C-reactive Protein Levels and Cardiovascular Outcomes After Febuxostat Treatment in Patients with Asymptomatic Hyperuricemia: Post-hoc Analysis of a Randomized Controlled Study

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Research Article

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Abstract

Purpose: Inflammation plays an important role in the initiation and progression of atherosclerosis, leading to poor clinical outcomes. Hyperuricemia is associated with the activation of the Nod-like receptor protein 3 inflammasome. Here, we investigated whether inhibition of inflammation using febuxostat lowered the risk of cardiovascular events.

Methods: This is a post-hoc analysis of the randomized trial, Febuxostat for Cerebral and CaRdiorenovascular Events PrEvEntion StuDy (FREED). In total, 1,067 patients (736 men and 331 women) were included in the analysis. We compared the serial changes in high-sensitivity C-reactive protein (hs-CRP) levels between febuxostat and non-febuxostat groups and assessed the correlation between the changes in uric acid (UA) and hs-CRP levels after febuxostat treatment. We also determined whether febuxostat could reduce a hard endpoint, defined as a composite of cardiovascular events and all-cause mortality.

Results: Serum UA levels in the febuxostat group were significantly lower than those in the non-febuxostat group after randomization ($p<0.05$). However, hs-CRP levels were comparable between the two groups during the study. No significant correlation was observed between the changes in UA and hs-CRP levels after febuxostat treatment. The hard endpoints did not differ significantly between the two groups. In patients with baseline hs-CRP levels $\geq$ 0.2 mg/dL or those administered 40 mg of febuxostat, the drug did not reduce hs-CRP levels or decrease the hard endpoint.

Conclusion: Febuxostat reduced the UA levels but did not affect the CRP levels, and therefore may fail to decrease cardiovascular outcomes after treatment.

Trial Registration: ClinicalTrial.gov (NCT01984749).

https://clinicaltrials.gov/ct2/show/NCT01984749

Introduction

Uric acid (UA) is a product of purine nucleotide metabolism. The presence of a non-functional human uricase-encoding gene leads to fluctuations in serum UA levels, which may result in the development of gout [1, 2]. Hyperuricemia has been associated with cerebral and cardiovascular disease and chronic kidney disease [3–6]. Xanthine oxidase inhibitors (XOIs) decrease serum UA levels and may exert a beneficial effect on the cardiovascular system by reducing oxidative stress in the vasculature [7]. Studies have shown that the XOI, allopurinol, can reduce recurrent myocardial infarction and cardiovascular events, although the detailed mechanisms have not been elucidated [8, 9].

Atherosclerosis is no longer considered to occur solely due to lipoprotein accumulation in the arterial wall, as inflammation plays an important role in the initiation and progression of this disease [10]. Anti-inflammatory therapy with canakinumab significantly lowers the rate of recurrent cardiovascular events

independent of the decrease in lipid levels [11]. Agents targeting vascular inflammation are used as adjunctive therapeutics for patients with residual inflammatory risk. Hyperuricemia is associated with inflammatory disorders, as soluble urate and monosodium urate crystals may induce inflammation [12–14]. In patients with asymptomatic hyperuricemia, allopurinol reduces UA levels, which has the beneficial effect of modulating inflammatory cytokine levels [15]. The XOI febuxostat suppresses Nod-like receptor protein 3 (NLRP3) inflammasome-mediated interleukin 1β (IL-1β) secretion and may ameliorate complex chronic inflammatory disorders in patients with hyperuricemia [16, 17].

Recently, the Febuxostat for Cerebral and CaRdiorenovascular Events PrEvEntion StuDy (FREED) demonstrated that compared to conventional therapy with lifestyle modifications, febuxostat significantly decreased UA levels, which was associated with a composite reduction of cerebral, cardiovascular, and renal events in older patients with asymptomatic hyperuricemia. However, FREED did not report a decrease in mortality, cerebrovascular disease, or non-fatal coronary artery disease [18]. We hypothesized that an approach involving inhibition of inflammation using febuxostat might lower cerebral and cardiovascular events and mortality, and investigated this hypothesis using post-hoc analysis of FREED data. Our results provide new insights into the potential of febuxostat as an anti-inflammatory agent with beneficial cardiovascular outcomes in a high-risk aged population with hyperuricemia.

Methods

The FREED was a randomized, open-label, and blinded study conducted following 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. All the patients registered with the FREED provided written informed consent. In this post-hoc analysis, 1,070 patients from the FREED were analyzed, and the requirement for informed consent was waived. The study was conducted between 2013 and 2017. Older patients (age: ≥65 years) with hyperuricemia (serum UA > 7.0 to ≤ 9.0 mg/dL) and one or more risk factors for cerebral, cardiovascular, or renal disease were enrolled in this study (detailed inclusion and exclusion criteria are provided elsewhere) [19]. Established risk factors for cerebral, cardiovascular, or renal disease were defined as a history of active hypertension, active type 2 diabetes mellitus, renal disease (estimated glomerular filtration rate [eGFR] of ≥ 30 to < 60 mL/min/1.73 m^2 within 3 months before enrollment), and cerebral or cardiovascular disease present for > 3 months before enrollment. Enrolled patients were followed up for 36 months.

An internet-based central dynamic randomization method was used to allocate 1,084 enrolled patients into febuxostat and non-febuxostat groups in a 1:1 ratio. Randomization was stratified according to sex; serum UA levels, presence of type 2 diabetes mellitus, cerebrovascular disease, or cardiovascular disease; eGFR; and the participating institution. Fourteen patients were excluded because of consent withdrawal (seven patients), inclusion ineligibility (five patients), loss at follow-up (one patient), and investigator's discretion (one patient) before data collection at baseline. Five patients in the febuxostat group and nine patients in the non-febuxostat group were excluded; in total, 1,070 patients were included in the intention-to-treat population, with 537 assigned to the febuxostat group and 533 to the non-febuxostat group.

Blood examination of the patients, including determination of serum UA levels, was conducted at the time of randomization, 4, 8, 12, and 24 weeks after randomization, and every 6 months during the subsequent years of the study. Febuxostat was orally administered once daily during the 36-month study, starting from the time of enrollment. The dose was increased 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. The febuxostat dose was adjusted to prevent serum UA from decreasing to < 2.0 mg/dL. Additionally, all patients underwent lifestyle modifications to manage their hyperuricemia. In the non-febuxostat group, administration of 100 mg oral allopurinol was considered if serum UA levels increased during the study, starting from the time of enrollment (see Figure, Supplemental Digital Content 2).

In this study, non-fatal cerebral and cardiovascular events and all-cause death during the study period were defined as the composite endpoint (a hard endpoint) as follows: (i) Death due to cerebral or cardiovascular disease; (ii) new or recurrent cerebrovascular disease (stroke [cerebral hemorrhage, cerebral infarction, subarachnoid hemorrhage, stroke of unknown type], transient ischemic attack); (iii) new or recurring non-fatal coronary artery disease (myocardial infarction, unstable angina); (iv) death due to other causes [18, 19].

Statistical analysis

Participants were encouraged to reduce UA levels based on previous guidelines on the management of gout, which state that achieving and maintaining a serum UA target level of at least < 6 mg/dL is strongly recommended for all patients receiving urate-lowering therapy [20, 21]. Data are expressed as the mean ± standard deviation and percentage unless otherwise stated. Continuous variables that did not show normal distribution were expressed as the median (25th – 75th percentile). Categorical variables were compared using the χ^2 test or Fisher's exact test, and continuous variables were compared using the Student's *t*-test or the Wilcoxon rank-sum test. Pearson's correlation coefficients were used to evaluate the relationships. Changes in UA and high-sensitivity C-reactive protein (hs-CRP) levels were calculated as the difference between those at 6 months and baseline. Repeated-measures analysis of variance was used to compare the differences in UA and hs-CRP levels between groups using Holm's test, if necessary. The time from randomization to the occurrence of death or any cerebral cardiovascular event was analyzed. The Kaplan–Meier method was used to estimate the event rate based on the time of onset of the events and was compared using Gray's test. A hard endpoint was analyzed using the Fine–Gray's subdistribution hazard model. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

FREED participants at baseline in the febuxostat and non-febuxostat groups

Hs-CRP levels were not measured at baseline for three patients (one in the febuxostat group and two in the non-febuxostat group); therefore, the data of 1,067 patients (536 in the febuxostat group and 531 in the non-febuxostat group) were analyzed. The baseline clinical characteristics are presented as a table in the supplementary material (Supplemental Digital Content 1). In the febuxostat group, the mean febuxostat dose per day was 29.1±12.3 mg at the endpoint, and 67.4% of the patients received 40 mg of the drug. In contrast, 27.1% of the patients in the non-febuxostat group received 100 mg of allopurinol. The median follow-up durations (from randomization to study endpoint) for the febuxostat and non-febuxostat groups were 35.5 and 35.1 months, respectively.

UA and hs-CRP levels and the hard endpoint

Serum UA levels were comparable at baseline between the febuxostat and non-febuxostat groups (7.54±1.06 vs 7.50±1.03 mg/dL, p=0.479). However, the levels were significantly lower in the febuxostat group than those in the non-febuxostat group after randomization (8 weeks, 5.01±1.19 vs 7.21±1.26 mg/dL, p<0.05; 12 weeks, 4.36±1.40 vs 7.13±1.27 mg/dL, p<0.05; 6 months, 4.31±1.35 vs 7.02±1.27 mg/dL, p<0.05; 12 months, 4.33±1.38 vs 7.05±1.26 mg/dL, p<0.05; 18 months, 4.28±1.29 vs 6.84±1.34 mg/dL, p<0.05; 24 months, 4.34±1.34 vs 6.94±1.21 mg/dL, p<0.05; 30 months, 4.22±1.21 vs 6.79±1.20 mg/dL, p<0.05; 36 months, 4.32±1.28 vs 6.67±1.28 mg/dL, p<0.05). At the endpoint, the serum UA 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<0.05) (Figure 1a).

Changes in hs-CRP levels are shown in Figure 1b. Hs-CRP levels were comparable at baseline (0.082 [0.040–0.172] vs 0.078 [0.039–0.167] mg/dL, p=0.643) and during the study between the febuxostat and non-febuxostat groups (6 months, 0.082 [0.043–0.189] vs 0.078 [0.037–0.178] mg/dL, p=1.000; 12 months, 0.081 [0.044–0.211] vs 0.071 [0.035–0.186] mg/dL, p=0.844; 24 months, 0.083 [0.043–0.184] vs 0.081 [0.037–0.172] mg/dL, p=1.000; 36 months, 0.083 [0.038–0.181] vs 0.082 [0.037–0.229] mg/dL, p=1.000; endpoint, 0.090 [0.044–0.236] vs 0.082 [0.038–0.223] mg/dL, p=0.855). Although UA levels were reduced by febuxostat at 6 months from baseline, there was no significant correlation between the changes in UA and hs-CRP levels (r=0.08, p=0.08) (Figure 2).

A hard endpoint was observed in 23 patients (4.3%) in the febuxostat group (cardiovascular mortality, six patients [1.1%]; cerebrovascular disease, nine patients [1.7%]; non-fatal coronary artery disease, four patients [0.7%]; death due to other causes, four patients [0.7%]) and 25 patients (4.7%) in the non-febuxostat group (cardiovascular mortality, six patients [1.1%]; cerebrovascular disease, seven patients [1.3%]; non-fatal coronary artery disease, seven patients [1.3%]; death due to other causes, five patients [0.9%]). The Kaplan–Meier curves for the hard endpoints are shown in Figure 3. The two groups did not differ significantly after adjusting for stratification factors for randomization (hazard ratio [HR], 0.889; 95% confidence interval [CI], 0.506–1.564).

Hard endpoint by baseline hs-CRP levels

We divided all patients treated with febuxostat into two groups according to hs-CRP levels at baseline, ≥0.2 or <0.2 mg/dL. After febuxostat treatment, the hs-CRP level in 122 patients was ≥0.2 mg/dL, while it was <0.2 mg/dL in 414 patients. Serum UA levels were comparable at baseline (7.68±1.12 vs 7.50±1.04 mg/dL, p=0.103) and were similarly reduced (8 weeks, 5.02±1.16 vs 5.01±1.20 mg/dL, p=1.000; 12 weeks, 4.10±1.34 vs 4.44±1.41 mg/dL, p=0.094; 6 months, 4.08±1.34 vs 4.38±1.35 mg/dL, p=0.094; 12 months, 4.09±1.48 vs 4.40±1.34 mg/dL, p=0.092; 18 months, 4.21±1.40 vs 4.30±1.25 mg/dL, p=1.000; 24 months, 4.05±1.38 vs 4.43±1.32 mg/dL, p=0.092; 30 months, 4.00±1.26 vs 4.27±1.20 mg/dL, p=0.224; 36 months, 4.07±1.24 vs 4.39±1.28 mg/dL, p=0.105). However, serum UA levels were lower in patients with hs-CRP ≥0.2 mg/dL at the endpoint (4.22±1.52 vs 4.59±1.51 mg/dL, p=0.007) (see Figure, Supplemental Digital Content 3a). Hs-CRP levels ≥0.2 mg/dL remained high at baseline (0.417 [0.268–0.500] vs 0.062 [0.032–0.103] mg/dL, p<0.05), during the study period (6 months, 0.212 [0.112–0.397] vs 0.066 [0.035–0.121] mg/dL, p<0.05; 12 months, 0.270 [0.121–0.500] vs 0.070 [0.037–0.139] mg/dL, p<0.05; 24 months, 0.195 [0.101–0.552] vs 0.069 [0.036–0.147] mg/dL, p<0.05; 36 months, 0.206 [0.085–0.445] vs 0.065 [0.030–0.134] mg/dL, p<0.05), and at the endpoint (0.266 [0.113–0.500] vs 0.069 [0.034–0.145] mg/dL, p<0.05) (see Figure, Supplemental Digital Content 4b). In the non-febuxostat group, hs-CRP levels were ≥0.2 mg/dL in 109 patients and <0.2 mg/dL in 422 patients. Serum UA levels were comparable at baseline (7.41±1.10 vs 7.52±1.01 mg/dL, p=0.341). Serum UA levels were also similar during the study (8 weeks, 7.05±1.22 vs 7.25±1.27 mg/dL, p=1.000; 12 weeks, 7.14±1.17 vs 7.12±1.29 mg/dL, p=1.000; 6 months, 6.95±1.40 vs 7.04±1.23 mg/dL, p=1.000; 12 months, 6.97±1.17 vs 7.07±1.28 mg/dL, p=1.000; 18 months, 6.72±1.25 vs 6.87±1.36 mg/dL, p=1.000; 24 months, 6.96±1.19 vs 6.94±1.22 mg/dL, p=1.000; 30 months, 6.67±1.22 vs 6.82±1.19 mg/dL, p=1.000; 36 months, 6.73±1.22 vs 6.66±1.30 mg/dL, p=1.000) and at the endpoint (6.81±1.36 vs 6.74±1.48 mg/dL, p=0.500) (see Figure, Supplemental Digital Content 4a). Hs-CRP levels ≥0.2 mg/dL remained high at baseline (0.395 [0.275–0.500] vs. 0.060 [0.033–0.101] mg/dL, p<0.05), during the study (6 months, 0.245 [0.121–0.500] vs 0.059 [0.031–0.125] mg/dL, p<0.05; 12 months, 0.225 [0.087–0.500] vs 0.060 [0.031–0.127] mg/dL, p<0.05; 24 month, 0.215 [0.101–0.440] vs 0.065 [0.033–0.126] mg/dL, p<0.05; 36 months, 0.215 [0.089–0.597] vs 0.067 [0.034–0.142] mg/dL, p<0.05), and at the endpoint (0.299 [0.108–0.500] vs 0.066 [0.035–0.139] mg/dL, p<0.05) (see Figure, Supplemental Digital Content 4b). A hard endpoint was observed more often in patients with baseline hs-CRP levels of ≥0.2 mg/dL than in those with hs-CRP levels of <0.2 mg/dL in both febuxostat (HR: 2.152, 95% CI: 0.892–5.190) (see Figure, Supplemental Digital Content 5a) and non-febuxostat groups (HR: 2.295, 95% CI: 1.010–5.216) (see Figure, Supplemental Digital Content 5b).

Limited to patients with baseline hs-CRP levels of ≥0.2 mg/dL (122 and 109 patients in the febuxostat and non-febuxostat groups, respectively), UA levels continued to be significantly lower in the febuxostat group than those in the non-febuxostat group during the study and at endpoint (p<0.05) (Figure 4a). However, CRP levels were similar during the study (6, 24, and 36 months, p=1.000; 12 months, p=0.750) and at the endpoint (p=0.571) between the febuxostat and non-febuxostat groups (Figure 4b). Kaplan–Meier curves for hard endpoints did not differ significantly between the two groups after adjusting for stratification factors for randomization (HR, 0.842; 95% CI, 0.322–2.201) (Figure 5).

A hard endpoint by 40 mg febuxostat or non-XOI treatment

We analyzed patients treated with 40 mg of febuxostat or non-XOIs. In total, 363 patients were treated with 40 mg of febuxostat, while 387 patients underwent non-XOI treatment. UA levels were significantly higher at baseline (7.62±1.04 vs 7.36±1.00 mg/dL, p=0.0004) but continued to be significantly lower in the febuxostat group than in the non-XOI treatment group after randomization (8 weeks, 4.94±1.16 vs 7.29±1.18 mg/dL, p<0.05; 12 weeks, 4.11±1.39 vs 7.21±1.15 mg/dL, p<0.05; 6 months, 4.01±1.29 vs 7.19±1.21 mg/dL, p<0.05; 12 months, 4.03±1.29 vs 7.30±1.11 mg/dL, p<0.05; 18 months, 4.06±1.28 vs 7.03±1.20 mg/dL, p<0.05; 24 months, 4.10±1.34 vs 7.19 ± 1.11 mg/dL, p<0.05; 30 months, 4.00±1.18 vs 7.01±1.11 mg/dL, p<0.05; 36 months, 4.06±1.17 vs 6.89±1.33 mg/dL, p<0.05). At the endpoint, the serum UA level in the febuxostat group was significantly lower than that in the non-febuxostat group (4.13±1.38 vs 6.96±1.44 mg/dL, p<0.05) (Figure 6a). However, hs-CRP levels were comparable at baseline (0.088 [0.043–0.215] vs 0.079 [0.041–0.165] mg/dL, p=0.196), during the study (6 months, 0.083 [0.043–0.196] vs 0.076 [0.035–0.172] mg/dL, p=1.000; 12 months, 0.081 [0.044–0.199] vs 0.072 [0.033–0.176] mg/dL, p=1.000; 24 months, 0.083 [0.041–0.182] vs 0.080 [0.037–0.165] mg/dL, p=1.000; 36 months, 0.084 [0.040–0.194] vs 0.088 [0.036–0.215] mg/dL, p=0.451), and at the endpoint (0.089 [0.043–0.235] vs 0.082 [0.039–0.215] mg/dL, p=0.644) between the febuxostat and non-febuxostat groups (Figure 6b). No changes in hs-CRP levels were observed in either group during the study period. Kaplan–Meier curves for hard endpoints did not differ significantly between the two groups after adjusting for stratification factors for randomization (HR, 0.577; 95% CI, 0.292–1.139) (Figure 7).

Discussion

Here, we found that febuxostat did not reduce hs-CRP levels and was not associated with fewer cardiovascular events and mortality compared to non-febuxostat treatment among patients with asymptomatic hyperuricemia whose conditions were stable, although they were at high risk of developing cardiovascular diseases. Febuxostat significantly reduced UA levels, although this change did not correlate with changes in CRP levels.

The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) and the Colchicine Cardiovascular Outcomes Trial (COLCOT) indicated that decreasing inflammation reduces the risk of cardiovascular disease, which suggests that upstream biomarkers of inflammation and intracellular sensors detecting endogenous danger signals must be targeted to achieve a desirable cardiovascular risk reduction [11, 22, 23]. For example, inhibition of the NLRP3-IL-1β axis may be critical for decreasing inflammation and cardiovascular risk. In addition to monosodium urate crystals, soluble urate can activate NLRP3 inflammation in association with increased production of mitochondrial reactive oxygen species via xanthine oxidase, leading to the secretion of IL-1β in the extracellular milieu [12, 16, 17, 24]. Febuxostat suppresses NLRP3 inflammasome-mediated IL-1β secretion *in vitro* and *in vivo* [17]. This may be a promising option for XOI-mediated control of inflammatory diseases and appears to be the most practical way to measure hs-CRP levels, a downstream surrogate biomarker for NLRP3-IL-1β pathway activity [11, 22, 23].

We did not observe any significant reduction in hs-CRP levels after febuxostat treatment, which may be linked to cardiovascular risk reduction in the present study. Whether febuxostat decreases the levels of pro-inflammatory cytokines, such as IL-1β, has not been demonstrated in the FREED study. Clinical studies on the reduction of pro-inflammatory cytokine levels with febuxostat treatment in patients with asymptomatic hyperuricemia, who are in a stable state although at risk for inflammatory disorders, are lacking. Therapeutic reduction of serum UA levels using allopurinol is associated with modulation of the inflammatory profile in patients with asymptomatic hyperuricemia; however, a decrease in CRP levels is not clear [15]. The present study revealed a median hs-CRP level of only 0.08 mg/dL at baseline; however, no reduction in hs-CRP levels was observed after febuxostat treatment in patients with ≥ 0.20 mg/dL hs-CRP at baseline. We analyzed patients treated with 40 mg of febuxostat, which appeared to exhibit the highest effect as an XOI in the present study compared to non-XOI treatments, although a significant decrease in hs-CRP levels leading to better outcomes was not observed.

The NLRP3 inflammasome is activated by a wide range of stimuli [25]. Soluble urate also activates the NLRP3 inflammasome and induces the production of IL-1β [24]. In addition to FREED, other studies have also shown that therapeutic strategies including febuxostat do not decrease cardiovascular events despite significant reductions in UA levels [18, 26, 27], suggesting that amelioration of the inflammatory flow induced via NLRP3 inflammasome activation may be difficult, although monosodium urate crystals and soluble urate levels are reduced upon febuxostat treatment in patients with asymptomatic hyperuricemia. Agents directly targeting the NLRP3-IL-1β pathway may decrease inflammation and cardiovascular risk [11, 22]. Thus, febuxostat may not sufficiently reduce intracellular UA concentrations in macrophages or endothelial cells.

This study has a number of limitations. First, FREED was not specifically designed to assess hs-CRP levels and clinical outcomes in trial participants. However, close prospective monitoring of serum UA levels from baseline to 36 months after randomization allowed accurate assessment of clinical events. Moreover, the randomized design of FREED ensured equal distribution of potential known and unknown confounding factors between the treatment and non-treatment groups. Second, dose escalation was performed, and the dose was increased up to 40 mg/day in 67.4% of the patients receiving febuxostat treatment. In the non-febuxostat group, patients underwent lifestyle modifications for the management of hyperuricemia, although 27.1% of the patients received 100 mg of allopurinol. We also compared patients in the febuxostat group with those who underwent lifestyle modifications in the non-febuxostat group, although the patients were not equally distributed between the groups in this study. Nonetheless, patient backgrounds were generally similar. Additional prospective evaluations might extend the present findings to other populations that are likely to benefit from XOIs. A trial with uricosuric agents may also be required to verify the effects of lowering serum UA and hs-CRP levels.

Conclusion

In this post-hoc analysis of a randomized controlled trial involving patients with asymptomatic hyperuricemia, treatment with febuxostat did not reduce CRP levels or result in fewer cardiovascular

events than treatment without febuxostat. These hypothesis-generating data highlight the unexpected potential of febuxostat as an anti-inflammatory agent for beneficial cardiovascular outcomes in a high-risk aged population with hyperuricemia. Further prospective confirmatory studies are warranted to identify populations that might benefit from lowering specific pro-inflammatory cytokine levels, leading to a reduction in CRP levels with febuxostat treatment.

Declarations

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Conflicts of interest

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Author contributions

Conceptualization, data curation, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing–original draft, writing–review, and editing: S.K.

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Project administration, resources, writing (review and editing): K.T.

Conceptualization, formal analysis, methodology, software, validation, review, and editing: K.M.

Conceptualization, investigation, supervision, validation, visualization, reviewing, and editing: I.H., Y.O., K.K., and Y.S.

Conceptualization, funding acquisition, investigation, methodology, supervision, validation, visualization, review, and editing: H.O.

Ethical approval

FREED was a multicenter, prospective, randomized, open-label, blinded endpoint, two-arm parallel treatment group study conducted as an investigator-initiated study following 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. The FREED protocol was reviewed by the central institutional review board before approval by the institutional review board of each participating study site, and all the patients registered with the FREED provided written informed consent. The FREED is registered at ClinicalTrial.gov (identification number: NCT01984749).

Consent to participate

All the patients registered with the FREED provided written informed consent. In this post-hoc analysis, 1,070 patients from the FREED were analyzed, and the requirement for informed consent was waived.

Data availability statement

The data underlying this article cannot be shared publicly because of the privacy of the individuals who participated in the study. The data will be shared upon reasonable request to the corresponding author.

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Figures

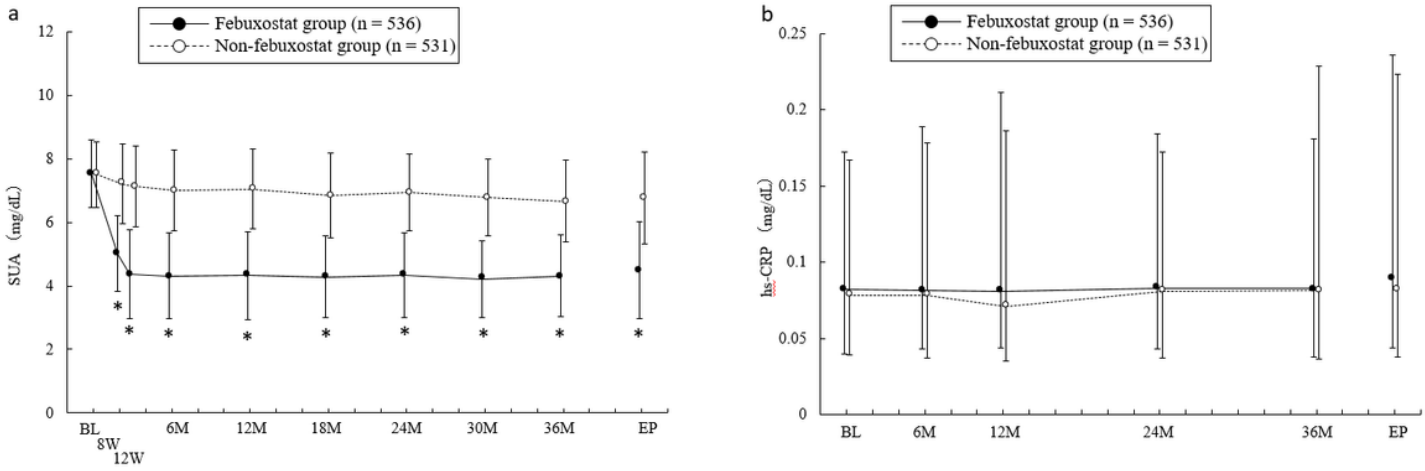

Figure 1

Changes in serum uric acid (a) and high-sensitivity C-reactive protein levels (b) in febuxostat and non-febuxostat groups. Closed circle, febuxostat group; open circle, non-febuxostat group. Values are presented as the mean ± standard deviation (a) or median (25^{th} to 75^{th} percentile range) (b). *p< 0.05 (Holm method).

hs-CRP, high-sensitivity C-reactive protein; EP, endpoint; SUA, serum uric acid

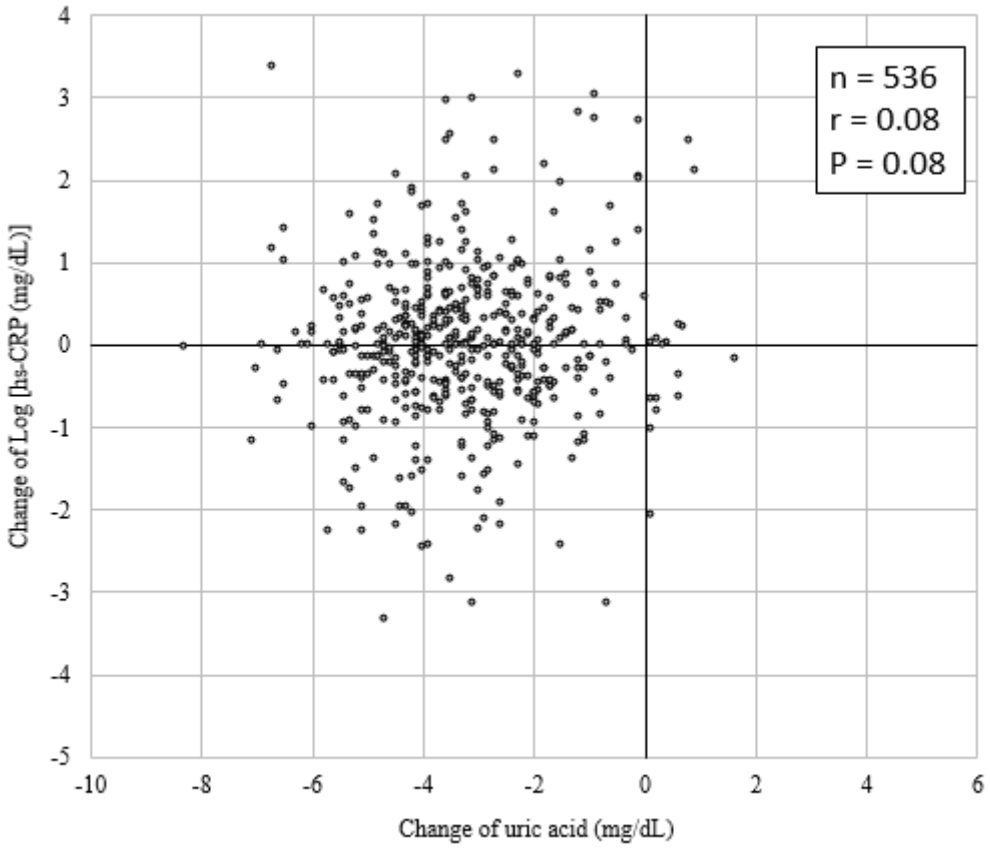

Figure 2

Relationship between changes in uric acid and high-sensitivity C-reactive protein levels from baseline log-transformed after 6 months of febuxostat treatment.

hs-CRP, high-sensitivity C-reactive protein

Figure 3

The Kaplan–Meier curves for hard endpoints. Black line, febuxostat group; red line, non-febuxostat group

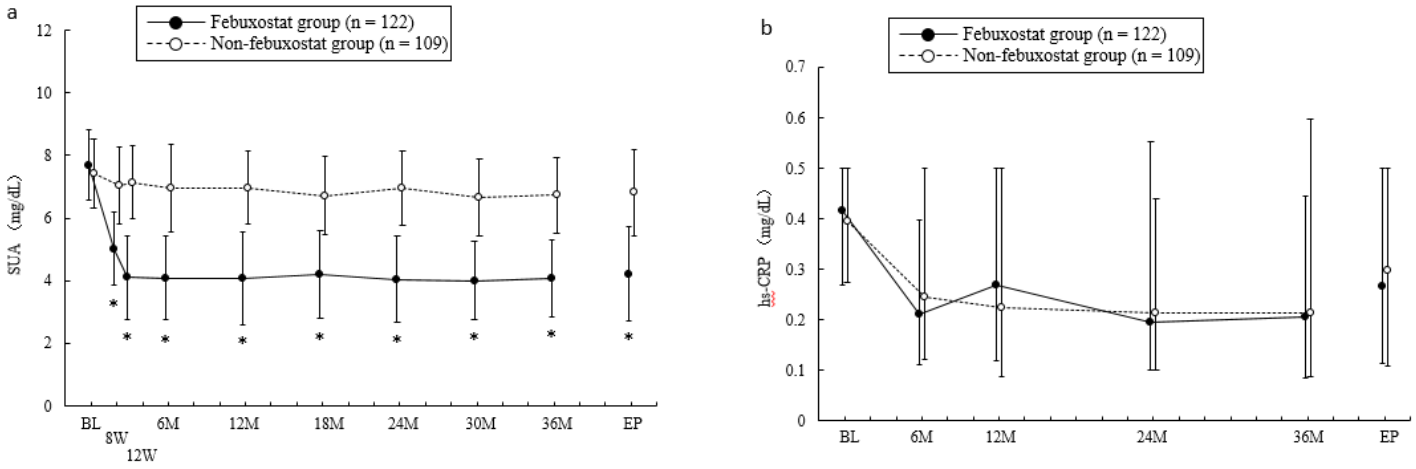

Figure 4

Changes in serum uric acid (a) and high-sensitivity C-reactive protein (b) levels in patients with high-sensitivity C-reactive protein levels of ≥0.2 mg/dL. Closed circle, febuxostat group; open circle, non-febuxostat group. Values are presented as the mean ± standard deviation (a) or median (25^{th} to 75^{th} percentile range) (b). *p<0.05 (Holm method).

hs-CRP, high-sensitivity C-reactive protein; EP, endpoint; SUA, serum uric acid

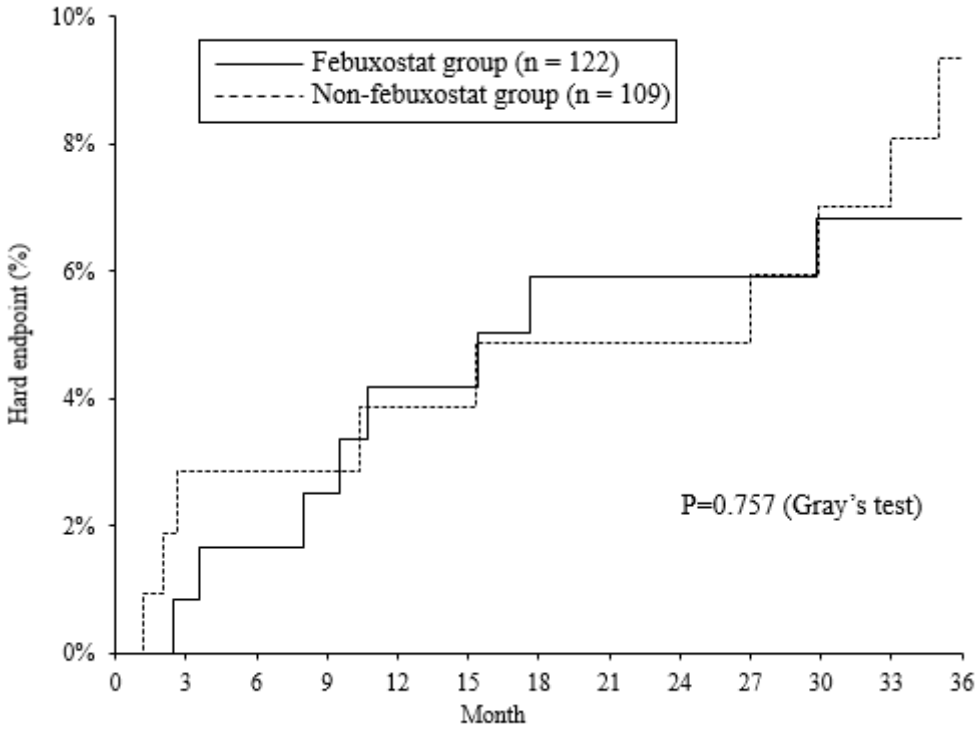

Figure 5

Kaplan–Meier curves for hard endpoints in patients with high-sensitivity C-reactive protein levels of ≥0.2 mg/dL. Black line, febuxostat group; black dotted line, non-febuxostat group

Figure 6

Changes in serum uric acid (a) and high-sensitivity C-reactive protein (b) levels in patients treated with 40 mg febuxostat and non-xanthine oxidase inhibitors. Closed circle, febuxostat group; open circle, non-febuxostat group. Values are presented as the mean ± standard deviation (a) or median (25^{th} to 75^{th} percentile range) (b). *p< 0.05.

hs-CRP, high-sensitivity C-reactive protein; EP, endpoint; SUA, serum uric acid; XOI, xanthine oxidase inhibitor

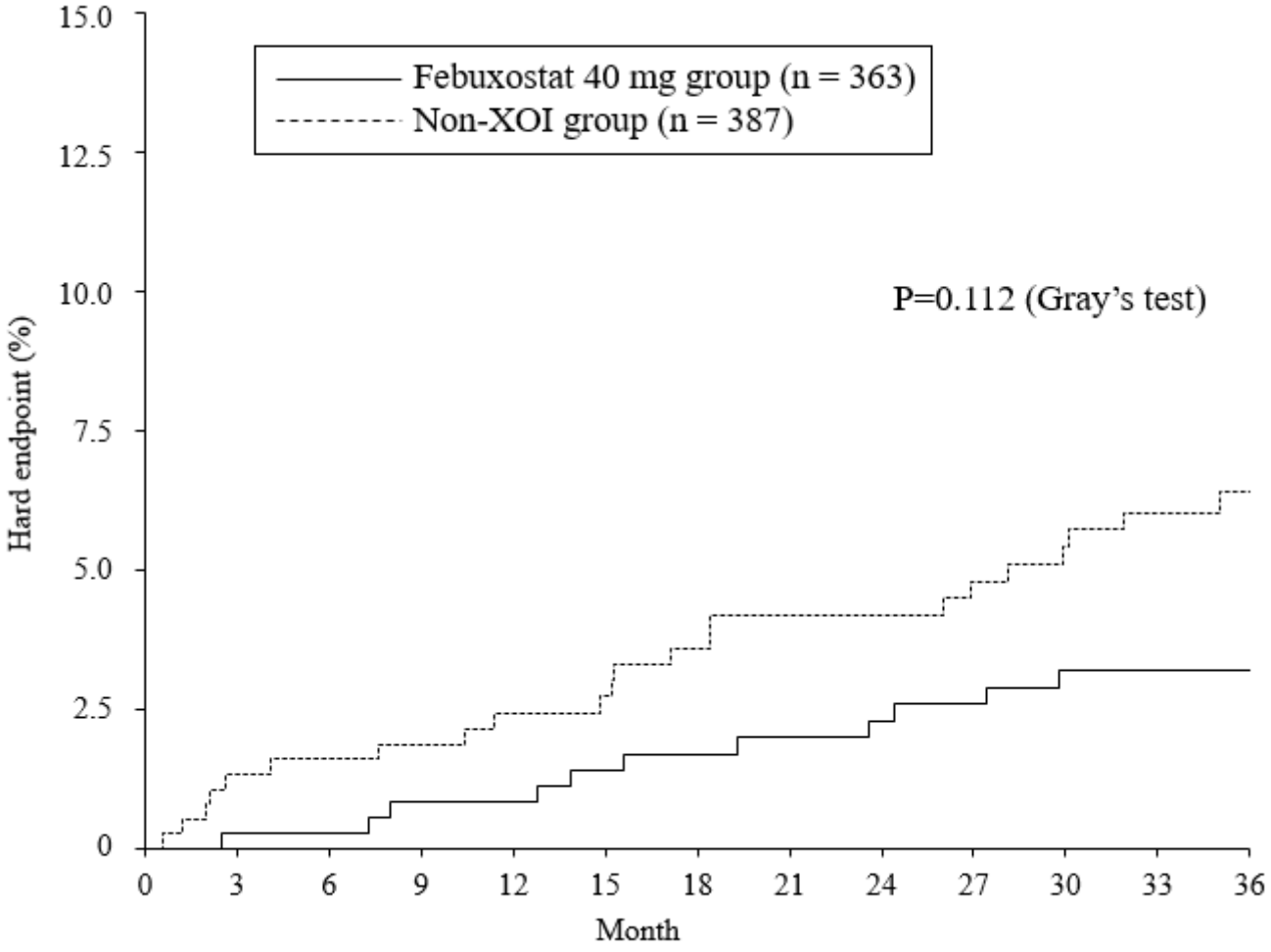

Figure 7

Kaplan–Meier curves for hard endpoints in patients treated with 40 mg febuxostat and non-xanthine oxidoreductase inhibitor. Black line, patients treated with 40 mg febuxostat; black dotted line, non-xanthine oxidoreductase inhibitor treatment.

XOI: xanthine oxidase inhibitor

Supplementary Files

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