol in patients with gout. *N Engl J Med*. 2018;378:1200–1210. doi: 10.1056/NEJMoa1710895
21. MacDonald TM, Ford I, Nuki G, Mackenzie IS, De Caterina R, Findlay E, Hallas J, Hawkey CJ, Ralston S, Walters M, Webster J, McMurray J, Perez Ruiz F, Jennings CG; Members of the FAST Study Group. Protocol of the Febuxostat versus Allopurinol Streamlined Trial (FAST): a large prospective, randomised, open, blinded endpoint study comparing the cardiovascular safety of allopurinol and febuxostat in the management of symptomatic hyperuricaemia. *BMJ Open*. 2014;4:e005354. doi: 10.1136/bmjopen-2014-005354
22. Hennessy S, Freeman C and Cunningham F. US Government claims databases. In: Strom B, Kimmel S., Hennessy S, eds. *Pharmacoepidemiology*. 5th ed. Philadelphia, PA: Wiley-Blackwell; 2012:209–223.
23. Andrade SE, Harrold LR, Tjia J, Cutrona SL, Saczynski JS, Dodd KS, Goldberg RJ, Gurwitz JH. A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data. *Pharmacoepidemiol Drug Saf*. 2012;21(suppl 1):100–128. doi: 10.1002/pds.2312
24. Kiyota Y, Schneeweiss S, Glynn RJ, Cannuscio CC, Avorn J, Solomon DH. Accuracy of Medicare claims-based diagnosis of acute myocardial infarction: estimating positive predictive value on the basis of review of hospital records. *Am Heart J*. 2004;148:99–104. doi: 10.1016/j.ahj.2004.02.013
25. Kumamaru H, Judd SE, Curtis JR, Ramachandran R, Hardy NC, Rhodes JD, Safford MM, Kissela BM, Howard G, Jalbert JJ, Brott TG, Setoguchi S. Validity of claims-based stroke algorithms in contemporary Medicare data: reasons for geographic and racial differences in stroke (REGARDS) study linked with Medicare claims. *Circ Cardiovasc Qual Outcomes*. 2014;7:611–619. doi: 10.1161/CIRCOUTCOMES.113.000743
26. Gagne JJ, Glynn RJ, Avorn J, Levin R, Schneeweiss S. A combined comorbidity score predicted mortality in elderly patients better than existing scores. *J Clin Epidemiol*. 2011;64:749–759. doi: 10.1016/j.jclinepi.2010.10.004
27. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat*. 2011;10:150–161. doi: 10.1002/pst.433
28. Franklin JM, Rassen JA, Ackermann D, Bartels DB, Schneeweiss S. Metrics for covariate balance in cohort studies of causal effects. *Stat Med*. 2014;33:1685–1699. doi: 10.1002/sim.6058
29. Yoshida K, Solomon DH, Kim SC. Active-comparator design and new-user design in observational studies. *Nat Rev Rheumatol*. 2015;11:437–441. doi: 10.1038/nrrheum.2015.30.
30. Singh JA, Cleveland J. Allopurinol and the risk of ventricular arrhythmias in the elderly: a study using US Medicare data. *BMC Med*. 2017;15:59. doi: 10.1186/s12916-017-0816-6

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