



Comparative effects of topiroxostat and febuxostat on arterial properties in hypertensive patients with hyperuricemia

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Abstract

Elevated serum uric acid is a cardiovascular risk factor in patients with hypertension, even when blood pressure (BP) is well controlled. Xanthine oxidoreductase inhibitors (XORi) reduce serum uric acid levels and have several other potential effects. This multicenter, randomized, open-label study compared the effects of two XORi, topiroxostat and febuxostat, on arterial stiffness, uric acid levels, and BP in hypertensive patients with hyperuricemia. Patients received topiroxostat 40–160 mg/day or febuxostat 10–60 mg/day, titrated to maintain serum uric acid <6 mg/dl, for 24 weeks. The primary endpoint was change in the cardio-ankle vascular index (CAVI) from baseline to 24 weeks. There were no significant changes in CAVI from baseline to 24 weeks (from 9.13 to 9.16 [febuxostat] and 8.98 to 9.01 [topiroxostat]). Compared with baseline, there were significant reductions in serum uric acid (–2.9 and –2.5 mg/dl; both $p < 0.001$) and morning home systolic BP (–3.6 and –5.1 mm Hg; both $p < 0.01$) after 24 weeks' treatment with febuxostat and topiroxostat. BP decreased to the greatest extent in the subgroup of patients with uncontrolled blood pressure at baseline. Topiroxostat, but not febuxostat, significantly decreased plasma xanthine oxidoreductase activity versus baseline. The urinary albumin-creatinine ratio (UACR) decreased significantly from baseline to 24 weeks with topiroxostat (–20.8%; $p = 0.021$), but not febuxostat (–8.8%; $p = 0.362$). In conclusion, neither topiroxostat nor febuxostat had any significant effects on arterial stiffness over 24 weeks' treatment.

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1 | INTRODUCTION

Xanthine oxidoreductase (XOR) is a crucial enzyme for the catabolism of purines. High XOR activity in the blood is associated with an increase in serum uric acid (UA) levels (leading to hyperuricemia) and elevated levels of reactive oxygen species (ROS; leading to tissue damage).

Hyperuricemia is an independent risk factor for incident hypertension, especially in women and younger individuals.¹ In addition, serum UA levels are independently associated with a non-dipping pattern of nocturnal BP.^{2,3} Vascular ROS production appears to be one mechanism by which XOR increases BP.⁴ These data suggest that high serum levels of UA could contribute to the development and progression of hypertension and chronic kidney disease (CKD). This is supported by the findings of epidemiological and clinical studies showing that hyperuricemia is an independent risk factor for cardiovascular morbidity and mortality, and the development of CKD and end-stage renal disease.^{5,6} Furthermore, the presence of elevated serum UA levels is associated with cardiovascular event risk in patients with hypertension, even when blood pressure (BP) is well controlled.⁷

Three XOR inhibitors (XORi) are currently used clinically in Japan: allopurinol, febuxostat and topiroxostat. Febuxostat and topiroxostat are used for the management of hyperuricemia in patients with or without gout. As a selective XORi, topiroxostat has been reported to be superior to febuxostat for suppressing XOR activity in some situations,^{8,9} but there is a general lack of comparative data for these agents.

XORi have been reported to have a number of other potential effects beyond their UA-lowering ability, including reductions in BP,^{10,11} cardiovascular risk,^{12,13} and albuminuria.¹⁴ However, data are limited,¹² findings are not consistent, and there is some concern about the cardiovascular safety of allopurinol and febuxostat.^{15,16} Data on the effects of XORi on arterial properties, including flow-mediated dilatation (FMD) and pulse wave velocity (PWV), are also inconsistent. Some studies have shown benefit¹⁷⁻²⁰ and others no effect.²¹ It is possible that effects may differ between agents in this class, but there is a relative lack of published data on the effects of topiroxostat on arterial properties. Therefore, the Beneficial Effect by Xanthine Oxidase Inhibitor on Endothelial Function Beyond Uric Acid (BEYOND-UA) study was designed to compare the effects of topiroxostat and febuxostat on arterial stiffness, UA levels and BP in patients with hyperuricemia and hypertension.

2 | METHODS

2.1 | Study design

This multicenter ($n = 31$), randomized, comparative, open-label, parallel study was conducted in Japan over the period March 2018 to December 2019. The trial was registered at the UMIN Clinical trials registry (UMIN000031096) and Japan Registry of Clinical Trials (jRCTs031180406). The study protocol was approved by the Jichi Medical University Clinical Research Ethics Committee

and Certified Review Board (Tochigi, Japan; CRB3180003), and all patients provided written informed consent prior to enrollment in the study. Study procedures were performed in accordance with Clinical Trials Act (Japan) and the principles outlined in the Declaration of Helsinki.

2.2 | Participants

Male and female patients aged 30–80 years with hyperuricemia (serum UA ≥ 7 mg/dl; untreated or treated with allopurinol), hypertension that had been treated with stable antihypertensive therapy for ≥ 3 months, CAVI of ≥ 8 and ≤ 12 , and who were willing to provide informed consent were eligible to participate in the study. Patients meeting any of the following exclusion criteria were not eligible: history of hypersensitivity to trial drugs or allopurinol; treatment with anti-hyperuricemic drugs during the study or within 4 weeks prior to enrollment; existing cancer diagnosis; gouty arthritis within 2 weeks before enrollment; aspartate aminotransferase or alanine aminotransferase >2 times the upper limit of normal; serious liver dysfunction (Child Pugh class B or C); renal dysfunction (estimated glomerular filtration rate <30 ml/min/1.73 m²); severe heart failure (New York Heart Association Class 3 or 4); history of acute coronary syndrome or stroke within the previous 3 months; and participation in another clinical trial within the previous 6 months.

2.3 | Intervention

Patients were randomized to receive treatment with topiroxostat starting at 40 mg/day then titrated to 80 mg/day at Week 4, to 120 mg/day at Week 8 and up to a maximum of 160 mg/day during Weeks 8–24 to maintain serum UA levels at <6 mg/dl, or to febuxostat starting at 10 mg/day titrated to 20 mg/day at Week 4, 40 mg/day Week 8 and up to a maximum of 60 mg/day during Weeks 8–24 to maintain serum UA at <6 mg/dl (Figure S1).

2.4 | Outcomes

The primary endpoint was the change in CAVI from baseline to 24 weeks. Secondary outcomes were as follows: change in CAVI from baseline to 12 weeks; change in brachial-ankle pulse wave velocity (ba-PWV), ankle-brachial index (ABI), and CAVI wave-form indices from baseline to 12 and 24 weeks; change in serum UA from baseline to 4, 8, 12 and 24 weeks; change in home BP and office BP from baseline to 4, 8, 12, and 24 weeks; change in high-sensitivity C-reactive protein, amino terminal pro B-type natriuretic peptide, high-sensitivity troponin T, liver-type fatty acid-binding protein, cystatin C, urinary albumin-creatinine ratio and 8-hydroxy-2'-deoxyguanosine from baseline to 12 and 24 weeks. Change in XOR activity from baseline to 12 and 24 weeks was investigated as an exploratory endpoint.

2.5 | Assessments

Cardio-ankle vascular index was measured at baseline, and after 12 and 24 weeks of treatment using a CAVI device (Vasera VS3000). Examinations were performed after a 5-minute rest period. The pressure of all cuffs was kept at 50 mm Hg to minimize the effect of cuff pressure on hemodynamics. BP was then measured. CAVI was determined using the following formula:

$CAVI = a [(2\rho/\Delta P) \times \ln(P_s/P_d) PWV^2] + b$, where a and b are constants, ρ is blood density, ΔP is $P_s - P_d$, P_s is systolic blood pressure, P_d is diastolic blood pressure, and PWV is pulse wave velocity.

Pulse wave velocity was determined by dividing vascular length by the time (T) taken for the pulse wave to travel from the aortic valve to the ankle. However, in practice, T was difficult to obtain because the time the blood left the aortic valve was difficult to identify from the sound of the valve opening. Therefore, because the time between the sound of the aortic valve closing and the notch of the brachial pulse wave is theoretically equal to the time between the sound of the aortic valve opening and the rise of the brachial pulse wave, T was determined by adding the time between the sound of the aortic valve closing and the notch of the brachial pulse wave, and the time between the rise of the brachial pulse wave and the rise of the ankle pulse wave.

Office and home BP were measured at baseline and after 4, 8, 12, and 24 weeks of treatment. All measurements were performed according to the latest guidelines available at the time the trial was conducted.²² Office BP was measured after ≥ 5 min of rest with the patient seated in a chair with the arm cuff level with the heart. Smoking was prohibited for 30 min before the measurement. Several consecutive measurements were taken at intervals of ≥ 1 min and the average of two measurements was used to define the office BP. Home BP measurement was performed using a cuff oscillometric device (HEM-7080-IC; Omron Healthcare Co., Ltd.). Patients were instructed to measure their morning home BP (two readings within 1 h after waking, taken after urination, before taking morning medications and after 1–2 min of seated rest) and evening home BP (two readings before bedtime after 1–2 min of seated rest) on five successive days immediately prior to their scheduled clinic visit. Plasma XOR activity measurement was performed by Sanwa Kagaku Kenkyusho Co., Ltd. using liquid chromatography/triple quadrupole mass spectrometry (LC/TQMS; Nexera HLC, SHIMADZU, Japan/QTRAP 4500, SCIEX) to detect [$^{13}C_2$, $^{15}N_2$]uric acid using [$^{13}C_2$, $^{15}N_2$]xanthine as a substrate, as previously reported.²³

2.6 | Statistical analysis

Assuming a 0.33-unit between-group difference in CAVI with a standard deviation (SD) of 0.76, it was calculated that 59 patients per group would be required to achieve 95% power with a 2-sided p -value of 0.05. Allowing for a 15% dropout rate, it was planned to enroll 70 patients per group (140 in total).

Patients who were non-compliant with the Ethical Guidelines for Clinical Research were excluded from all analyses (both efficacy and safety). The full analysis set (FAS) included all enrolled patients who received at least one dose of study medication after enrollment and had at least one set of data during treatment. The safety analysis set (SAS) included all patients who had received at least one dose of study medication after enrollment.

Mixed-effects model repeated measures (MMRM) analysis was used to compare the changes in CAVI and other outcomes from baseline to week 4, week 8, week 12, and week 24. MMRM included the randomized study group, time point (0, 4, 8, 12, and 24 weeks), interaction between the study group and time points as fixed effects, and age and sex as covariates. A 2-sided test was used, and p -values of <0.05 were considered statistically significant. Intergroup comparisons were tested with a t test for continuous variables, and Pearson's chi-squared test or Fisher's exact test was used for dichotomous data. Data were analyzed using SAS version 9.4 (SAS Institute) at the Jet Academy, Tokyo, Japan.

3 | RESULTS

3.1 | Subjects

Five of the 140 eligible patients withdrew consent, meaning that 135 patients were randomized to treatment (67 in the topiroxostat group and 68 in the febuxostat group; Figure 1). The majority of patients were male, and diabetes and dyslipidemia were the most common comorbidities (Table 1). Mean office BP at baseline was 138/80 mm Hg, and the most commonly used antihypertensive agents were angiotensin receptor blockers and calcium channel blockers (Table 1). The two treatment groups were well matched for baseline characteristics (Table 1). Two patients in the topiroxostat group and five in the febuxostat group were switched from previous allopurinol therapy. Baseline XOR activity data were only available for a small number of patients (11 in the topiroxostat group and 10 in the febuxostat group); baseline XOR activity was significantly higher in the topiroxostat versus febuxostat group (89.2 vs. 33.9 pmol/h/ml, 95% CI for the difference, 16.9–93.8; $p = 0.006$).

3.2 | Arterial stiffness

There were no significant changes from baseline or between treatment groups in arterial stiffness, measured using CAVI or ba-PWV (Figure 2). The ABI also remained relatively unchanged during the study, with a very small difference between groups (0.03, 95% CI 0.000–0.06).

3.3 | Uric acid levels and XOR activity

Serum UA levels decreased significantly from baseline ($p < 0.01$) during treatment in both the topiroxostat and febuxostat groups,

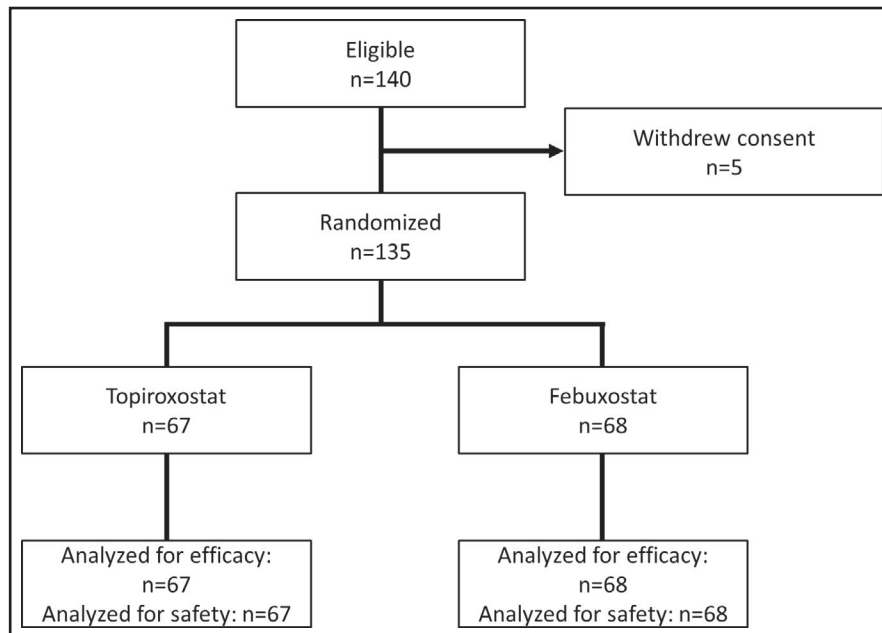


FIGURE 1 Study flow chart

without any significant between-group difference (Figure 3). In the subgroup of patients with available data, baseline XOR activity was higher in the topiroxostat group and decreased significantly during treatment, but there were no changes in XOR activity from baseline in the febuxostat group (Figure 3).

3.4 | Morning home blood pressure

Overall, there was a significant reduction from baseline in morning home SBP in both treatment groups, with no significant difference between the effects of topiroxostat and febuxostat (Figure 4A). In the subset of patients with well-controlled SBP at baseline (<135 mm Hg), there was no significant change in morning home SBP during treatment with either agent, except for at Week 8 in the febuxostat group (Figure 4B). In contrast, the subgroup of patients with uncontrolled BP at baseline (SBP \geq 135 mm Hg) showed statistically significant reductions from baseline in morning home SBP during treatment with topiroxostat (-8.6 mm Hg) or febuxostat (-6.3 mm Hg; Figure 4C). [Correction added on January 24, 2021, after first Online publication: The term “topiroxosta” has been changed to “febuxostat”].

3.5 | Urinary albumin-creatinine ratio and renal function

The UACR significantly decreased from baseline during treatment with topiroxostat, both overall (by $\geq 20\%$) and in the subgroup of patients with microalbuminuria at baseline (by $\geq 45\%$), with no significant difference in the change from baseline between the topiroxostat and febuxostat groups (Figure 5). In the overall population, the change from baseline in UACR in the topiroxostat group was no

longer statistically significant after adjustment for morning and office SBP, whereas significant reductions persisted in the subgroup with microalbuminuria even after adjustment for morning and office SBP (42.7% reduction from baseline; $p = 0.016$; Figure S2).

Although there was a significant reduction in eGFR from baseline after 24 weeks' treatment with topiroxostat (-2.2 ml/min/ 1.73 m² [95% confidence interval $-4.0, -0.3$]; $p = 0.02$), there were no significant differences of the change from baseline in eGFR at 12 and 24 weeks between the topiroxostat and febuxostat groups.

3.6 | Oxidative stress, inflammatory, and other biomarkers

No important changes in biomarkers were seen during treatment with topiroxostat or febuxostat (Table S1).

3.7 | Safety

Treatment with topiroxostat and febuxostat was well tolerated. Adverse events in the topiroxostat group included gout (three patients), and arthralgia, nausea, cholelithiasis and malaise (one patient each). In the febuxostat group, one patient each reported muscle pain, arthralgia, and cramp.

4 | DISCUSSION

This is the first randomized controlled trial comparing the XORi topiroxostat and febuxostat on arterial stiffness parameters. The

TABLE 1 Patient demographic and clinical characteristics at baseline

Variables	Topiroxostat (n = 67)	Febuxostat (n = 68)	p-value
Age, years	68.4 ± 7.3	67.2 ± 8.1	0.35
Male, %	82.1	82.4	1.00
Weight, kg	68.2 ± 10.6	70.2 ± 12.1	0.33
Body mass index, kg/m ²	25.6 ± 3.5	25.6 ± 3.2	0.88
Smoking, %	20.9	20.6	1.00
Drinking, %	70.1	70.6	1.00
Medical history, %			
Diabetes mellitus	20.9	30.9	0.24
Dyslipidemia	35.8	47.1	0.22
Chronic kidney disease	3.0	5.9	0.68
Liver disease	4.5	2.9	0.68
Stroke	3.0	4.4	1.00
Heart failure	6.0	2.9	0.44
Coronary artery disease	9.0	7.4	0.76
Non-valvular atrial fibrillation	7.5	11.8	0.56
Antihypertensives, %			
ACE inhibitors	4.5	5.9	1.00
ARB	71.6	66.2	0.58
Calcium channel blocker	53.7	57.4	0.73
Beta blocker	19.4	26.5	0.41
Alpha blocker	3.0	0.0	0.24
Diuretics	25.4	25.0	1.00
Antidiabetic therapy, %	16.4	22.1	0.51
Uric acid, mg/dl	7.8 ± 1.2	7.8 ± 1.2	0.86
Creatinine, mg/dl	0.91 ± 0.22	0.98 ± 0.36	0.20
eGFR, ml/min/1.73 m ²	64.5 ± 15.9	61.8 ± 16.7	0.34
UACR, mg/g Cr	15 (8, 70)	18 (8, 52)	0.23
Cystatin C, mg/L	1.07 ± 0.24	1.15 ± 0.36	0.17
hs-CRP, ng/ml	1030 (380, 1840)	577 (408, 1215)	0.46
NT-pro BNP, pg/ml	74 (32, 153)	58 (24, 114)	0.88
hs-TnT, ng/ml	0.009 (0.006, 0.014)	0.009 (0.007, 0.016)	0.42
L-FABP, ng/ml	2.2 (1.0, 4.9)	2.7 (1.1, 4.9)	0.39
8-OHdG, ng/ml	3.9 (1.0, 5.7)	3.7 (1.6, 6.7)	0.43
Office SBP, mm Hg	138.0 ± 16.4	138.8 ± 18.2	0.79
Office DBP, mm Hg	79.8 ± 10.5	81.1 ± 10.2	0.47
Office HR, beats/min	71.4 ± 11.2	69.7 ± 10.9	0.38
Morning home SBP, mm Hg	134.0 ± 14.1	137.0 ± 13.0	0.20
Morning home DBP, mm Hg	82.9 ± 12.0	84.2 ± 9.8	0.51
Morning home HR, beats/min	69.1 ± 11.0	68.1 ± 9.9	0.60
Evening home SBP, mm Hg	124.7 ± 14.6	127.5 ± 14.0	0.26
Evening home DBP, mm Hg	76.2 ± 11.9	77.2 ± 10.2	0.60
Evening home HR, beats/min	71.5 ± 11.0	72.5 ± 10.3	0.62
CAVI	9.1 ± 1.4	9.2 ± 1.1	0.64
ABI	1.12 ± 0.08	1.13 ± 0.10	0.56
ba-PWV, m/s	20.0 ± 6.4	19.4 ± 3.5	0.50

Note: Values are mean ± standard deviation, median (interquartile range), or percentage of patients.

Abbreviations: 8-OHdG, 8-hydroxy-2'-deoxyguanosine; ABI, ankle-brachial pressure index; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ba-PWV, brachial-ankle pulse wave velocity; CAVI, cardio-ankle vascular index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HR, heart rate; hs-CRP, high sensitive C-reactive protein; hs-TnT, high-sensitivity cardiac troponin T; L-FABP, liver-type fatty acid-binding protein; NT-proBNP, amino terminal-pro B-type natriuretic peptide; SBP, systolic blood pressure; UACR, urinary albumin-creatinine ratio.

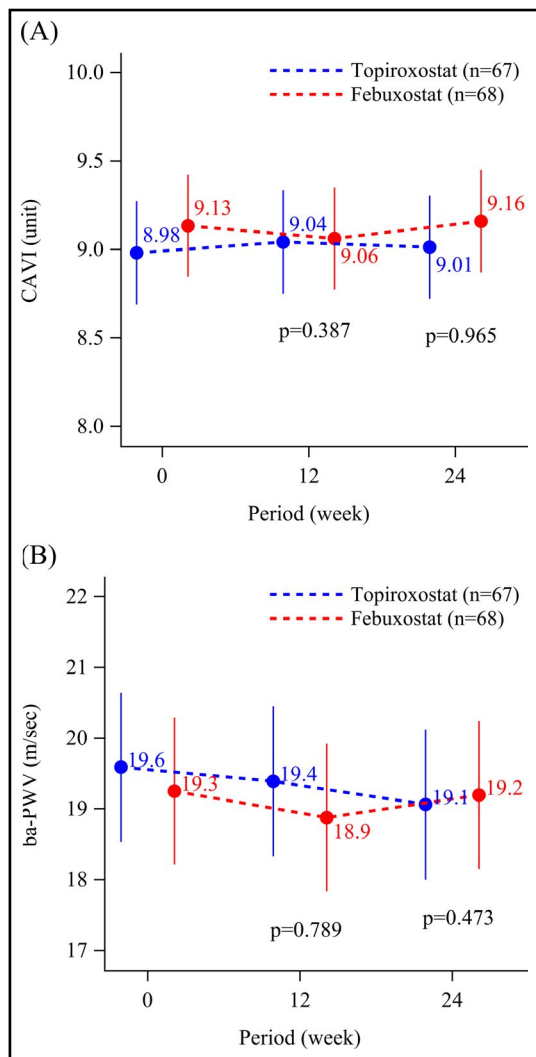


FIGURE 2 Changes from baseline in the cardio-ankle vascular index (CAVI) (A) and brachial-ankle pulse wave velocity (ba-PWV) (B). Points and bar represent the least-squares mean and 95% confidence interval using the mixed-effects model with repeated measures adjusted for sex and age. *p*-values are for the between-group difference change from baseline

rationale for investigating the effects of XORi on arterial stiffness is because high UA levels have been reported to increase PWV by inhibiting the cholinergic response.²⁴ Therefore, lowering serum UA might have beneficial effects on arterial stiffness. However, neither agent in our study had any significant effect on arterial stiffness in hyperuricemic patients with hypertension over 24 weeks. This is also the first study to evaluate the effects of XORi on CAVI as a measure of arterial stiffness. Previous studies have looked at the effects of XORi on arterial stiffness assessed using PWV. There were no changes in either arterial stiffness parameter in our study.

The findings of this study are in contrast to some previous investigations showing potential beneficial effects of XORi on markers of arterial function and stiffness. Data from a systematic review and meta-analysis of randomized controlled trials of

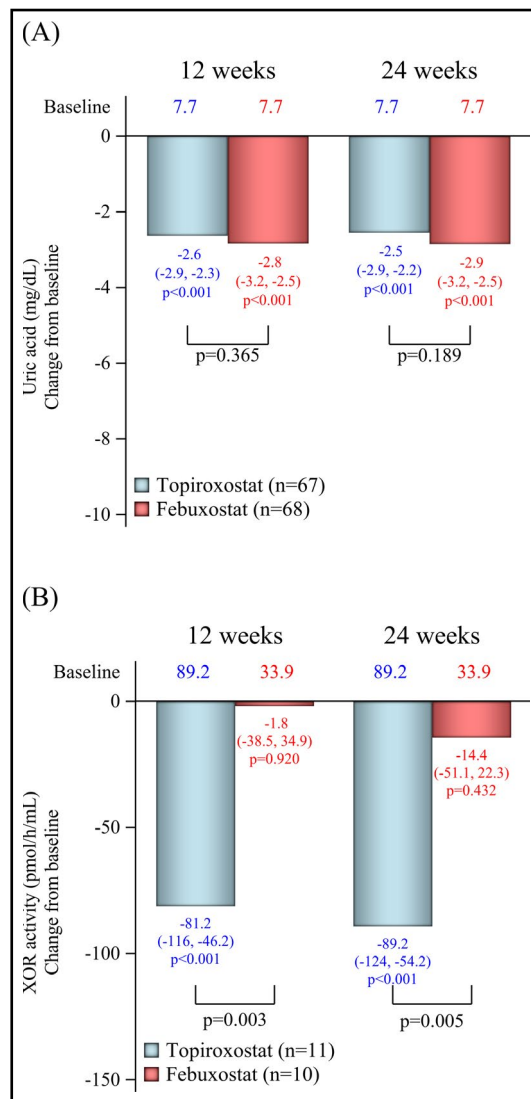


FIGURE 3 Changes from baseline in serum uric acid levels (A) and xanthine oxidoreductase (XOR) activity (B). Bars represent the least-squares mean using the mixed-effects model with repeated measures adjusted for sex and age (absolute values and associated 95% confidence intervals are shown below each bar)

allopurinol found that treatment was associated with a significant increase in flow-mediated diameter (FMD, as a measure of endothelial function).¹⁷ FMD also improved during 8 weeks' treatment with topiroxostat in a retrospective cohort study of patients with hyperuricemia and cardiovascular risk,¹⁸ and in a 12-week randomized controlled clinical trial that enrolled patients with hypertension and hyperuricemia.²⁰ In another meta-analysis, treatment with allopurinol significantly improved one measure of arterial stiffness (augmentation index) but not another (PWV).²⁵ In a study of cardiac surgery patients, PWV improved significantly from baseline during 6 months of treatment with febuxostat, but not allopurinol.¹⁹ [Correction added on January 24, 2021, after first Online publication: The term "topiroxosta" has been changed to "febuxostat"].

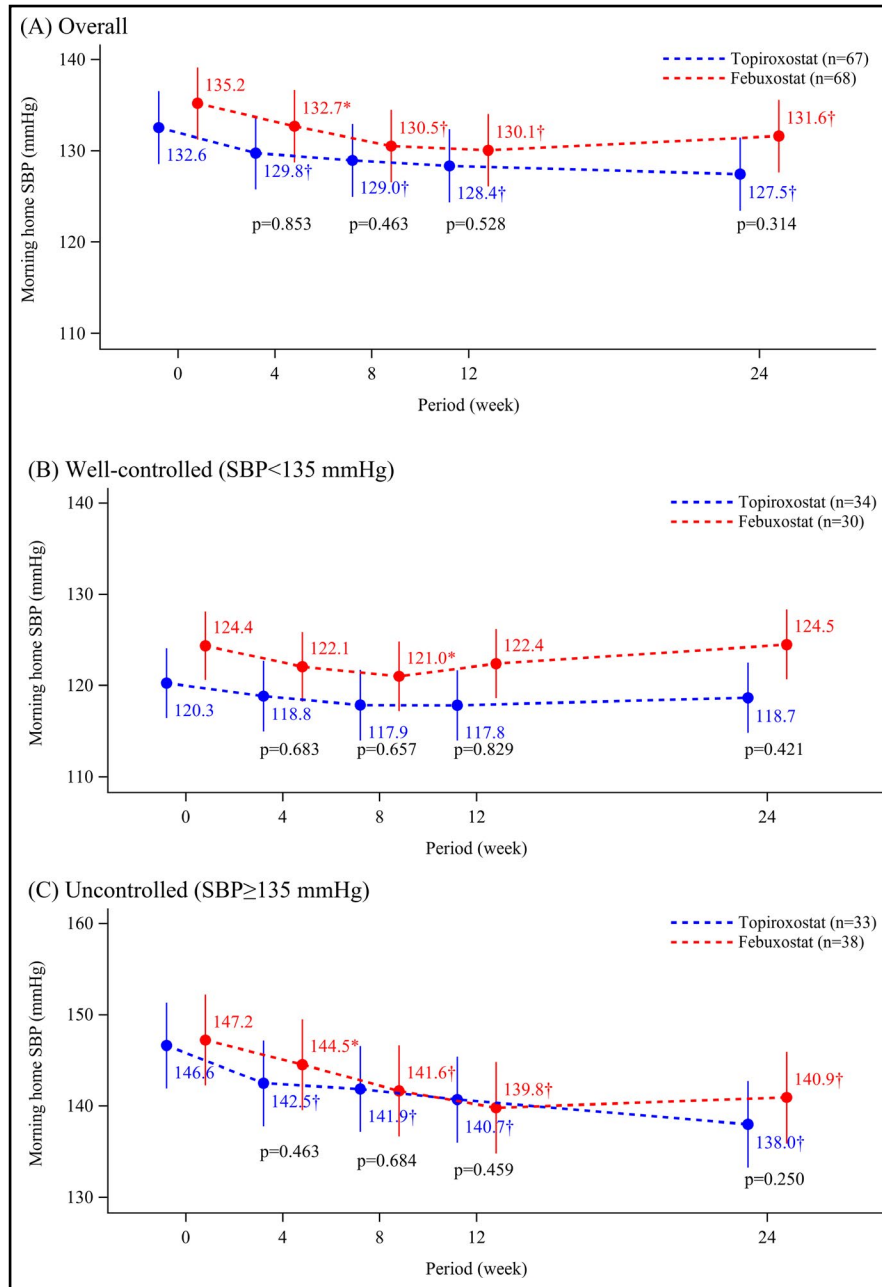


FIGURE 4 Changes from baseline in morning home systolic blood pressure (SBP) in the overall study population (A), in patients with well-controlled morning home SBP at baseline (SBP < 135 mm Hg) (B), and in patients with uncontrolled morning home SBP at baseline (SBP ≥ 135 mm Hg) (C). Points and bar represent the least-squares mean and 95% confidence interval using the mixed-effects model with repeated measures adjusted for sex and age. *p*-values are for the between-group difference change from baseline. **p* < 0.05 for change from baseline; †*p* < 0.01 for change from baseline

Currently available data on the effects of XOR inhibitors on arterial properties are inconsistent, and our study is not the first time that a lack of effect of XORi on arterial properties has been reported. Treatment with allopurinol had no effect on arterial stiffness (PWV) despite a significant reduction in serum UA concentration in 66 patients with chronic heart failure.²¹ Furthermore, 24 months of febuxostat treatment did not delay carotid atherosclerosis progression (assessed using intima-media thickness [IMT]) compared with non-pharmacological hyperuricemia management in Japanese patients with asymptomatic hyperuricemia.²⁶

There are a number of potential explanations for our study findings. The first is that improvements in endothelial function during treatment with XORi, as previously documented with allopurinol¹⁷ and topiroxostat,¹⁸ may precede changes in arterial stiffness. Arterial stiffness is considered to reflect effects on smooth muscle cells more than endothelial cells, and therefore, a longer duration of therapy and follow-up might be needed to detect the effects of XORi treatment on arterial stiffness parameters. This possibility is supported by data showing that endothelial dysfunction is associated with progression of arterial stiffness (measured using ba-PWV) after 3 years' follow-up in

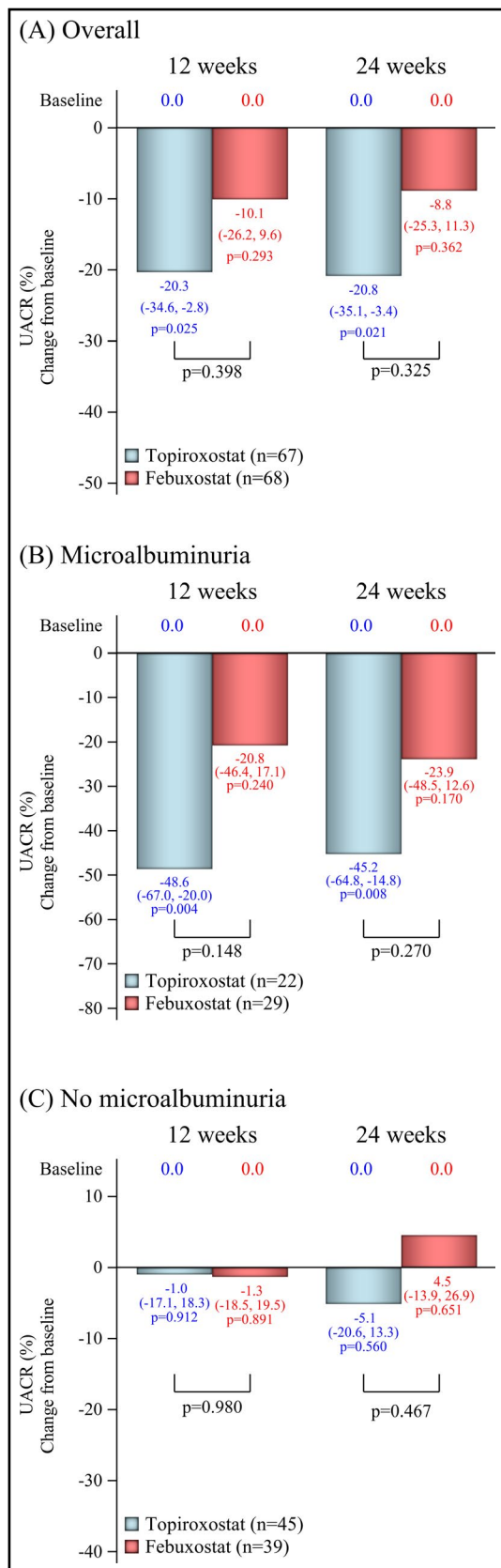


FIGURE 5 Percent change from baseline in the urinary albumin-creatinine ratio (UACR) in the overall study population (A), in patients with microalbuminuria at baseline (B), and in patients without microalbuminuria at baseline (C). Bars represent the least-squares mean using the mixed-effects model with repeated measures adjusted for sex and age (absolute values and associated 95% confidence intervals are shown below each bar). Percent change from baseline values was back-transformed from natural log. *p*-values are for the between-group difference in change from baseline

in this endpoint. In addition, the design and treated populations vary widely between studies, highlighting a lack of cohesive, consistent, and comparative data in this area. [Correction added on January 24, 2021 after first Online publication: The term “allopurinol” has been changed to “allopurinol” and reference citation “20” was removed]

In terms of renal function in our study population who had hyperuricemia and hypertension, secondary endpoint analysis showed significant reductions in the UACR from baseline in the topiroxostat group, but not during treatment with febuxostat. Topiroxostat also significantly reduced the UACR compared with baseline and placebo in a randomized, double-blind crossover study including CKD stage G3 patients with hyperuricemia and gout,²⁸ and in diabetic nephropathy patients with hyperuricemia and gout in an open-label study.¹⁴ These data may indicate potential renoprotective effects of topiroxostat.

Although within-group changes were not the primary endpoint of this study, the UACR-lowering effect seen during topiroxostat treatment in patients without CKD was a novel finding. A high UACR has been reported to increase the risk of end-stage renal failure, and cardiovascular and all-cause death, including in patients with normal or high eGFR (CKD stage G1; eGFR ≥ 90 ml/min/1.73 m²).²⁹ Theoretically, then, topiroxostat may be able to attenuate the onset of CKD and reduce cardiovascular event risk, possibly due to potent XORi activity. Animal study data showed that the 50% inhibitory concentration (IC₅₀) of febuxostat against plasma XOR in vitro was 12-fold higher than that of topiroxostat, and only the effects of febuxostat were affected by the presence of plasma proteins.⁸ In a mouse model, both topiroxostat and febuxostat significantly reduced the UACR, but only changes with topiroxostat were dose dependent.⁸ In addition, a reduction in urinary protein levels has been documented in patients with hyperuricemia and CKD after switching from febuxostat to topiroxostat.³⁰ The beneficial effects of topiroxostat on UACR might be attributable to its inhibitory action on XOR binding to surface membrane of endothelial cells, which causes endothelial dysfunction in glomerular afferent arterioles, as well as other vessels.³¹ Preclinical data suggest that reductions in oxidative stress during treatment with XORi are likely to contribute to the renoprotective effects of these agents.^{32,33} It is also possible that the reduction of UACR by topiroxostat treatment identified in the current study may represent an improvement in endothelial function.

There are a number of potential mechanisms by which high levels of UA might contribute to the development of hypertension. Firstly, UA activates the renin-angiotensin system (RAS), reduces

patients with hypertension.²⁷ Furthermore, in contrast to the current trial, arterial stiffness was not the primary endpoint of the majority of previous studies, limiting the power to detect significant changes

endothelial nitric oxide bioavailability (by decreasing nitric oxide synthase expression), up-regulates aldose reductase, causes mitochondrial dysfunction, and stimulates superoxide generation, leading to endothelial dysfunction and renal vasoconstriction.³⁴ Subsequently, structural vascular damage (such as afferent arteriopathy) and mild interstitial inflammation develop.³⁵ This contributes to a salt-sensitive and UA-dependent hypertensive state.^{35,36} Salt-sensitive mechanisms relating to sodium absorption in the kidney may also be involved.³⁷ Furthermore, XOR activity in the blood has been reported to be associated with both insulin resistance and BP, probably as a result of oxidative stress.^{4,38,39} Angiotensin II has also been reported to induce activation of vascular endothelial xanthine oxidase, promoting a negative spiral that contributes to endothelial dysfunction and increases BP.⁴⁰

Although it was only a secondary endpoint in the current study, we report for the first time a significant reduction from baseline in morning home BP during treatment with topiroxostat and febuxostat (Figure 4A). These changes were primarily seen in the subgroup of patients with uncontrolled morning home systolic BP at baseline (Figure 4C). Treatment with allopurinol has also been shown to be associated with small but significant reductions in BP.¹⁰ We hypothesize that reductions in XOR activity in the blood contributed to the reductions in BP seen in our study, and that XORi might represent a potential therapeutic option for hyperuricemic patients with high BP. The ability of the treatments in the current study to significantly reduce morning home SBP is clinically relevant because uncontrolled morning hypertension is an important risk factor for stroke and coronary events.^{29,41}

Regardless of the mechanism by which topiroxostat contributes to reductions in BP and the UACR, there are important clinical implications of these effects. Recently, the FREED study reported that febuxostat reduced the risk of cerebral, cardiovascular and renal events, and all-cause mortality compared with the control group in elderly patients with hyperuricemia (HR 0.750, 95% CI 0.592–0.950; $p = 0.017$).⁴² It was suggested that improvements in renal function contributed to these beneficial effects, indicating that there could be a close and important correlation between CKD and cardiovascular disease—"the cardio-renal interaction." In the current study, topiroxostat therapy was associated with improvements in renal function in hyperuricemic patients with hypertension, and may therefore have a beneficial effect on prognosis via "the cardio-renal interaction." However, neither the Japanese guideline on management of hyperuricemia and gout (JGMHG) 3rd edition⁴³ nor the 2020 American College of Rheumatology Guideline for the Management of Gout⁴⁴ provide any recommendation for the pharmacological treatment of asymptomatic hyperuricemia with hypertension to protect against cardiovascular events. Therefore, additional evidence is needed to inform future guideline updates.

Several limitations need to be taken into account when interpreting the findings of this study. The most important limitation is the open-label design of the study, which makes it more difficult to control for bias. In addition, the study duration may have been insufficient to fully evaluate and detect the effects of the study treatments

on arterial stiffness. Endothelial dysfunction probably precedes the development of arterial stiffness, but this study did not include markers of endothelial dysfunction (eg, FMD). Therefore, it is possible that a longer duration of action and the inclusion of additional endpoints may have provided better information on the gradual decline in arterial function over time in patients with hyperuricemia and hypertension, and the effects of treatment with XORi. However, the absence of a placebo group in the trial means that the natural history of recorded parameters is unknown. The lack of a placebo control group also means that within-group changes in parameters such as BP and the UACR should be interpreted with caution. Finally, the external validity of the findings is limited by the single ethnicity nature of the study population (Japanese).

5 | CONCLUSIONS

This randomized clinical trial did not detect any significant effects of the XORi topiroxostat and febuxostat on arterial stiffness parameters in patients with hyperuricemia and hypertension. Placebo-controlled trials are required to better understand the promising effects of XORi on the UACR and BP. Additional research is also needed to further elucidate the longer term effects of treatment with XORi on arterial function, as an important measure of cardiovascular risk.

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AUTHOR CONTRIBUTIONS

Kazuomi Kario involved in study conception and design. Masafumi Nishizawa, Mari Kiuchi, Arihiro Kiyosue, Fumishi Tomita, Hiroshi Ohtani, Yasuhisa Abe, Hideyo Kuga, Satoshi Miyazaki, Takatoshi Kasai, Makiko Hongou, Takanori Yasu, Jin Kuramochi, Yoshihiro Fukumoto, and Satoshi Hoshide involved in data preparation. Kazuomi Kario and Ichiro Hisatome involved in data analysis and interpretation. All authors involved in Drafting and revising of the manuscript and final approval of the submitted manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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