Febuxostat Therapy for Patients With Stage 3 CKD and Asymptomatic Hyperuricemia: A Randomized Trial

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Rationale & Objective: Epidemiologic and clinical studies have suggested that urate-lowering therapy may slow the progression of chronic kidney disease (CKD). However, definitive evidence is lacking.

Study Design: Randomized, double-blind, placebo-controlled trial.

Setting & Participants: 467 patients with stage 3 CKD and asymptomatic hyperuricemia at 55 medical institutions in Japan.

Intervention: Participants were randomly assigned in a 1:1 ratio to receive febuxostat or placebo for 108 weeks.

Outcomes: The primary end point was the slope (in mL/min/1.73 m^2 per year) of estimated glomerular filtration rate (eGFR). Secondary end points included changes in eGFRs and serum uric acid levels at 24, 48, 72, and 108 weeks of follow-up and the event of doubling of serum creatinine level or initiation of dialysis therapy.

Results: Of 443 patients who were randomly assigned, 219 and 222 assigned to febuxostat and placebo, respectively, were included in the analysis. There was no significant difference in mean eGFR slope between the febuxostat (0.23 ± 5.26 mL/min/1.73 m^2 per year) and placebo (−0.47 ± 4.48 mL/min/1.73 m^2 per year) groups (difference, 0.70; 95% CI, −0.21 to 1.62; $P = 0.1$). Subgroup analysis demonstrated a significant benefit from febuxostat in patients without proteinuria ($P = 0.005$) and for whom serum creatinine concentration was lower than the median ($P = 0.009$). The incidence of gouty arthritis was significantly lower ($P = 0.007$) in the febuxostat group (0.91%) than in the placebo group (5.86%). Adverse events specific to febuxostat were not observed.

Limitations: GFR was estimated rather than measured, and patients with stages 4 and 5 CKD were excluded.

Conclusions: Compared to placebo, febuxostat did not mitigate the decline in kidney function among patients with stage 3 CKD and asymptomatic hyperuricemia.

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Trial Registration: Registered at the UMIN (University Hospital Medical Information Network) Clinical Trials Registry with study number UMIN000008343.

Complete author and article information, including a list of the FEATHER Study Investigators, provided before references.

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Previous clinical studies have indicated that hyperuricemia is a potentially modifiable risk factor for the development and progression of chronic kidney disease (CKD).[1-4] Some small controlled clinical studies have shown that urate-lowering therapy with allopurinol can retard CKD progression.[5-8] Nevertheless, sufficient clinical evidence to support widespread use of the therapy to slow CKD progression is not available.[1] Furthermore, information for the effects of xanthine oxidase inhibitors on early kidney damage is sparse or lacking.[9]

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Febuxostat, a novel potent nonpurine-selective inhibitor of xanthine oxidase for oral use, is metabolized predominantly in the liver by glucuronidation, with only 1% to 6% of the dose being excreted unchanged through the kidneys.[10] Hence, decreased glomerular filtration rate (GFR) has little impact on the pharmacokinetic profile of febuxostat,[11] allowing its safe administration for patients with low GFRs.

In consideration of the demand for an adequately powered randomized trial to evaluate the benefits and risks of urate-lowering therapy in patients with CKD,[12] we conducted the present study to test the hypothesis that febuxostat is superior to placebo in suppressing estimated GFR (eGFR) decline in Japanese patients with stage 3 CKD who had asymptomatic hyperuricemia.

Methods

Patients

Patients were eligible for enrollment if they were 20 years or older, had hyperuricemia (uric acid concentration > 7.0-10.0 mg/dL), had stage 3 CKD,[12] had no history of gout, and provided written informed consent. eGFR was calculated according to the equation defined by the Japanese Society of Nephrology.[13] Key exclusion criteria were patients who had poorly controlled diabetes mellitus (DM; hemoglobin $A_{1c} \geq 8.4\%$ in the National Glycohemoglobin Standardization Program), systolic blood pressure (SBP) ≥ 160 mm Hg, diastolic blood pressure (DBP) ≥ 100 mm Hg, alanine or

aspartate aminotransferase level more than 2-fold the upper limit defined at the institution, ≥50% variation in serum creatinine concentration within 12 weeks before eligibility confirmation, severe complications (eg, nephrotic syndrome), hemodialysis therapy, and kidney transplantation.

Study Design and Participants

FEATHER (Febuxostat Versus Placebo Randomized Controlled Trial Regarding Reduced Renal Function in Patients With Hyperuricemia Complicated by Chronic Kidney Disease Stage 3) was a multicenter, randomized, double-blind, parallel-group, placebo-controlled trial. Details of the study rationale, design, and methods have been described previously.[14] Case report forms were collected to form the datasets.

We conducted the present study in accordance with the Declaration of Helsinki. The study protocol was approved by local/regional ethics committees. FEATHER was registered as UMIN000008343 in the UMIN (University Hospital Medical Information Network) Clinical Trials Registry.

Study Treatment and Randomization

Patients were assigned to receive febuxostat or placebo according to 1:1 dynamic randomization. The following doses were used: loading daily dose, 10 mg given as one 10-mg tablet once daily on days 1 to 28 after study onset; escalated daily dose, 20 mg given as one 20-mg tablet at weeks 4 to 7; and maintenance daily dose, 40 mg given as one 40-mg tablet once daily at weeks 8 to 108.

Dynamic randomization was conducted by the enrollment center (the Japan Clinical Research Support Unit, a not-for-profit organization in Tokyo, Japan) according to the minimization method using the following allocation adjustment factors: site (each site), sex (male or female), age (<65 or ≥65 years), serum uric acid concentration (<8.0 or ≥8.0 mg/dL), qualitative urinary protein (positive or negative), and DM as a coexisting condition (present or absent).

Personnel who were involved in this trial (eg, investigators, nurses, data collectors, and trial staff) were unaware of the relevant assignments. Patients were monitored at baseline and weeks 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, and 108 after study onset. The study was discontinued if serum uric acid concentrations were >12.0 mg/dL, eGFR declined by ≥50% within 24 weeks, the investigator decided (at his or her discretion) on treatment discontinuation due to adverse events (AEs), a prohibited concurrent therapy was required, a female patient became pregnant, or the patient requested withdrawal. Prohibited concurrent therapy was treatment with specified drugs (mercaptopurine hydrate, azathiopurine, vidarabine, and didanosine) and urate-lowering agents (allopurinol, benzbromarone, probenecid, bucolome, and febuxostat).

Patient Evaluation

Patients underwent tests and examinations as scheduled, the details of which are described in the published protocol.[14] During the study period, serum and urinary uric acid concentrations were measured by a central laboratory. Measurement results were concealed to investigators and patients until code breaking.

Primary and Secondary End Points

The primary end point was eGFR slope (mL/min/1.73 m^2 per year). Secondary end points were as follows: eGFR changes (in mL/min/1.73 m^2 and in percentage terms) from baseline to weeks 24, 48, 72, and 108; serum uric acid concentration changes (in mg/dL and in percentage terms) from baseline to weeks 24, 48, 72, and 108; a decrease in serum uric acid concentration to ≤6.0 mg/dL; kidney events (doubling of serum creatinine concentration and initiation of dialysis therapy) from baseline to week 108; a 30% decline in eGFR; changes from baseline to week 108 in markers for oxidation stress, inflammation, and cardiovascular events; gouty arthritis; and AEs from baseline to week 108. Predefined subgroup analyses of eGFR slope were conducted for sex (male, female), age, serum uric acid concentration, urine protein, body mass index, DM, CKD stage, serum creatinine concentration, smoking, ischemic heart disease, cerebrovascular disorder, aortic disease, peripheral artery disease, and lifestyle-related disease. Mean values for eGFR and their 95% confidence intervals (CIs) were determined from baseline to week 108 using a repeated-measures model with a compound-symmetry working covariance matrix and robust variance adjustment. Missing data were presumed to be missing completely, without conducting sensitivity analysis or imputation for them. A statistical analysis was made that replaced the outliers of the slope which corresponded to ±50% or greater change per year with ±50% because they potentially occur due to a small number of time points for assessment and/or errors in serum creatinine measurements.

Time-Course Changes in Laboratory Data and Vital Signs

Time-course changes in serum creatinine, eGFR, proteinuria, SBP, and DBP values were determined.

Statistical Analyses

Data were collected by the Japan Clinical Research Support Unit. All efficacy analyses of the primary and secondary end points were conducted based on the intention-to-treat principle in the full analysis set of patients, with the exception of 1 patient who was included inappropriately and another who did not visit the hospital. Patients with baseline measurements were assessed for changes and percent changes from baseline. The 95% CIs were calculated for the mean values of between-group differences, and the regression line was applied to eGFRs serially calculated for each patient to examine between-group differences in eGFR slope according to t test. Time-course changes in eGFR and serum uric acid values from baseline through week 108 were analyzed according to generalized estimating equation repeated-measures analysis in the study population and subgroups. The

structure of compound symmetry was presumed as the variance structure. Baseline values for eGFR, serum uric acid concentration, and SBP and DBP were used as covariates with respect to their time courses at respective time points. Time to decreases in serum uric acid concentrations to ≤6.0 mg/dL, time to kidney events, and time to 30% decrease in eGFR were estimated according to the Kaplan-Meier method and were analyzed for between-group comparisons according to log-rank test. Incidences of AEs were analyzed according to Fisher exact probability test. Numbers of patients required to demonstrate a between-group difference in subgroups of patients with stage 3a CKD and those with stage 3b CKD at a 2-tailed significance level of 0.05 and power of 80% were calculated to be 89 each in the febuxostat and placebo groups (178 patients each in the 2 subgroups; a total of 356 patients with stage 3 CKD). Under these conditions, power for between-group comparisons in patients with stage 3 CKD is 94.2%. In consideration of the estimated withdrawal rate of 11% during the study period, target numbers of patients with stage 3a CKD and those with stage 3b CKD were set to be 100 each (200 patients in the 2 groups; a total of 400 patients). Sample size was calculated by estimating the eGFR slope difference of 2.7 mL/min/1.73 m^2 per year with a standard deviation of 7.2. *P* values were calculated using *t* test, Fisher exact test, and Pearson χ^2 test. $P < 0.05$ was considered statistically significant. All statistical analyzes were made using SAS software (version 9.4, SAS Institute Inc).

A post hoc analysis was conducted to examine the effects of febuxostat treatment on blood pressures in the patient population.

Results

Study Patients

A total of 467 patients (363 men and 104 women; mean age, 65.6 years) were enrolled; 24 were subsequently excluded. Among 443 randomly assigned patients, 1 did not make the first visit to the hospital. Consequently, 442

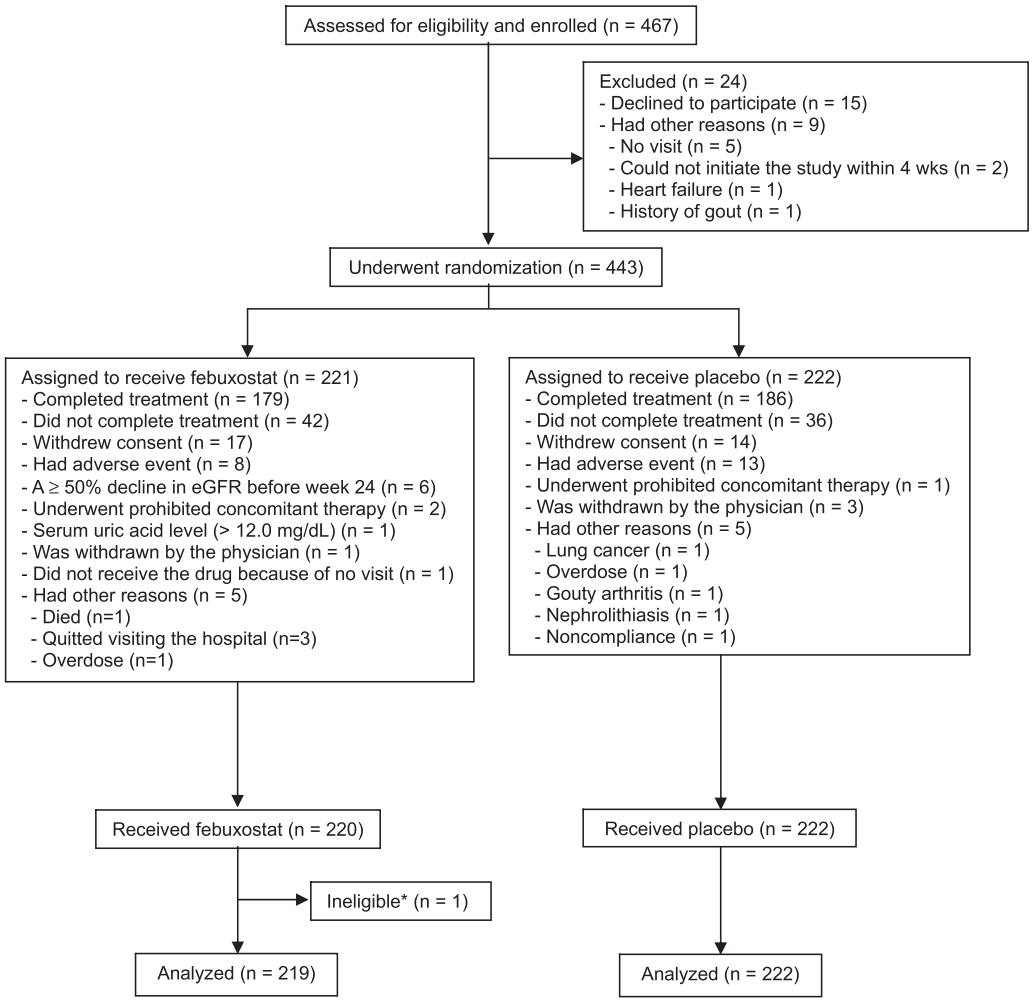

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram. *Found after the initiation of administration. Abbreviation: eGFR, estimated glomerular filtration rate.

patients (94.6% of enrolled patients) received febuxostat (220 patients) or placebo (222 patients); however, 1 patient was found to be ineligible after the initiation of administration. Hence, 219 and 222 patients in the febuxostat and placebo groups had at least 1 evaluable visit after the onset of oral administration, respectively (Fig 1). Study groups were well matched with respect to site, sex, age, serum uric acid concentration, proteinuria, and DM. No significant difference was found between the febuxostat group and placebo group for demographic and clinical characteristics of patients at baseline, with the exception of SBP and use of angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers (Table 1).

Patients were enrolled from November 7, 2012, through January 17, 2014, at 55 medical institutions in Japan. The last visits occurred from March 21, 2013, through February 29, 2016, and 365 (82.4%) patients who had undergone random assignment completed the study. The most frequent reasons for discontinuation were consent withdrawal (17 and 14 patients in the febuxostat and placebo groups, respectively) and AEs (8 and 13 patients, respectively; Fig 1).

Primary and Secondary End Points

Statistical analysis of population mean values of the individual patients' eGFR slopes per year revealed no significant difference in mean eGFR slope between the febuxostat (0.23 ± 5.26 mL/min/1.73 m^2 per year) and placebo (-0.47 ± 4.48 mL/min/1.73 m^2 per year) groups (difference, 0.70; 95% CI, −0.21 to 1.62; P = 0.1). Between-group difference in the means of eGFR tended to increase at week 24 or later (Fig 2A). The means of eGFRs in the febuxostat and placebo groups were as follows: at baseline, 45.2 (95% CI, 43.8-46.6) and 44.9 (95% CI, 43.5-46.3) mL/min/1.73 m^2; at week 108, 45.1 (95% CI, 43.7-46.6) and 44.3 (95% CI, 42.8-45.7) mL/min/1.73 m^2, respectively. Between-group difference in eGFR changes at week 108 was 0.5 (95% CI, −0.5 to 1.6) mL/min/1.73 m^2 (P = 0.3).

Between-group differences in eGFR slopes in patients with stage 3a CKD and those with stage 3b CKD were 1.22 (95% CI, −0.08 to 2.51) mL/min/1.73m^2 (P = 0.06) and 0.21 (95% CI, −1.07 to 1.50) mL/min/1.73m^2 (P = 0.8), respectively. Subgroup analysis of the eGFR slope (Table 2) revealed a significant difference of 1.79 (95% CI, 0.55-3.03) mL/min/1.73 m^2 per year (P = 0.005) in patients without proteinuria (Fig 2B) and a significant difference of 1.76 (95% CI, 0.44-3.07) mL/min/1.73 m^2 per year (P = 0.009) in patients for whom serum creatinine level was lower than the median (Fig 2C). eGFR slopes diverged significantly between the febuxostat and placebo groups over time with respect to these proteinuria and serum creatinine concentration categories (P for time-by-treatment effects = 0.01 and 0.02, respectively).

Serum uric acid concentrations decreased significantly in the febuxostat group at week 4 (to 6.0 [95% CI,

Table 1. Characteristics of Study Participants at Baseline

	Placebo (n = 222)	Febuxostat (n = 219)	*P*
Demographic and Clinical Characteristics			
Age, y	65.4 ± 12.3	65.3 ± 11.8	0.9[a]
Age category			
<65 y	90 (40.5%)	90 (41.1%)	
65-74 y	75 (33.8%)	81 (37.0%)	
≥75 y	57 (25.7%)	48 (21.9%)	
Male sex	171 (77.0%)	170 (77.6%)	0.9[b]
Diabetes mellitus	68 (30.6%)	64 (29.2%)	0.8[b]
Proteinuria	103 (46.4%)	107 (48.9%)	0.6[b]
CKD stage			0.9[b]
3a	106 (47.7%)	106 (48.4%)	
3b	116 (52.3%)	113 (51.6%)	
Smoking status			0.9[a]
Current smoker	29 (13.1%)	28 (12.8%)	
Former smoker	102 (45.9%)	103 (47.0%)	
Lifetime nonsmoker	91 (41.0%)	88 (40.2%)	
Body weight, kg	66.1 ± 11.2	66.1 ± 13.1	0.9[c]
Body mass index, kg/m^2	24.7 ± 3.6	24.9 ± 4.4	0.7[c]
Blood pressure			
Systolic, mm Hg	129.6 ± 14.9	132.5 ± 15.0	0.04[c]
Diastolic, mm Hg	77.3 ± 11.3	77.9 ± 10.7	0.6[c]
Coexisting conditions			
Ischemic heart disease	14 (6.3%)	19 (8.7%)	0.4[c]
Cerebrovascular disease	17 (7.7%)	29 (13.2%)	0.06[c]
Aortic disease	3 (1.4%)	7 (3.2%)	0.2[c]
Peripheral artery disease	4 (1.8%)	3 (1.4%)	0.9[c]
Lifestyle-related disease	207 (93.2%)	211 (96.3%)	0.2[c]
Medications			
ACE inhibitor and/or ARB	163 (73.4%)	181 (82.6%)	0.02[c]
Statins	74 (33.3%)	93 (42.5%)	0.05[c]
β-Blockers	30 (13.5%)	40 (18.3%)	0.2[c]
Antidiabetic drugs	52 (23.4%)	46 (21.0%)	0.6[c]
Diuretics	36 (16.2%)	45 (20.5%)	0.3[c]
Laboratory Results			
Serum uric acid, mg/dL	7.8 ± 0.9	7.8 ± 0.9	0.9[c]
Estimated GFR, mL/min/1.73 m^2	44.9 ± 9.7	45.2 ± 9.5	0.7[c]
Serum creatinine, mg/dL	1.3 ± 0.3	1.2 ± 0.3	0.7[c]
Hemoglobin A_{1c}, %	6.1 ± 0.7	6.0 ± 0.6	0.07[c]
UACR, mg/g	120.5 [17.2-517.0]	124.0 [19.1-525.0]	0.9[d]
Smoking status			0.9[a]
Current smoker	29 (13.1%)	28 (12.8%)	
Former smoker	102 (45.9%)	103 (47.0%)	
Lifetime nonsmoker	91 (41.0%)	88 (40.2%)	

Note: Values for categorical variables are given as count (percentage); values for continuous variables, as mean ± standard deviation; non-normally distributed data, as median [quartile 1-quartile 3].
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; GFR, glomerular filtration rate; UACR, urinary albumin-creatinine ratio.
P values are from: [a]χ^2 test, [b]Fisher exact test, [c]*t* test, or [d]Wilcoxon rank sum test.

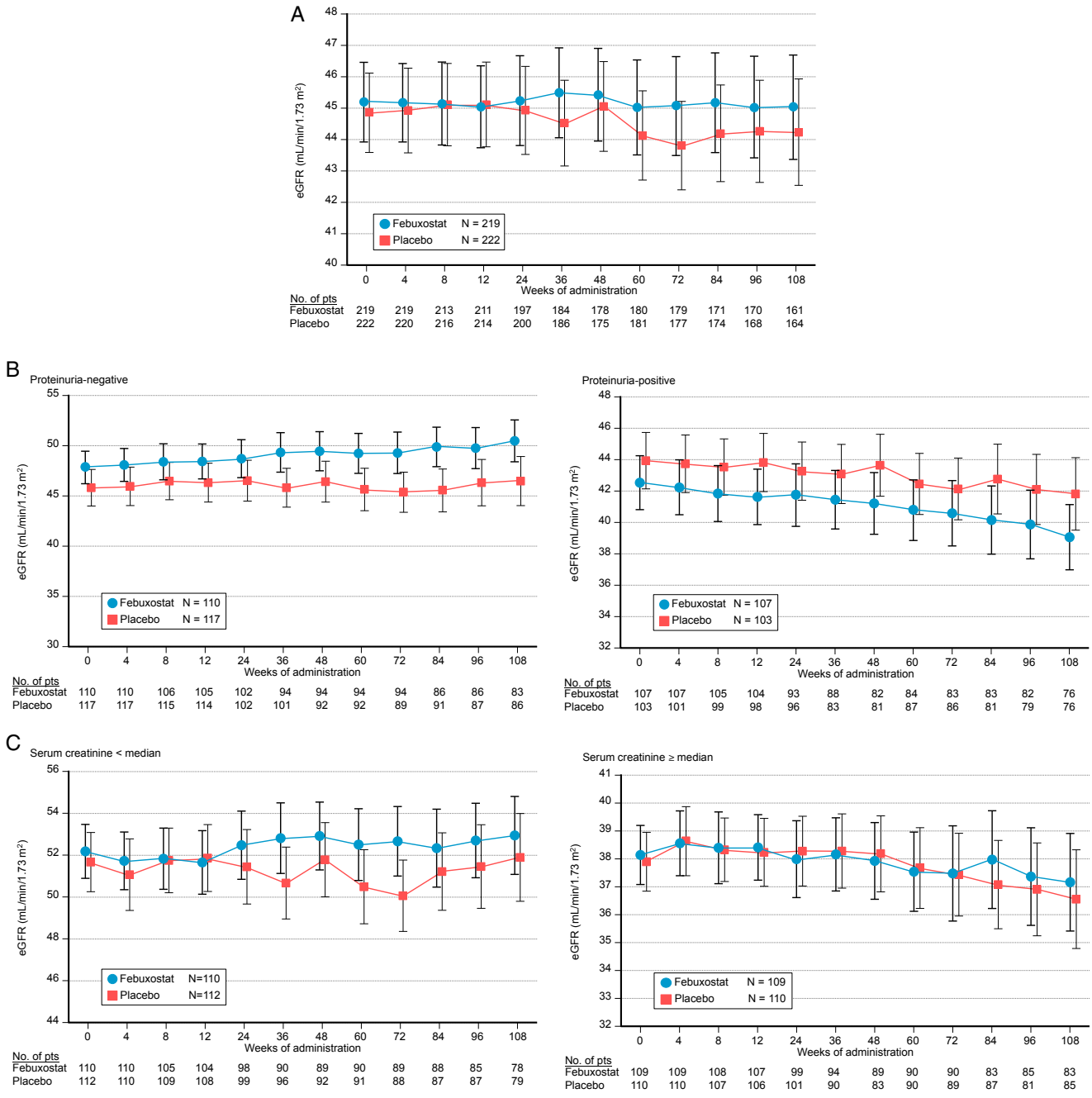

Figure 2. Time-course changes in estimated glomerular filtration rates (eGFRs) from week 0 through week 108 of treatment. (A) Study population; (B) proteinuria, negative/positive; (C) serum creatinine level less than or equal to or greater than the median. eGFRs were determined using generalized estimating equation repeated-measures analysis, with time as a categorical variable. Mean ± 95% confidence interval.

5.8-6.1] mg/dL) or later, with ongoing decreases up to week 12, when a plateau was reached (at 4.2 [95% CI, 4.1-4.4] mg/dL), persisting up to week 108 (mean of 4.2 [95% CI, 4.0-4.4] mg/dL; Fig 3). Proportions of patients for whom serum uric acid concentrations decreased to ≤6.0 mg/dL at least 1 time during the treatment period were 96.8% in the febuxostat group and 18.5% in the placebo group. Serum uric acid concentration was >12.0 mg/dL in 1 patient in the febuxostat group. Incidences of kidney events were 2 each in the placebo and febuxostat groups. The incidence of gouty arthritis was significantly lower ($P = 0.007$) in the febuxostat group (0.9% [2/219]) versus the placebo group (5.9% [13/222]).

Vital Signs

SBP and DBP after the onset of oral administration tended to be lower in the febuxostat group than in the placebo

group (Fig 4). Mean estimates of SBP in the febuxostat and placebo groups at week 0 were 132.5 (95% CI, 130.6-134.5) and 129.6 (95% CI, 127.7-131.6) mm Hg, respectively; average estimates at weeks 36 to 108 were 128.9 (95% CI, 127.4-130.4) and 130.1 (95% CI, 128.5-131.7) mm Hg, respectively. The difference in mean estimates of SBP between groups was −1.2 (95% CI, −3.4 to 1.0 mm Hg; P = 0.3). Mean estimates of DBP in the febuxostat and placebo groups at week 0 were 77.9 (795% CI, 6.5-79.3) and 77.3 (95% CI, 75.8-78.8) mm Hg, respectively; average estimates of DBP at weeks 36 to 108 were 74.7 (95% CI, 73.5-75.9) and 76.3 (95% CI, 75.1-77.5) mm Hg, respectively. The difference in mean estimates of DBP between groups was −1.6 (95% CI, −3.3 to 0.1 mm Hg; P = 0.06).

Safety

AEs and serious AEs (SAEs) were assessed for 219 and 222 patients in the febuxostat and placebo groups, respectively. AEs occurred in 56.6% (124/219) of patients in the febuxostat group and 60.8% (135/222) of patients in the placebo group; neither AEs and SAEs specific to febuxostat were found nor was a significant between-group difference detected with respect to the overall incidences of AEs (P = 0.4) and SAEs (P = 0.2). Decreased eGFR, hypersensitivity (eg, rash), liver dysfunction, cardiovascular disorders (eg, myocardial infarction), and stroke (eg, cerebral infarction) developed in the placebo group in 13, 10, 9, 7, and 2 patients, respectively. In the febuxostat group, 8, 7, 4, 4, and 1 patients developed reduced eGFR, hypersensitivity, liver dysfunction, cardiovascular disorders, and stroke, respectively. However, AEs other than these occurred in greater numbers of patients: 128 and 119 patients in the placebo and febuxostat group, respectively. SAEs were similar for the febuxostat group (48 of 219 [21.9%]) and placebo group (37 of 222 [16.7%]). Chief SAEs were reduced eGFR, cardiovascular disorders, and stroke in both the febuxostat and placebo groups. Furthermore, 2 patients died; 1 due to lung cancer in the placebo group and 1 due to an unspecified cause in the febuxostat group (Table 3).

Discussion

In the Japanese general population, including among individuals with stage 3 CKD, rates of eGFR decline have been reported to be low, ranging between 0.31 and 0.42 mL/min/1.73 m^2 per year depending on the age groups examined.[15] Likewise, in the present study, eGFR slope in the placebo group was as low as −0.47 ± 4.48 mL/min/1.73 m^2 per year.

The mentioned natural history of CKD inherent in the Japanese population probably made the between-group difference in eGFR slope less likely to occur. Nevertheless, our study provides 3 major findings of clinical interest.

The first major finding is that the decline in eGFR (expressed as eGFR slope) in patients who did not have proteinuria or whose serum creatinine level was lower than the median was significantly suppressed in the febuxostat group. Thus, our study provides valuable clinical information on the effect of an xanthine oxidase inhibitor on proteinuria in patients with CKD and a suggestion that febuxostat is presumably more effective for patients with less kidney damage as manifested by: (1) greater eGFR in patients without proteinuria (difference, 3.6 [95% CI, 1.8-5.3] mL/min/1.73 m^2; P < 0.001) and (2) lower serum creatinine levels. However, no significant between-group difference was found in patients with stage 3a CKD and those with stage 3b CKD.

The second major finding is that febuxostat therapy was demonstrated to stem the development of gouty arthritis in patients with CKD and asymptomatic hyperuricemia.

The third major finding is that febuxostat tended to decrease DBP in patients with CKD and asymptomatic hyperuricemia, which is partially in line with previous cohort and intervention clinical studies.

Experimental evidence suggests that uric acid may harm patients with CKD through contributions to inflammation intensification and CKD progression.[3] A large number of clinical observational studies[4,16-27] and a small number of controlled trials[5-8,28] have investigated the potential association between increased serum uric acid concentration and kidney events. Consequently, many studies, including the Cardiovascular Health Study, which involved 5,808 patients with 5 years of follow-up,[17] showed a significant relationship between increased uric acid concentration and CKD progression. Although these studies suggest that decreasing serum uric acid concentration may retard CKD progression, urate-lowering therapy for patients with CKD cannot be advocated proactively because of their limitations (eg, small number of participants, short follow-up, and study design).[3] Moreover, the Modification of Diet in Renal Disease (MDRD) Study,[29] in which 840 patients with stages 3 to 4 CKD were followed up for 10 years, did not find uric acid concentration to be an independent risk factor for progression to kidney failure. Thus, there are conflicting clinical outcomes with respect to the kidney-protective effect of decreasing uric acid levels in patients with CKD.[3]

Sircar et al[30] conducted a 6-month, single-center, double-blind, placebo-controlled trial of febuxostat in patients with CKD stages 3 and 4 involving hyperuricemia and reported that febuxostat significantly slowed the decline in eGFR as compared to placebo. However, their study differs from ours in the composition of enrolled patients, given that they included patients with CKD stage 4.

In a double-blind placebo-controlled study of topiroxostat in hyperuricemic patients with stage 3 CKD with or without gout that examined the effects on serum uric acid levels and urinary albumin excretion,[31] no between-group difference in eGFR change or a reduction in eGFR in the placebo group at completion was found, as was the case with our study. However, in another randomized,

Table 2. Subgroup Analysis of eGFR Slopes

Subgroup	Group	N	Mean	Between-Group Difference (95% CI)	*P*[a]	*P* for Interaction[a]
Sex						0.3
Male	Placebo	171	−0.18	0.41 (−0.64 to 1.46)	0.4	
	Febuxostat	170	0.23			
Female	Placebo	51	−1.42	1.68 (−0.21 to 3.57)	0.08	
	Febuxostat	49	0.27			
Age						0.7
<65 y	Placebo	90	−0.48	0.47 (−0.83 to 1.77)	0.5	
	Febuxostat	90	−0.01			
≥65 y	Placebo	132	−0.46	0.86 (−0.40 to 2.13)	0.2	
	Febuxostat	129	0.41			
Serum uric acid						0.4
<8.0 mg/dL	Placebo	140	−0.74	1.03 (−0.16 to 2.23)	0.09	
	Febuxostat	119	0.30			
≥8.0 mg/dL	Placebo	82	−0.01	0.17 (−1.28 to 1.61)	0.8	
	Febuxostat	100	0.16			
Proteinuria						0.01
Absent	Placebo	117	−0.10	1.79 (0.55 to 3.03)	0.005	
	Febuxostat	110	1.69			
Present	Placebo	103	−0.88	−0.50 (−1.80 to 0.81)	0.5	
	Febuxostat	107	−1.37			
BMI						0.6
<25 kg/m^2	Placebo	127	−0.66	0.89 (−0.25 to 2.03)	0.1	
	Febuxostat	130	0.23			
≥25 kg/m^2	Placebo	95	−0.21	0.45 (−1.07 to 1.97)	0.6	
	Febuxostat	89	0.24			
Diabetes mellitus						0.7
Absent	Placebo	154	−0.30	0.56 (−0.45 to 1.58)	0.3	
	Febuxostat	155	0.26			
Present	Placebo	68	−0.84	1.01 (−0.95 to 2.96)	0.3	
	Febuxostat	64	0.17			
CKD stage						0.3
3a	Placebo	106	−0.14	1.22 (−0.08 to 2.51)	0.06	
	Febuxostat	106	1.08			
3b	Placebo	116	−0.77	0.21 (−1.07 to 1.50)	0.8	
	Febuxostat	113	−0.56			
Serum creatinine						0.02
<Median	Placebo	112	−0.57	1.76 (0.44 to 3.07)	0.009	
	Febuxostat	110	1.19			
≥Median	Placebo	110	−0.37	−0.37 (−1.62 to 0.89)	0.6	
	Febuxostat	109	−0.73			
Smoking						0.2
Current/former smoker	Placebo	131	−0.09	0.15 (−0.95 to 1.25)	0.8	
	Febuxostat	131	0.06			
Lifetime nonsmoker	Placebo	91	−1.01	1.50 (−0.08 to 3.09)	0.06	
	Febuxostat	88	0.50			
Ischemic heart disease						0.2
Absent	Placebo	208	−0.50	0.50 (−0.41 to 1.41)	0.3	
	Febuxostat	200	−0.00			
Present	Placebo	14	0.01	2.72 (−2.27 to 7.70)	0.3	
	Febuxostat	19	2.73			
Cerebrovascular disease						0.8
Absent	Placebo	205	−0.43	0.66 (−0.31 to 1.64)	0.2	
	Febuxostat	190	0.23			
Present	Placebo	17	−0.87	1.14 (−1.71 to 3.99)	0.4	
	Febuxostat	29	0.27			

(Continued)

Table 2 (Cont'd). Subgroup Analysis of eGFR Slopes

Subgroup	Group	N	Mean	Between-Group Difference (95% CI)	P[a]	P for Interaction[a]
Peripheral artery disease						0.01
Absent	Placebo	218	−0.34	0.53 (−0.38 to 1.44)	0.3	
	Febuxostat	216	0.20			
Present	Placebo	4	−7.62	10.61 (−3.38 to 24.61)	0.1	
	Febuxostat	3	3.00			
Lifestyle-related disease						0.2
Absent	Placebo	15	1.21	−1.97 (−6.16 to 2.23)	0.3	
	Febuxostat	8	−0.76			
Present	Placebo	207	−0.59	0.86 (−0.08 to 1.80)	0.07	
	Febuxostat	211	0.27			

Abbreviations: BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.
[a]*t* test.

double-blind, placebo-controlled, parallel-group study of topiroxostat (UPWARD Study) that examined urate-lowering and renoprotective effects in patients with diabetic nephropathy and hyperuricemia,[32] a between-group difference in change in eGFR was found and a reduction in eGFR in the placebo group at completion was observed. Therefore, the reported clinical effects of urate-lowering therapy on eGFR are inconsistent. Since the eGFR slope was highly likely to be less steep for patients with stage 3 CKD in the placebo group, any divergence in eGFR slopes was possibly not sufficient to generate a significant difference between the febuxostat and placebo groups. Based on our experience with this placebo-controlled study, we consider that future studies should be further refined to include patients with stage 4 CKD, as done by Sircar et al,[30] and to make the patient group more homogeneous (eg, patients with DM or patients without DM only).

The US Food and Drug Administration issued a warning about the increased risk for heart-related death and all-cause deaths[33] with febuxostat compared to allopurinol, and White et al[34] reported that all-cause and cardiovascular mortality were higher with febuxostat than with allopurinol. In the present trial, nevertheless, we did not find an increased number of cardiovascular events with febuxostat in comparison to placebo.

Several prior preclinical and clinical studies have suggested the association of serum uric acid concentrations and blood pressures.[27,35-37] Hyperuricemia was suggested to increase the risk for developing hypertension.[35,38] However, post hoc analysis of our data did not reveal any obvious effect of febuxostat on blood pressures. Increased

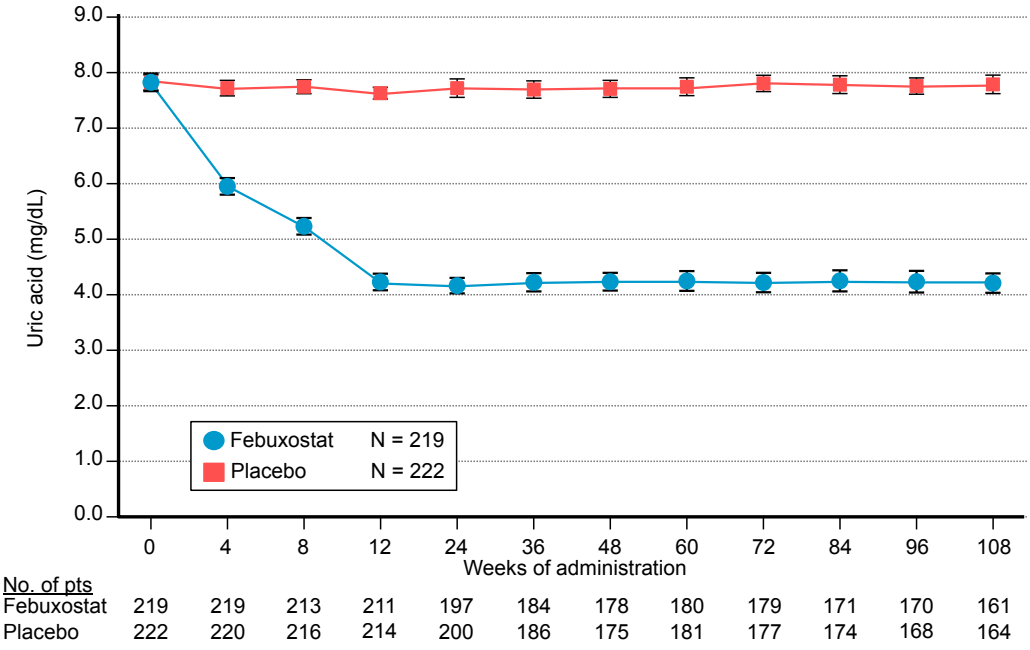

Figure 3. Time course changes in serum uric acid concentrations from week 0 through week 108 of treatment. Mean ± 95% confidence interval.

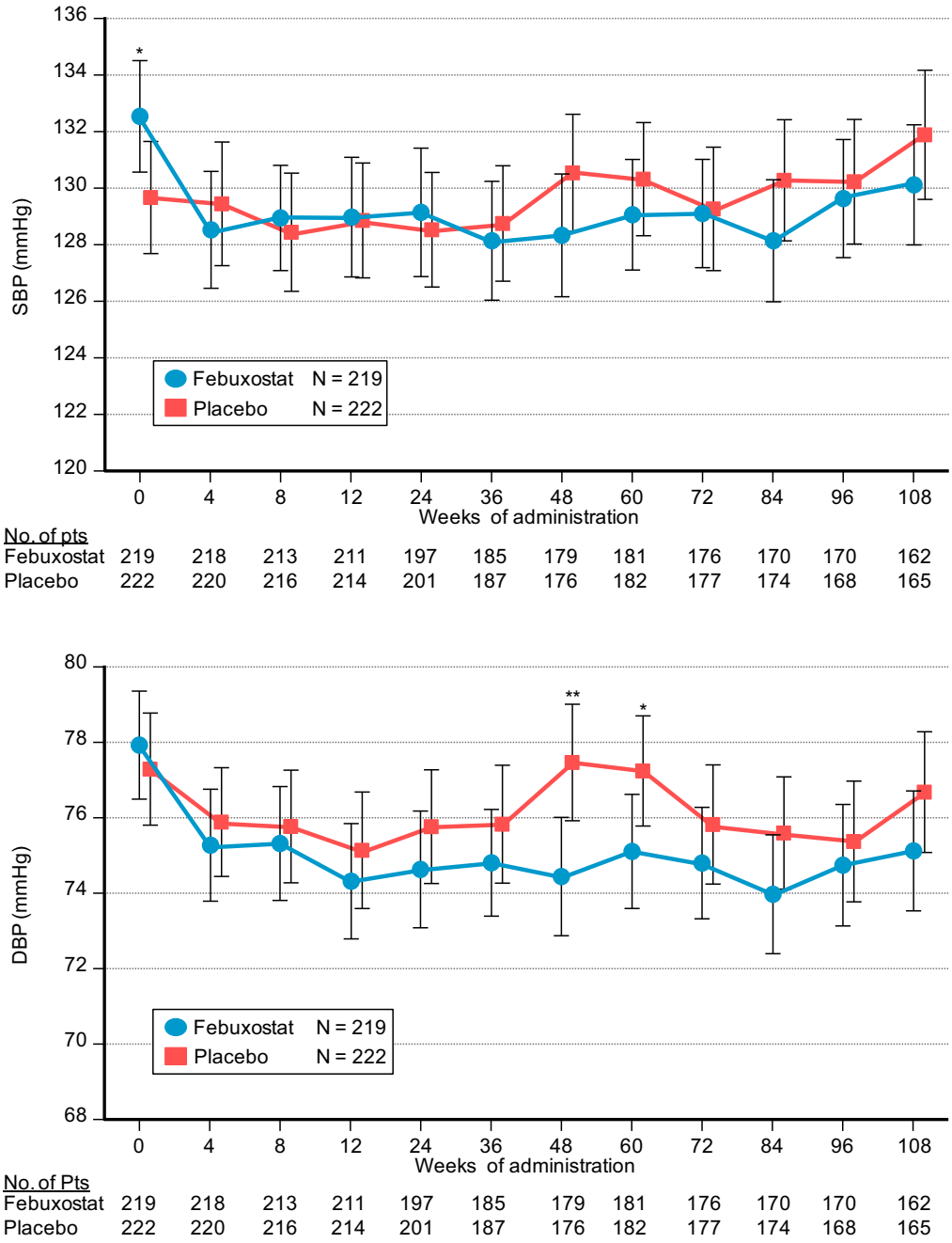

Figure 4. Time course changes in blood pressures from week 0 through week 108 of treatment. Mean ± 95% confidence interval. *$P < 0.05$, **$P < 0.01$. Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

uric acid concentrations induce vasoreactive hypertension through postulated mechanisms (eg, increased renin, decreased nitric oxide, and vascular and interstitial inflammation),[39] and renin-angiotensin system blockade is beneficial for human diabetic nephropathy.[40] In the present study, 82.6% of patients in the febuxostat group received renin-angiotensin system inhibitors at baseline and their renin-angiotensin systems were presumed to be considerably inhibited. We speculate that this may be responsible, at least in part, for the lack of an obvious blood pressure–lowering effect of febuxostat in our patients.

Our study has several limitations. First, we used estimated instead of measured GFR. Imprecision and biases inherent in eGFR are greater at higher GFRs, thus restricting the accuracy of classification in the mildly decreased GFR group.[3] Second, patients with stage 4 or 5 CKD were excluded from the present study because of clinical concerns about the rapid deterioration in kidney function in a short period; this exclusion, together with the reported lack of a steep eGFR slope in a sample of the Japanese general population that included patients with stage 3 CKD probably made it difficult to generate a significant difference in the

Table 3. Adverse Events Until Week 108 of Treatment

	Placebo (n = 222)	Febuxostat (n = 219)
No. of adverse events	135 (60.8)	124 (56.6)
Hypersensitivity (eg, rash and eruption)	10 [0]	7 [0]
Liver dysfunction[a]	9 [0]	4 [0]
Reduced eGFR[a]	13 [3]	8 [3]
Cardiovascular disorders (eg, MI, angina pectoris, HF, and aortic aneurysm)	7 [3]	4 [3]
Stroke (cerebral infarction, cerebral hemorrhage, and subarachnoid hemorrhage)	2 [2]	1 [1]
Other abnormalities	128 [33]	119 [44]
Respiratory (including infections)	42 [5]	33 [4]
Gastrointestinal	32 [9]	39 [12]
Infections	10 [0]	7 [0]
Musculoskeletal	37 [5]	34 [8]
Blood chemistry	11 [0]	8 [0]
Cardiovascular system	9 [3]	3 [2]
Blood pressure changes	8 [0]	3 [0]
Arrhythmias	3 [1]	4 [3]
Ophthalmologic	11 [4]	10 [6]
Otorhinolaryngologic	15 [3]	19 [1]
Oral surgical and dental	6 [0]	5 [1]
Urologic	11 [2]	6 [4]
Endocrinologic (including DM and dyslipidemia)	14 [1]	10 [4]
Dermatologic	9 [1]	10 [1]
Central nervous system	4 [2]	2 [1]
Death	1[b] [1]	1[c] [1]
Others	10 [2]	13 [1]

Note: Numbers in brackets represent the number of serious adverse events. Blood pressure changes found by the attending physician
Abbreviations: DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HF, heart failure; MI, myocardial infarction.
[a]Found by the attending physician.
[b]Caused by lung cancer.
[c]Unspecified cause.

primary end point between study groups. Third, findings from the study may not be generalizable outside of Japan because of the exclusively Japanese study population and the use of a Japan-specific eGFR equation.

In conclusion, febuxostat did not show a statistically significant suppressing effect on eGFR decline as compared to placebo in patients with stage 3 CKD and asymptomatic hyperuricemia.

Supplementary Material

Table S1: Time-course changes in laboratory values.

Table S2: Numbers of adverse events per person-year.

Table S3: Numbers of serious adverse events per person-year.

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