Comparison of Febuxostat and Allopurinol for Hyperuricemia in Cardiac Surgery Patients (NU-FLASH Trial)

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Background: Febuxostat has been reported to have a stronger effect on hyperuricemia than allopurinol.

Methods and Results: Cardiac surgery patients with hyperuricemia (n=141) were randomized to a febuxostat group or an allopurinol group. The study was single-blind, so the treatment was not known by the investigators. The primary endpoint was serum uric acid (UA) level. Secondary endpoints included serum creatinine, urinary albumin, cystatin-C, oxidized low-density lipoprotein (LDL), eicosapentaenoic acid/araachidonic acid ratio, total cholesterol, triglycerides, LDL, high-density lipoprotein, high-sensitivity C-reactive protein, blood pressure, heart rate, pulse wave velocity (PWV), ejection fraction, left ventricular mass index (LVMI), and adverse reactions. UA level was significantly lower in the febuxostat group than the allopurinol group from 1 month of treatment onward. Serum creatinine, urinary albumin, cystatin-C and oxidized LDL were also significantly lower in the febuxostat group. There were no significant changes in systolic blood pressure, PWV, and LVMI in the allopurinol group, but these parameters all had a significant decrease in the febuxostat group.

Conclusions: Febuxostat was effective for high-risk cardiac surgery patients with hyperuricemia because it reduced UA more markedly than allopurinol. Febuxostat also had a renoprotective effect, inhibited oxidative stress, showed anti-atherogenic activity, reduced blood pressure, and decreased PWV and LVMI. (Circ J 2013; 77: 2043–2049)

Key Words: Allopurinol; Febuxostat; Hyperuricemia
cidating the efficacy and systemic effects of febuxostat.

**Methods**

**Study Protocol**

The subjects were 141 outpatients with serum UA ≥8 mg/dl who were not on anti-hyperuricemic therapy, and who underwent cardiac surgery at Nihon University Hospital at least 1 year previously. The age range of the eligible patients was ≥20 years to <90 years.

Exclusion criteria were (1) renal dysfunction with an estimated glomerular filtration rate (eGFR) ≤20 ml · min⁻¹ · 1.73 m⁻²; (2) hepatic dysfunction (aspartate aminotransferase [AST] >39 U/L or alanine aminotransferase [ALT] >44 U/L); (3) treatment with mercaptopurine hydrate or azathiopurine; (4) pregnancy; and (5) other reasons that made patients unsuitable for this study as judged by the attending physician. In this study, patients were randomly assigned to oral treatment with febuxostat (Teijin Pharma, Tokyo, Japan) or allopurinol (GlaxoSmithKline, Tokyo, Japan) using the lottery method. This study used a single-blind method where the treatment assigned was known by the patients but not by the investigators and measurers. The details of the study were explained to each patient and informed consent was obtained. Approval of the institutional review board was also obtained and the study was registered with the University Hospital Medical Information Network (study ID: UMIN000005964).

**Endpoints**

The primary endpoint was serum UA level after treatment. The secondary endpoints were as follows: serum creatinine (s-Cr), eGFR, urinary albumin, cystatin-C, oxidized low-density lipoprotein (O-LDL), eicosapentaenoic acid/arachidonic acid (EPA/AA) ratio, total cholesterol (T-cho), triglycerides (TG), LDL, high-density lipoprotein (HDL), high-sensitivity C-reactive protein (hs-CRP), blood pressure in both arms (systolic, mean, and diastolic pressure; SBP, mBP, and DBP), heart rate (HR), pulse wave velocity (PWV), ejection fraction (EF), left ventricular mass index (LVMI) measured on echocardiography, and adverse reactions.

UA, s-Cr, T-cho, TG, LDL, and HDL were measured before the start of treatment as well as after 1, 3, and 6 months of treatment, while urinary albumin, cystatin-C, O-LDL, and the EPA/AA ratio were measured before treatment and after 3 and 6 months of treatment. EF and LVMI were evaluated by a specialist echocardiographer (using VIVID 7; GE Healthcare Japan, Tokyo, Japan) according to the formula of Devereux et al before and after 6 months of treatment. PWV was measured with Form ABI/PWV (BP-203RPE II; Omron-Colin, Tokyo, Japan) before and after 6 months of treatment, and BP and HR were measured simultaneously. Adverse reactions were classified as acute attacks of gout, skin reactions, renal dysfunction (increase of s-Cr by ≥50%), hepatic dysfunction (increase of AST/ALT by ≥50%), gastrointestinal symptoms, and allergic reactions. Management of the reactions (discontinuation of the test drug etc) was decided by the attending physician. The target serum UA level was ≤6.0 mg/dl, and the dose of each test drug was increased up to a maximum of 60 mg/day for febuxostat or 300 mg/day for allopurinol. In patients with eGFR ≤30 ml · min⁻¹ · 1.73 m⁻², the maximum daily dose was 40 mg for febuxostat and 200 mg for allopurinol. eGFR was calculated according to the methods proposed for Japanese persons by the Japanese Society of Nephrology (men, 194 × sCr⁻¹.094 × age⁻0.287; women, 194 × sCr⁻¹.094 × age⁻0.287 × 0.739).

**Statistical Analysis**

For parametric data, results are expressed as mean±SEM. For time-course analysis, repeated-measures ANOVA with Fisher’s
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Results

Among the 150 registered patients, 6 patients with eGFR ≤20 ml·min⁻¹·1.73 m⁻² and 3 patients with hepatic dysfunction were excluded, and a total of 141 patients were included, that is, 71 were assigned to the febuxostat group and 70 to the allopurinol group. Allopurinol was discontinued in 1 patient who developed acute liver abscess after 4 months of treatment. This patient died at 6 months after the start of treatment. Finally, 71 patients were available for analysis in the febuxostat group and 69 patients were analyzed in the allopurinol group after follow-up (Figure 1). The baseline characteristics of the 2 groups are listed in Table 1. Among the 113 patients with hypertension, some were being treated with angiotensin II receptor blocker (ARB), angiotensin-converting enzyme inhibitor (ACEI), β-blocker, or furosemide after cardiac surgery not for anti-hypertensive purposes but for cardioprotective or diuretic purposes. Among the present subjects, only 7 in each in the 2 groups were not being treated with either ARB, ACEI, β-blocker, or furosemide.

Primary Endpoint

UA There was no significant difference in UA between the 2 groups before the start of treatment (8.61±0.96 mg/dl in the febuxostat group vs. 8.56±0.98 mg/dl in the allopurinol group, P=0.7329; Figure 2), but the UA level was significantly lower in the febuxostat group than the allopurinol group from 1 month after the start of treatment (1 month, P<0.0001; 3 months, P=0.001; 6 months, P=0.0009). The target UA level (≤6.0 mg/dl) was achieved in 71.8% of the febuxostat group and in 30.4% of the allopurinol group after 1 month of treatment, while it was respectively reached in 91.5% and in 65.2% after 3 months, and in 95.8% and in 69.6% after 6 months. These rates were all significantly higher in the febuxostat group than the allo-

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Data given as mean±SEM or n. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; IHD, ischemic heart disease.
There were no significant differences in pretreatment s-Cr or eGFR between the 2 groups (s-Cr, P=0.9406; eGFR, P=0.7114; Table 2). s-Cr was significantly lower after 1 and 6 months of treatment in the febuxostat group than the allopurinol group (1 month, P=0.0498; 6 months, P=0.0412), and it had a significant decrease relative to baseline at all timepoints in this group (all P<0.0001). There were no significant differences in eGFR between the febuxostat group and the allopurinol group after the start of treatment (1 month, P=0.1375; 3 months, P=0.3267; 6 months, P=0.1132), but there was a significant increase relative to baseline at all timepoints in the febuxostat group (all P<0.0001).

### Urinary Albumin

There was no difference in the pretreatment level between the 2 groups (P=0.9545), but the albumin levels measured after 3 and 6 months were significantly lower in the febuxostat group than the allopurinol group (3 months, P<0.0001; 6 months, P=0.00016).

### Secondary endpoints

#### s-Cr and eGFR

- **Secondary endpoints**

  **s-Cr and eGFR.** There were no differences in pretreatment s-Cr or eGFR between the 2 groups (s-Cr, P=0.9406; eGFR, P=0.7114; Table 2). s-Cr was significantly lower after 1 and 6 months of treatment in the febuxostat group than the allopurinol group (1 month, P=0.0498; 6 months, P=0.0412), and it had a significant decrease relative to baseline at all timepoints in this group (all P<0.0001). There were no significant differences in eGFR between the febuxostat group and the allopurinol group after the start of treatment (1 month, P=0.1375; 3 months, P=0.3267; 6 months, P=0.1132), but there was a significant increase relative to baseline at all timepoints in the febuxostat group (all P<0.0001).

### Urinary Albumin

There was no difference in the pretreatment level between the 2 groups (P=0.9545), but the albumin levels measured after 3 and 6 months were significantly lower in the febuxostat group than the allopurinol group (3 months,
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Left, \( P=0.4123 \) and also no difference in the 6-month level (right, \( P=0.0092 \); left, \( P=0.135 \)), but there was a significant decrease at 6 months vs. baseline in the febuxostat group (right, \( P=0.001 \); left, \( P=0.0004 \); Figures 3, 4). In addition, there was no difference in pretreatment mBP between the 2 groups (right, \( P=0.6203 \); left, \( P=0.9941 \)) and also no difference in the 6-month level (right, \( P=0.3856 \); left, \( P=0.1641 \)), but the 6-month mBP was significantly lower than baseline in the febuxostat group (right, \( P=0.0024 \); left, \( P=0.0004 \)). Furthermore, there was no difference in pretreatment DBP between the 2 groups (right, \( P=0.4809 \); left, \( P=0.3759 \)) and also no difference in the 6 month level (right, \( P=0.0796 \); left, \( P=0.2266 \)), but the 6 month level was significantly lower than the pretreatment level in the febuxostat group (right, \( P=0.0024 \); left, \( P=0.0004 \)). There was also no difference in pretreatment PWV between the 2 groups (right, \( P=0.5373 \); left, \( P=0.7556 \)) and also no difference in PWV after 6 months (right, \( P=0.665 \); left, \( P=0.1835 \)) but the 6 month level was significantly lower than the pretreatment value in the febuxostat group (right, \( P=0.0276 \); left, \( P=0.0127 \)).

**EF and LVMI** There were no differences in pretreatment

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**Figure 3.** Change in blood pressure.
EF and LVMI between the 2 groups (EF, P=0.6544; LVMI, P=0.5989; Table 3; Figure 5). There was also no difference in EF at 6 months between the 2 groups, but LVMI was significantly lower in the febuxostat group than the allopurinol group after 6 months (P<0.0001).

Adverse Reactions   Treatment was not discontinued due to adverse reactions in any patient from either group, but mild attacks of gout occurred in 1 patient from each group after 1 month of treatment. These episodes soon resolved. In the febuxostat group, hepatic function parameters (AST, ALT) showed a 30% increase in 2 patients after 1 month of treatment, but this improved by the next examination.

Discussion

In this study, febuxostat reduced serum UA more markedly than allopurinol. In addition, febuxostat had a renoprotective effect based on the levels of urinary albumin and cystatin-C, as well as inhibiting oxidative stress, based on the O-LDL. Furthermore, the EPA/AA ratio (an index of arteriosclerosis) was significantly increased in the febuxostat group, while PWV and LVMI were significantly lower in the febuxostat group than the allopurinol group.

It has already been reported that febuxostat achieves a significant early decrease of UA compared with allopurinol. Allopurinol is excreted via the kidneys and its active metabolite (oxipurinol) has low lipid solubility, so a decrease of the dosage is needed in patients with renal dysfunction. In contrast, efficacy and tolerability of febuxostat have been demonstrated without dosage adjustment because it has no active metabolites and biliary excretion occurs in addition to renal excretion. Siu et al reported that allopurinol inhibits the progression of renal dysfunction by lowering the UA level and decreasing s-Cr in CKD patients with hyperuricemia. Goicoechea et al compared allopurinol with placebo in 113 CKD patients and reported a significant decrease of UA and significant improvement of eGFR, as well as a 71% decrease of cardiovascular events in the allopurinol group. The US febuxostat study assessed the influence of febuxostat on renal function in 116 patients and found that a greater decrease of serum UA led to stronger inhibition of the decline in renal function. Detailed investigation, however, has not been conducted in Japan, so we measured urinary albumin and cystatin-C in addition to s-Cr and eGFR as indexes of renal function in the present study. The usefulness of urinary albumin and cystatin-C as indexes of renal function has been reported previously. In the present study, febuxostat significantly improved urinary albumin and cystatin-C after 3 months in addition to s-Cr and eGFR compared with allopurinol, indicating that it had a more potent renoprotective effect, presumably by lowering the serum UA more markedly.

In humans, UA is produced as the terminal metabolite of purine metabolism via xanthine oxidase. Xanthine oxidase is involved in the production of reactive oxygen species, and it has been reported that production of reactive oxygen by endothelial-bound xanthine oxidase is more potently inhibited by febuxostat than by allopurinol. In this study, O-LDL was used as an index of oxidative stress. The effect of febuxostat on O-LDL has not been reported before, but Rajendra et al reported that O-LDL was decreased by allopurinol. That study, however, used a considerably higher allopurinol dose (600 mg/day); and no change of O-LDL was observed after allopurinol treatment in the present study because the dose range was lower (100–300 mg). In contrast, O-LDL was significantly decreased by febuxostat and was significantly lower in the febuxostat group than the allopurinol group, thereby demonstrating inhibition of oxidative stress. There have been no reports with regard to the effect on the EPA/AA ratio (an index of arteriosclerosis) of allopurinol or febuxostat. In this study, an anti-atherogenic effect was not observed with allopurinol, but treatment with febuxostat decreased this ratio. It has already been reported that febuxostat achieves a significant early decrease of UA compared with allopurinol. Allopurinol is excreted via the kidneys and its active metabolite (oxipurinol) has low lipid solubility, so a decrease of the dosage is needed in patients with renal dysfunction. In contrast, efficacy and tolerability of febuxostat have been demonstrated without dosage adjustment because it has no active metabolites and biliary excretion occurs in addition to renal excretion.
patients, and reported that lowering UA is important for improving arterial stiffness, while high UA increases the PWV by inhibiting the cholinergic response. In the present study, PWV and LVMI were decreased in the febuxostat group, presumably because blood pressure was reduced by febuxostat, which was more potent at reducing UA, oxidative stress, and atherogenesis than allopurinol, resulting in a decrease of PWV and LVMI.

Rajendra et al reported that high-dose allopurinol is effective for vascular oxidative stress, and has the potential to reduce the incidence of cardiovascular event. Noman et al carried out exercise testing in 65 patients with stable angina and reported that time to ST depression and time to occurrence of chest pain were significantly increased in patients treated with high-dose allopurinol, and that brain natriuretic peptide was also decreased in the allopurinol group. Kao et al reported in 53 CKD patients that endothelial function according to flow-mediated dilation and LVMI, indices of vascular endothelial damage, is significantly decreased in the allopurinol group, and Hirsch et al studied patients with heart failure and reported that allopurinol acutely improves the relative and absolute concentrations of myocardial high-energy phosphates and ATP flux through creatine kinase. Allopurinol is beginning to be reported to decrease the risk of cardiovascular events due to its preventive effects against vascular endothelial damage, and its anti-atherogenic effect. It is expected that febuxostat would have results equal to or better than those reports, but studies on this subject have not been done at present. The present study has shown that febuxostat had a stronger UA-lowering effect and renoprotective effect, and was also superior to allopurinol in inhibiting oxidative stress atherogenesis, hypertension, and vascular endothelial damage. Thus, febuxostat was considered to be more likely to prevent cardiovascular events than allopurinol. The effect of febuxostat on cardiovascular events, however, is an interesting point that requires investigation in a larger number of subjects over a longer period in the future.

Conclusion
In addition to reducing UA to a significantly lower level than allopurinol, febuxostat had a renoprotective effect, inhibited oxidative stress, displayed anti-atherogenic activity, had an anti-atherosclerotic effect, and prevented vascular endothelial damage in cardiac surgery patients with hyperuricemia. As a result, febuxostat was considered to have the potential to prevent cardiovascular event.

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Disclosures
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References

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