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FASTTRACK CLINICAL RESEARCH
Disease management

Febuxostat for Cerebral and CaRdiorenovascular Events PrEvEntion StuDy

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Aims To compare the occurrence of cerebral, cardiovascular, and renal events in patients with hyperuricaemia treated with febuxostat and those treated with conventional therapy with lifestyle modification.

Methods and results This multicentre, prospective, randomized open-label, blinded endpoint study was done in 141 hospitals in Japan. A total of 1070 patients were included in the intention-to-treat population. Elderly patients with hyperuricaemia (serum uric acid >7.0 to ≤9.0 mg/dL) at risk for cerebral, cardiovascular, or renal disease, defined by the presence of hypertension, Type 2 diabetes, renal disease, or history of cerebral or cardiovascular disease, were randomized to febuxostat and non-febuxostat groups and were observed for 36 months. Cerebral, cardiovascular, and renal events and all deaths were defined as the primary composite event. The serum uric acid level at endpoint (withdrawal or completion of the study) in the febuxostat ($n = 537$) and non-febuxostat groups ($n = 533$) was 4.50 ± 1.52 and 6.76 ± 1.45 mg/dL, respectively ($P < 0.001$). The primary composite event rate was significantly lower in the febuxostat group than in non-febuxostat treatment [hazard ratio (HR) 0.750, 95% confidence interval (CI) 0.592–0.950; $P = 0.017$] and the most frequent event was renal impairment (febuxostat group: 16.2%, non-febuxostat group: 20.5%; HR 0.745, 95% CI 0.562–0.987; $P = 0.041$).

Conclusion Febuxostat lowers uric acid and delays the progression of renal dysfunction.

Registration ClinicalTrials.gov (NCT01984749).

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Keywords Febuxostat • Hyperuricaemia • Elderly patient • Cerebral disease • Cardiovascular disease • Renal disease

Introduction

Hyperuricaemia, an abnormally high serum uric acid level, is the cause of gout and is associated with arthritis and tophus.[1,2] Uric acid-lowering agents can prevent the recurrence of urate deposition-related diseases.[3] Previous studies revealed that hyperuricaemia may contribute to the development and progression of chronic kidney disease (CKD), cerebral and cardiovascular diseases, and mortality.[4–8] The metabolism of purine bases generates hypoxanthine, which is converted to uric acid in a two-step process catalysed by xanthine oxidoreductase, leading to a production of reactive oxygen species, which may be deeply associated with the development of cardiovascular events. Febuxostat, a nonpurine xanthine oxidoreductase inhibitor (XOI), was approved in 2011 in Japan, and clinical evaluation showed that febuxostat has a more potent serum uric acid-lowering action compared with allopurinol.[9,10] However, the superiority of XOI for better cardiovascular outcomes is controversial.[11,12] A recent cohort study revealed that there was no difference in the risk of all cause death and cardiovascular events between patients with febuxostat compared with allopurinol.[12] The Febuxostat vs. Placebo Randomized Controlled Trial Regarding Reduced Renal Function in Patients With Hyperuricaemia Complicated by Chronic Kidney Disease (CKD) Stage 3 (FEATHER) study demonstrated that febuxostat did not show a suppressing effect on the estimated glomerular filtration rate (eGFR) decline compared with placebo in patients with Stage 3 CKD and asymptomatic hyperuricaemia.[13] The Food and Drug Administration required the comparison of febuxostat and allopurinol for risk of serious adverse cardiovascular events; thus, a randomized controlled trial, the Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial, was performed. It clarified that all-cause mortality and cardiovascular mortality were higher with febuxostat treatment than with allopurinol treatment in gout patients with cardiovascular disease.[14] However, it remains to be elucidated whether the mortality results of the CARES trial are due to beneficial effects of allopurinol or deleterious effects of febuxostat.

In the present randomized controlled trial, Febuxostat for Cerebral and CaRdiorenovascular Events PrEvEntion StuDy (FREED), we aimed to compare the occurrence of cerebral, cardiovascular, and renal events in elderly patients with hyperuricaemia at risk for cerebral or cardiorenovascular disease treated with febuxostat and those treated with conventional therapy with lifestyle modification.

Methods

Study design

The study design and rationale have been reported previously.[15] Briefly, this study was a multicentre, prospective, randomized open-label, blinded endpoint, two-arm parallel treatment groups study conducted as an investigator-initiated study in accordance with the principles of the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies issued by the Ministry of Health, Labour and Welfare in Japan. This study protocol was reviewed by the central institutional review board prior to approval by the institutional review board of each participating study site, and all of the patients registered to this study gave written informed consent. A steering committee created the protocol of the FREED study, observed the progress and made decisions about the management of the study. The members of the Independent Data Monitoring Committee and Events Evaluation Committee, who were unaware of the treatment assignments, objectively assessed the safety and adjudicated all suspected endpoint events. This study was funded by a grant from Teijin Pharma Limited that was paid to the Kumamoto Circulation Society according to a support contract, but the sponsor had no involvement in the planning, implementation, analysis, or interpretation of study results. This study was registered at ClinicalTrials.gov (identification number NCT01984749).

Study population

Elderly patients aged 65 years or older with hyperuricaemia (serum uric acid >7.0 to ≤9.0 mg/dL) who had one or more risks for cerebral, cardiovascular, or renal disease were enrolled in this study before randomization (detailed inclusion and exclusion criteria are provided in Supplementary material online, *Table S1*). Established risks for cerebral, cardiovascular, or renal disease were defined as a history of or active hypertension, a history of or active Type 2 diabetes mellitus, renal disease (eGFR ≥30 to <60 mL/min/1.73 m^2 within 3 months prior to enrolment), and a history of cerebral or cardiovascular disease occurring >3 months prior to enrolment. The patients enrolled were followed up for 36 months. All participants provided written informed consent.

Randomization, dose adjustment, and procedure

Patients were randomly assigned in a 1:1 ratio to either febuxostat or non-febuxostat group. Randomization was stratified in accordance with sex, serum uric acid (<7.5 or ≥7.5 mg/dL), Type 2 diabetes mellitus, cerebrovascular or cardiovascular disease, eGFR (<45 or ≥45 mL/min/1.73 m^2), and each institution.

The treatment protocol of the study is shown in Supplementary material online, *Figure S1*. Outpatient visits were scheduled at screening, at enrolment, at randomization, at 4, 8, 12, 24 weeks after randomization and every 6 months during subsequent years of the study. In the febuxostat group, the investigators prescribed the febuxostat preparation (Feburic® tablets; Teijin Pharma Limited, Tokyo, Japan). Febuxostat has been orally administered once daily during the 36-month study period starting from the time of enrolment. Dose increase was performed as follows: (i) the starting febuxostat dose was 10 mg/day; (ii) at week 4, the dose was increased to 20 mg/day; (iii) at week 8, the dose was increased to the target dose of 40 mg/day. In the non-febuxostat group, administration of 100 mg of oral allopurinol was considered if serum uric acid was elevated during the study period starting from the time of enrolment. The dose of both febuxostat and allopurinol was adjusted to prevent

serum uric acid from decreasing to <2.0 mg/dL. Additionally, all patients underwent lifestyle modification for the management of hyperuricaemia. Serial proportion of patients with serum uric acid level <6.0 mg/dL and serum uric acid at endpoint were assessed. Regarding concomitant therapies during the study period, concurrent diseases and adverse events were appropriately treated at the discretion of the physicians in charge of this study. Therapies that already started at the time of enrolment in this study were continued during the study period without any change as much as possible. The following medications were not started or discontinued and their dosage was not changed as much as possible: antiplatelet agents, antihypertensive agents, antidiabetic agents, and antidyslipidaemic agents. Data on concomitant therapies were collected from the time of enrolment until study completion or withdrawal from the study.

Study endpoint

Fatal and non-fatal cerebral, cardiovascular and renal events, and death other than cerebral or cardiorenal vascular disease during the study period were defined as the primary composite endpoint in the study, which consisted of the following: (i) death due to cerebral, cardiovascular, or renal disease; (ii) new or recurring cerebrovascular disease [stroke (cerebral haemorrhage, cerebral infarction, subarachnoid haemorrhage, stroke of unknown type), transient ischaemic attack]; (iii) new or recurring non-fatal coronary artery disease (myocardial infarction, unstable angina); (iv) cardiac failure requiring hospitalization; (v) arteriosclerotic disease requiring treatment (aortic aneurysm, aortic dissection, and arteriosclerosis obliterans); (vi) renal impairment [development of microalbuminuria (≥30 to <300 mg/g·creatinine (Cr))/mild proteinuria (≥0.15 to <0.50 g/g·Cr), progression to overt albuminuria (≥300 mg/g·Cr)/severe proteinuria (≥0.50 g/g·Cr), or worsening of overt albuminuria confirmed by two consecutive laboratory tests performed after the initiation of study treatment; doubling of serum Cr level; progression to end-stage renal disease]; (vii) new atrial fibrillation (including paroxysmal atrial fibrillation); (viii) death due to other cause (Supplementary material online, *Table S2*). The secondary endpoint consisted of each component of cerebral, cardiovascular, and renal vascular events, and a hard endpoint was defined as a composite of death due to any cause, cerebrovascular disease or non-fatal coronary artery disease. Estimated glomerular filtration rate slopes per year were compared between the febuxostat and non-febuxostat groups. The relationship between serum uric acid at 12 weeks after randomization and primary composite endpoint was also assessed. The following parameters were assessed as the exploratory endpoint: (i) absolute values and changes in high-sensitivity C-reactive protein (hs-CRP), N-terminal pro-brain natriuretic peptide (NT-proBNP), and haemoglobin A1c (HbA1c); (ii) occurrence of malignant tumours; (iii) occurrence of venous thrombosis requiring treatment.

Statistical analysis

Approximately 500 patients were in each group to detect a difference in the occurrence of the primary composite endpoint between two groups, with 80% power at a two-sided 5% significant level.[15] Data were analysed using the intention-to-treat (ITT) population and expressed as mean ± standard deviation and percentage unless otherwise stated. Continuous variables that did not show a normal distribution are expressed as medians (25th to 75th percentile ranges). A safety analysis was also performed in the ITT population. The repeated-measure analysis of variance was used to compare the time course difference of uric acid levels between the two groups. The time from randomization to occurrence of any cerebral, cardiovascular, and renal events or all deaths was analysed. The Kaplan–Meier method was used to estimate the event rate based on the time of onset of the events and Greenwood's method was used to calculate the two-sided 95% confidence interval (CI). Intergroup comparisons were performed using the Cox proportional hazards model including stratification factors for randomization as a covariate. Secondary endpoints were analysed using Fine and Gray's subdistribution hazard model. The eGFR slope of each patient was calculated from a regression line of a series of eGFR values. Between-group difference of eGFR slopes and its 95% CI were calculated and examined by Wilcoxon rank sum test. The statistical significance level was set at $P < 0.05$. Statistical analysis was performed with SAS version 9.4 (SAS Institute, Cary, NC, USA) by persons in charge of statistical analysis, as instructed by the responsible biostatistician. The Independent Data Monitoring Committee had the responsibility to decide the continuation of this study in accordance with the assessment of the results of the interim analysis scheduled in advance.[15]

Results

Study patients

A total of 1184 patients (men and women) from 141 institutions throughout Japan from November 2013 to October 2014 were enrolled; 100 who declined to participate were subsequently excluded. Residual 1084 patients were randomly assigned, but 14 patients were excluded from the randomized population as a result of consent withdrawal (seven patients), inclusion ineligibility or exclusion criteria (five patients), loss at follow-up (one patient), and investigator's discretion (one patient) prior to data collection at baseline. Thus, 1070 patients were included in the ITT population, with 537 assigned to the febuxostat group and 533 assigned to the non-febuxostat group (*Figure 1*). Baseline patient characteristics were well balanced between the two groups (*Table 1* and Supplementary material online, *Table S3*). The maximum dose during the study period and the dose at endpoint (withdrawal or completion of the study) of the febuxostat group are shown in Supplementary material online, *Table S4*. The mean febuxostat dose per day was 29.1 ± 12.3 mg at endpoint, and 67.4% of the patients received 40 mg in the febuxostat group, whereas 27.2% of the patients received 100 mg allopurinol in the non-febuxostat group (*Figure 1*). Supplementary material online, *Figure S2* shows the serum uric acid level at the initiation of allopurinol administration (mean ± standard deviation 8.18 ± 1.05 mg/dL).

The median follow-up duration (from randomization to endpoint of the study) in the febuxostat and non-febuxostat groups was 35.5 and 35.1 months, respectively. The overall withdraw ratio for reasons other than the primary composite endpoint during the study was 17.0% (16.8% in the febuxostat group and 17.3% in the non-febuxostat group). Patient reason and agreement withdrawal was 9.3% and 8.5%, respectively. There were no patients with continuous levels of serum uric acid >11.0 mg/dL in either group (*Figure 1*).

Serum uric acid

Changes in mean serum uric acid level during the study are shown in *Figure 2*. Serum uric acid levels were comparable at baseline between the febuxostat and non-febuxostat groups. However, the levels continued to be significantly lower in the febuxostat group than in the non-febuxostat group after randomization ($P < 0.001$). At endpoint, the serum uric acid level in the febuxostat group was significantly lower than that in the non-febuxostat group (4.50 ± 1.52 vs. 6.76 ± 1.45 mg/dL, $P < 0.001$).

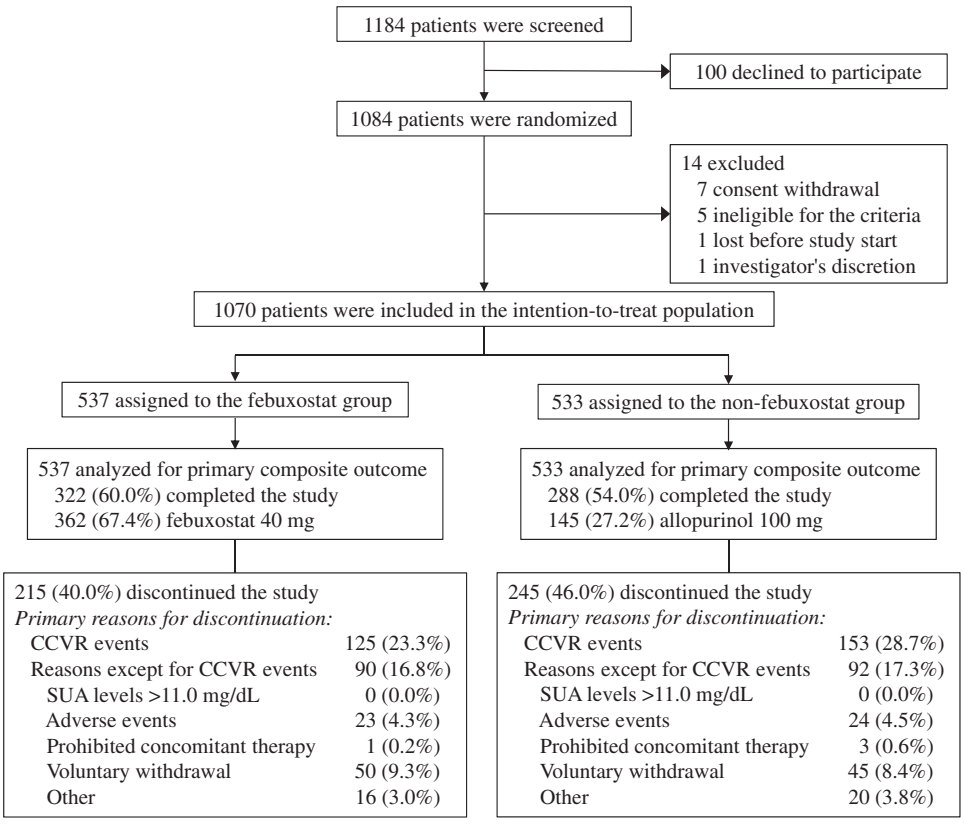


Figure 1 Patient distribution. CCVR, cerebral, cardiovascular and renal; SUA, serum uric acid.

The proportion of patients with serum uric acid levels <6.0 mg/dL are shown in Supplementary material online, *Table S5*. More than 85% of the patients in the febuxostat group achieved uric acid levels <6.0 mg/dL within 12 weeks, whereas less than 30% of the patients in the non-febuxostat group achieved uric acid levels <6.0 mg/dL at endpoint (Supplementary material online, *Figure S3*).

Primary endpoint

During the study period, the primary composite endpoint was observed in 125 patients (23.3%) in the febuxostat group and in 153 patients (28.7%) in the non-febuxostat group (*Table 2*). The Kaplan–Meier curves for the primary composite endpoint are shown in *Take home figure*. There was significant difference in the primary composite endpoint between the two groups after adjustment with stratification factors for randomization.

Secondary endpoint

In the individual component of the primary composite endpoint, the most frequent event was renal impairment (*Table 2*). Amongst renal impairment, the development of microalbuminuria or mild proteinuria was common in the febuxostat and non-febuxostat groups (Supplementary material online, *Table S6*). Regarding a hard endpoint, there was a no significant difference between the groups (*Table 2* and Supplementary material online, *Figure S4*).

The hazard risk of the primary endpoint in each prespecified subgroup by baseline variables is shown in *Figure 3*. Significant heterogeneity for possible interactions between febuxostat treatment and baseline variable was not observed in subgroup. Supplementary material online, *Figure S5* shows the serial changes in eGFR during the study period. Estimated glomerular filtration rate slopes per year revealed no significant difference in the mean eGFR slope between the febuxostat and non-febuxostat groups [-0.37 (-2.32 to 1.44) vs. -0.69 (-2.63 to 1.39) mL/min/1.73 m^2, $P = 0.606$]. No significant relationship was observed between serum uric acid at 12 weeks after randomization and primary composite endpoint ($n = 980$, $P = 0.121$) (Supplementary material online, *Figure S6A*). However, serum uric acid level >7 mg/dL was a strong risk factor compared with >5 to ≤6 mg/dL after adjustment with stratification factors for randomization (Supplementary material online, *Figure S6B*).

Exploratory endpoint

The hs-CRP and NT-proBNP levels at each measured point and at endpoint were comparable between febuxostat and non-febuxostat groups. However, the HbA1c levels at 30 months ($P = 0.024$), 36 months ($P = 0.021$) and at endpoint ($P = 0.035$) were significantly lower in the febuxostat group than in the non-febuxostat group (Supplementary material online, *Figure S7*).

Table 1 Baseline characteristics of the study patients

	Total (n = 1070)	Febuxostat group (n = 537)	Non-febuxostat group (n = 533)	P-value (febuxostat vs. non-febuxostat)
Male	739 (69.1)	371 (69.1)	368 (69.0)	1.000
Age (years)	75.7 ± 6.6	75.4 ± 6.7	76.0 ± 6.5	0.137
Body mass index (kg/m^2)	24.67 ± 3.68	24.74 ± 3.71	24.61 ± 3.65	0.325
Haemoglobin (g/dL)	13.51 ± 1.63	13.55 ± 1.60	13.46 ± 1.65	0.424
Total protein (g/dL)	7.20 ± 0.46	7.20 ± 0.45	7.19 ± 0.46	0.928
Total bilirubin (mg/dL)	0.60 ± 0.28	0.62 ± 0.30	0.59 ± 0.28	0.299
Hypertension	1007 (94.1)	506 (94.2)	501 (94.0)	0.897
Systolic blood pressure (mmHg)	132.6 ± 14.4	132.9 ± 14.8	132.3 ± 14.0	0.426
Diastolic blood pressure (mmHg)	73.5 ± 10.2	73.5 ± 10.2	73.6 ± 10.2	0.716
Type 2 diabetes	396 (37.0)	197 (36.7)	199 (37.3)	0.849
Haemoglobin A1c (%)	5.87 ± 0.62	5.87 ± 0.63	5.87 ± 0.60	0.815
Hyperlipidaemia	622 (58.1)	317 (59.0)	305 (57.2)	0.577
LDL cholesterol (mg/dL)	107.3 ± 29.7	108.3 ± 31.2	106.3 ± 28.1	0.421
HDL cholesterol (mg/dL)	54.3 ± 14.9	54.2 ± 14.9	54.4 ± 15.0	0.812
Triglyceride (mg/dL)	137.0 (96.0–191.0)	135.0 (96.0–193.5)	138.0 (94.0–189.0)	0.757
Renal disease[a]	707 (66.1)	357 (66.5)	350 (65.7)	0.796
eGFR (mL/min/1.73 m^2)	54.98 ± 14.64	54.62 ± 14.11	55.35 ± 15.16	0.608
Alcohol habit	477 (44.6)	239 (44.5)	238 (44.7)	1.000
Active smoking	461 (43.1)	222 (41.3)	239 (44.8)	0.267
Coronary artery disease	90 (8.4)	45 (8.4)	45 (8.4)	1.000
Chronic heart failure	74 (6.9)	41 (7.6)	33 (6.2)	0.393
Stroke	86 (8.0)	39 (7.3)	47 (8.8)	0.370
Vascular disease	25 (2.3)	9 (1.7)	16 (3.0)	0.162
Malignant tumour	32 (3.0)	15 (2.8)	17 (3.2)	0.724
hs-CRP (mg/dL)	0.080 (0.040–0.170)	0.082 (0.040–0.172)	0.078 (0.039–0.167)	0.520
NT-proBNP (pg/mL)	119.0 (59.0–264.0)	114.0 (58.0–268.0)	124.0 (62.0–263.0)	0.328
Serum uric acid (mg/dL)	7.52 ± 1.05	7.54 ± 1.06	7.50 ± 1.03	0.324
Urinary albumin (mg/g·Cr)	17.8 (7.8–64.3)	17.4 (7.5–54.8)	19.5 (8.3–67.45)	0.278
Urinary protein (g/g·Cr)	0.084 (0.044–0.165)	0.082 (0.043–0.163)	0.086 (0.044–0.170)	0.558

Values are presented as n (%), mean ± standard deviation, or median (25th–75th percentile ranges).
Cr, creatinine; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; NT-proBNP, N-terminal pro-brain natriuretic peptide.
[a]Renal disease defined as eGFR <60 mL/min/1.73 m^2.

The occurrence of malignant tumours in the febuxostat [n = 21 (3.9%)] and non-febuxostat groups [n = 25 (4.7%)] was comparable (P = 0.529). Venous thrombosis requiring treatment was not observed in either group, but the development of gout flares was lesser in the febuxostat group [n = 6 (1.1%)] than in the non-febuxostat group [n = 14 (2.6%), P = 0.069) during the study period.

Discussion

The present FREED study demonstrated that febuxostat significantly decreased serum uric acid levels, and its effect was associated with reduction of cerebral, cardiovascular, and renal events as the primary composite endpoint in patients aged 65 years or older with hyperuricaemia compared with conventional therapy with lifestyle modification. In a primary composite endpoint, renal events were clearly reduced by febuxostat treatment. Our results are consistent with and expanded those of previous studies.[16,17] The FREED study showed a large difference in the lowering of the uric acid level in the febuxostat and non-febuxostat (conventional therapy) groups. Oxidative stress generated by the metabolic converting step from xanthine to uric acid may enhance the progression of atherosclerosis through induction of endothelial injury.[18,19] Thus, it is a reasonable therapy for hyperuricaemia to control serum uric acid level with strong uric acid-lowering effect of XOI, which may lead to better cardiovascular outcomes.

In the CARES trial, all-cause mortality and cardiovascular mortality were higher with febuxostat than those with allopurinol, but these two XOIs yielded similar result with respect to rates of adverse cerebral and cardiovascular events.[14] The FREED study demonstrated that lowering of uric acid with febuxostat may contribute to better prognosis than conventional therapy in our primary composite

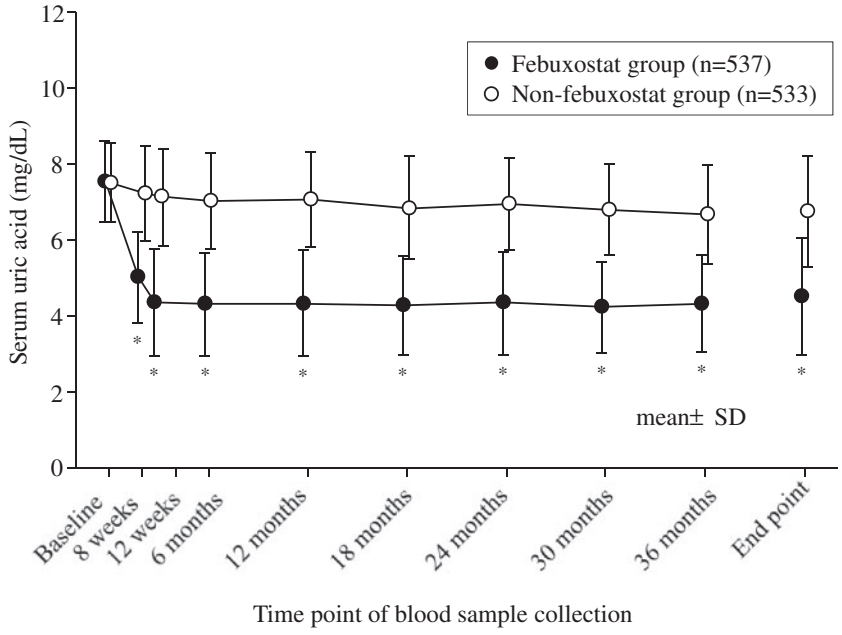


Figure 2 Serial changes in serum uric acid level in the febuxostat and non-febuxostat groups. Analysis of variance and Holm method as a *post hoc* analysis were used. Closed circle, febuxostat group; open circle, non-febuxostat group. Values are presented as mean ± standard deviation. *$P < 0.001$ (Holm method).

Table 2 Hazard ratio and 95% CIs for component of the primary and secondary endpoints

	Febuxostat group ($n = 537$)	Non-febuxostat group ($n = 533$)	Hazard ratio (95% confidence interval)	*P*-value
Primary endpoint				
Composite of death due to any cause, cerebrovascular disease, non-fatal coronary artery disease, heart failure requiring hospitalization, arteriosclerotic disease requiring treatment, renal impairment, and atrial fibrillation	125 (23.3)	153 (28.7)	0.750 (0.592–0.950)	0.017
Secondary endpoints				
Death due to cerebral, cardiovascular, or renal disease	6 (1.1)	6 (1.1)	0.958 (0.314–2.926)	0.940
Cerebrovascular disease	9 (1.7)	7 (1.3)	1.271 (0.479–3.371)	0.630
Non-fatal coronary artery disease	4 (0.7)	7 (1.3)	0.559 (0.167–1.869)	0.345
Heart failure requiring hospitalization	9 (1.7)	12 (2.3)	0.699 (0.290–1.689)	0.427
Arteriosclerotic disease requiring treatment	2 (0.4)	3 (0.6)	0.644 (0.107–3.873)	0.631
Renal impairment	87 (16.2)	109 (20.5)	0.745 (0.562–0.987)	0.041
Atrial fibrillation	4 (0.7)	3 (0.6)	1.320 (0.292–5.968)	0.719
Death due to other causes	4 (0.7)	6 (1.1)	0.635 (0.179–2.253)	0.482
Hard endpoint: composite of death due to any cause, cerebrovascular disease, or non-fatal coronary artery disease	23 (4.3)	26 (4.9)	0.861 (0.492–1.506)	0.600

Values are presented as *n* (%).
CI, confidence interval.

outcome, although fatal and non-fatal cerebral and cardiovascular events were similar. Differences in these results can be attributed to the presence of gout. For example, in the CARES trial, there was an interaction between febuxostat and allopurinol groups in terms of non-steroidal anti-inflammatory drugs use and absence of low-dose aspirin use, which could lead to increased cardiovascular events.[20] Moreover, approximately half of the patients discontinued treatment during the trial. According to Choi *et al.*,[21] the use of non-XOI or

	Febuxostat group (n=537)		Non-febuxostat group (n=533)		Hazard ratio (95% CI)	p Value*
	n/N	%	n/N	%		
Sex						
Male	76/371	20.5	109/368	29.6	0.634 (0.473-0.851)	0.062
Female	49/166	29.5	44/165	26.7	1.076 (0.712-1.626)	
Age						
<75 years	43/250	17.2	69/241	28.6	0.578 (0.394-0.847)	0.088
≥75 years	82/287	28.6	84/292	28.8	0.889 (0.654-1.206)	
Body mass index						
<25 kg/m^2	68/282	24.1	86/299	28.8	0.805 (0.585-1.108)	0.529
≥25 kg/m^2	55/243	22.6	64/221	29.0	0.683 (0.475-0.982)	
Active smoking						
Yes	48/222	21.6	77/239	32.2	0.635 (0.442-0.913)	0.232
No	77/315	24.4	76/294	25.9	0.859 (0.624-1.183)	
Alcohol habitat						
Yes	45/239	18.8	70/238	29.4	0.586 (0.402-0.854)	0.112
No	80/298	26.8	83/295	28.1	0.878 (0.645-1.195)	
Hypertension						
Yes	120/506	23.7	141/501	28.1	0.779 (0.610-0.994)	0.235
No	5/31	16.1	12/32	37.5	0.501 (0.167-1.500)	
Type 2 diabetes						
Yes	48/197	24.4	65/199	32.7	0.678 (0.466-0.987)	0.524
No	77/340	22.6	88/334	26.3	0.804 (0.592-1.093)	
Hyperlipidaemia						
Yes	69/317	21.8	89/305	29.2	0.674 (0.491-0.924)	0.339
No	56/220	25.5	64/228	28.1	0.849 (0.591-1.218)	
Coronary artery disease						
Yes	15/45	33.3	19/45	42.2	0.636 (0.318-1.271)	0.475
No	110/492	22.4	134/488	27.5	0.775 (0.602-0.998)	
Chronic heart failure						
Yes	16/41	39.0	13/33	39.4	0.807 (0.365-1.784)	0.981
No	109/496	22.0	140/500	28.0	0.744 (0.579-0.956)	
Stroke						
Yes	9/39	23.1	15/47	31.9	0.668 (0.286-1.563)	0.767
No	116/498	23.3	138/486	28.4	0.750 (0.586-0.961)	
Vascular disease						
Yes	3/9	33.3	7/16	43.8	1.084 (0.233-5.048)	0.986
No	122/528	23.1	146/517	28.2	0.755 (0.593-0.960)	
Malignant tumour						
Yes	2/15	13.3	6/17	35.3	0.411 (0.068-2.484)	0.233
No	123/522	23.6	147/516	28.5	0.769 (0.605-0.977)	
Antiplatelet agents						
Yes	43/159	27.0	56/179	31.3	0.716 (0.479-1.071)	0.648
No	82/378	21.7	97/354	27.4	0.785 (0.584-1.054)	
Serum uric acid						
<7.5 mg/dL	28/152	18.4	45/155	29.0	0.546 (0.338-0.881)	0.180
≥7.5 mg/dL	97/385	25.2	108/378	28.6	0.827 (0.629-1.089)	
Estimated glomerular filter rate						
<60 mL/min/1.73 m^2	93/357	26.1	87/302	28.8	0.791 (0.578-1.081)	0.751
≥60 mL/min/1.73 m^2	32/180	17.8	65/229	28.4	0.744 (0.515-1.076)	
Total protein						
<6.5 g/dL	3/23	13.0	12/30	40.0	0.319 (0.079-1.298)	0.122
≥6.5 g/dL	122/513	23.8	140/501	27.9	0.790 (0.619-1.008)	
Haemoglobin						
<13 g/dL	47/167	28.1	62/195	31.8	0.828 (0.564-1.214)	0.634
≥13 g/dL	78/369	21.1	90/336	26.8	0.733 (0.540-0.994)	
Total bilirubin						
<1.2 mg/dL	120/511	23.5	146/515	28.3	0.760 (0.596-0.967)	0.649
≥1.2 mg/dL	5/25	20.0	6/16	37.5	0.538 (0.098-2.944)	
hs-CRP						
<0.1 mg/dL	66/306	21.6	88/313	28.1	0.698 (0.506-0.961)	0.464
≥0.1 mg/dL	59/230	25.7	64/218	29.4	0.823 (0.577-1.175)	
NT-proBNP						
<125 pg/mL	56/283	19.8	69/267	25.8	0.719 (0.505-1.024)	0.661
≥125 pg/mL	69/253	27.3	83/264	31.4	0.797 (0.578-1.098)	
Urinary albumin						
<30 mg/g·Cr	69/337	205	76/305	24.9	0.710 (0.509-0.988)	0.608
≥30 mg/g·Cr	56/198	28.3	76/223	34.1	0.785 (0.554-1.114)	
Urinary protein						
<0.15 g/g·Cr	88/388	22.7	102/373	27.3	0.751 (0.563-1.001)	0.871
≥0.15 g/g·Cr	37/147	25.2	50/155	32.3	0.784 (0.509-1.209)	

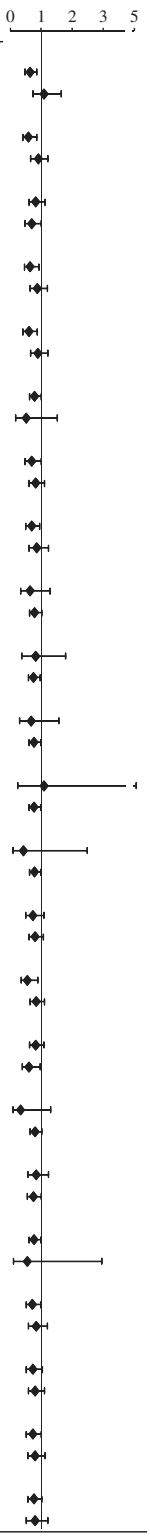
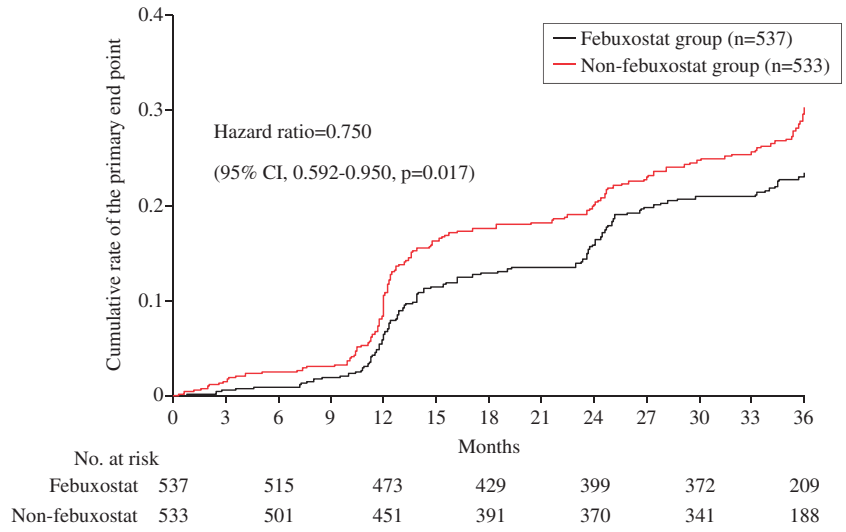


Figure 3 The 95% confidence interval and adjusted hazard ratios for the primary composite event. **P*-value less than 5% indicates significant heterogeneity of hazard ratios between the two groups. CI, confidence interval; Cr, creatinine; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro-brain natriuretic peptide.



Take home figure The Kaplan–Meier curves for the primary composite event. Black line, febuxostat group; red line, non-febuxostat group.

placebo group is needed to determine whether the results of the CARES trial were due to the beneficial effects of allopurinol or the deleterious effects of febuxostat. Since it is unethical to compare the treatment with XOI with placebo, our findings might address this question, but our results do not solve this problem directly. In our comparison of the use of febuxostat and conventional therapy with allopurinol 100 mg as low as 27% of the patients, we had a low number of patient dropouts. Our results showed that major cerebrocardiovascular events and mortality were similar between the febuxostat and non-febuxostat groups. The FEATHER study did not find an increased number of cardiovascular events with febuxostat in comparison to placebo,[13] which can lead to the conclusion that, in the CARES trial, allopurinol may have a beneficial impact on mortality rather than febuxostat having deleterious effects.

There was a large difference in the incidence of renal impairment, assessed by the development of albuminuria or proteinuria, which would lead to the progression of CKD. Patients with CKD have increased morbidity and mortality as a result of cardiovascular events. Therefore, albuminuria is not only a risk factor for adverse cardiovascular outcomes but may also be a therapeutic target or an indicator of therapeutic response.[22,23] Febuxostat decreased the exacerbation of albuminuria or proteinuria in the FREED study, and it has been suggested that febuxostat has better renoprotective effect than allopurinol.[17] However, febuxostat could not improve the serial change of eGFR, similar to the result of the FEATHER study. Compared with the renal protection from XOIs, febuxostat may not aggravate kidney function, but no cardiovascular protection may be expected. Based on the results of the CARES trial, the FEATHER study and the present study, treatment with febuxostat did not reduce major cerebrocardiovascular events. Febuxostat decreased the development of gout attacks in the present study. However, no significant reduction in hs-CRP was demonstrated in the febuxostat group compared with the non-febuxostat group during the study period. Secondary explanatory analysis of the CANTOS trial, showing a reduction of inflammation and a lower rate of recurrent cardiovascular events, recently disclosed that canakinumab administration was associated with reduced risk for gout attacks without any change in serum uric acid levels.[24] Hybrid treatment with febuxostat and inhibitors of interleukin-1β may be useful not only in preventing gout attacks but also in yielding cerebral, cardiovascular, and renal benefits.

Our study should be interpreted with caution. First, we included patients with asymptomatic hyperuricaemia without gout, which was different from previous studies, including the CARES trial. Although comparison of our results with those of previous studies would be difficult, our findings are an important for hyperuricaemic patients without gout in the primary care setting.

Second, our sample size was limited, and we employed not only hard endpoints but also relatively soft endpoints, such as development of albuminuria/proteinuria. Additionally, observation period was relatively short. However, the deterioration of renal function as a part of our primary composite outcome is an important marker for CKD,[25] because the prevalence of patients with CKD was predicted as 13% of the Japanese adult population.[26] Our findings have possible important applications in the preventive therapy of asymptomatic hyperuricaemic patients with high renal risk.

High serum uric acid level has a clear relationship with development of renal disease.[27,28] Febuxostat was also reported to be more suitable than allopurinol for patients with moderate to severe renal dysfunction.[29] These findings, as well as the result of our study, shows that evaluation of soft endpoints may be clinically important for patients with hyperuricaemia treated with febuxostat.

In conclusion, febuxostat lowers uric acid and delays the progression of renal dysfunction.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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