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

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-

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

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

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-

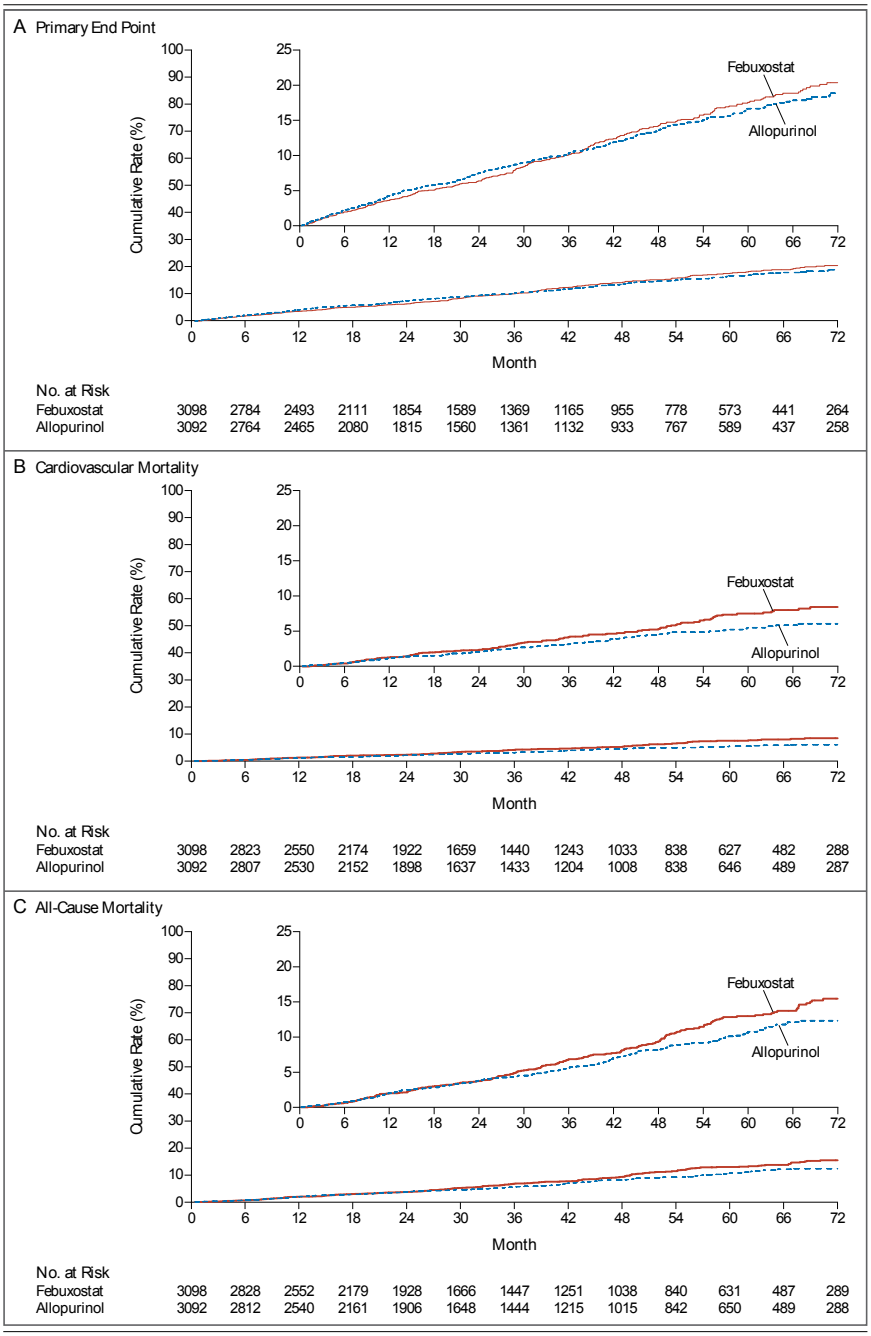

Figure 1 (facing page). Cumulative Kaplan–Meier Estimates of the Time to the First Occurrence of an Adjudicated End-Point Event.

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,

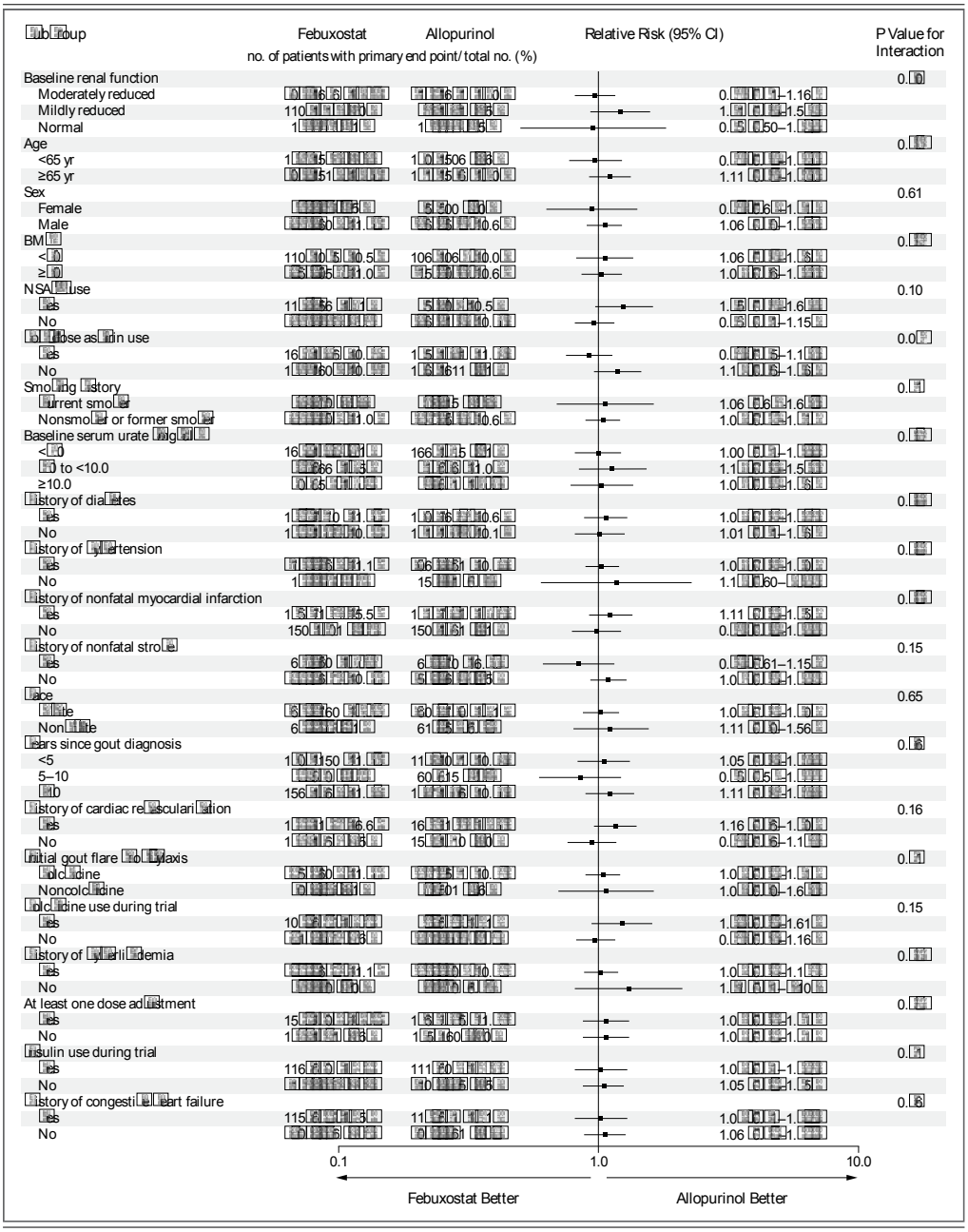

Figure 2 (facing page). Risk Ratios for the Primary End Point According to Subgroup.

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.

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Iguazu Falls, Argentina and Brazil

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