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Original

Therapeutic Effects of Allopurinol and Topiroxostat in Chronic Kidney Disease Patients with Hyperuricemia

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SUMMARY

Patients with chronic kidney disease (CKD) are at high risk for developing cardiovascular diseases, and hyperuricemia is associated with the progression of renal dysfunction and the incidence of cardiovascular events. Allopurinol (Alp), a xanthine oxidase inhibitor (XOi), has been shown to improve the prognosis of CKD patients by inhibiting renal dysfunction and cardiovascular events. However, Alp possibly causes some serious side effects especially in patients with impaired renal function. Newer XOi such as febuxostat and topiroxostat (Tpx) can be safely used in CKD patients, while it has been reported that the incidence of cardiovascular death was rather higher in gout patients with cardiovascular diseases given febuxostat than those given Alp. In this study, we compared the effects of Alp and Tpx on cardiovascular risk profile in CKD patients. Thirty-five CKD patients were given Alp (50, 100, 200 mg/day) or Tpx (40, 80, 160 mg/day) for 3-6 months in a random crossover manner, and the indices of cardiovascular risk were evaluated at the end of each treatment period. Hypouricemic effect was more prominent in Tpx than Alp (5.8 vs 6.4 mg/dL, $p=0.001$). There were significant differences in systolic blood pressure (Tpx 122 vs Alp 127 mmHg, $p=0.004$), serum creatinine (1.72 vs 1.93 mg/dL, $p=0.002$), plasma brain natriuretic peptide (43 vs 63 pg/mL, $p=0.022$), and the parameter of oxidative stress (reactive oxygen metabolite : 314 vs 342 U. CARR, $p=0.010$). However, serum LDL-cholesterol (113 vs 102 mg/dL, $p=0.008$) were significantly higher in Tpx than in Alp. Although attention should be paid to the effects on serum lipid profile, Tpx is supposedly more effective in inhibiting cardiovascular disorders and slowing the progression of renal dysfunction in hyperuricemic CKD patients.

Key words : uric acid, hyperuricemia, chronic kidney disease, xanthine oxidase inhibitor, topiroxostat, allopurinol

INTRODUCTION

Hyperuricemia is assumed as one of lifestyle-related diseases as well as hypertension, dyslipidemia and diabetes mellitus. Duration of these lifestyle-related diseases, in a long term, promote the occurrence and progression of arteriosclerosis and thereby increase the risk of cardiovascular diseases such as stroke and coronary artery disease. In clinical practice, it is often experienced that a patient is complicated with multiple lifestyle-related diseases which means they do not occur independently but their pathogeneses are intimately interrelated to each other[1~4]. In order to effectively prevent the incidence of cardiovascular diseases and resultant organ failures such as end-stage renal disease (ESRD) and heart failure, it is important

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to make comprehensive intervention in lifestyle-related diseases simultaneously and achieve strict control and persistent improvement. Among the lifestyle-related diseases, the etiology of hyperuricemia is closely related to renal dysfunction because uric acid is mainly excreted into urine[5]. Therefore, the preservation of renal function should be considered in the management of hyperuricemia.

On the other hand, it has become well-recognized that the chronic kidney disease (CKD), manifested by reduced renal function and proteinuria, is prevalent and contribute not only to the development of ESRD but also to the incidence of cardiovascular diseases[6,7]. As serum uric acid is prone to be increased by reduced renal function, the management of hyperuricemia is thought to be important especially in patients with CKD in order to prevent cardiovascular diseases and improve the prognosis. As the antihyperuricemic drugs for CKD patients, production inhibitors of uric acid rather than uricosuric drugs are preferentially used because the effects of the latter are restricted by renal dysfunction. Allopurinol (Alp) is dominantly used so far as a xanthine oxidase inhibitor (XOi) which suppress the uric acid generation. Lately, newer XOi such as febuxostat and topiroxostat (Tpx) have been introduced into clinical use and the prescriptions of these new XOi are increasing[8].

In this study, the effects of a new XOi, Tpx, were compared to the traditional XOi, Alp, on the cardiovascular risk profile in patients with CKD who are assumed to be at high risk of cardiovascular diseases.

METHODS

The subjects enrolled in this study were 35 patients with CKD and hyperuricemia whose serum uric acid was 8 mg/dL or higher and/or who were taking antihyperuricemic drugs. 24 patients were not taking antihyperuricemic drugs, while 6 and 5 patients were taking febuxostat and topiroxostat, respectively. CKD was defined as having proteinuria (≥0.15 g per g creatinine) including microalbuminuria (≥20 mg for men and ≥30 mg for women per g creatinine) and/or estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2[9]. However, patients undergoing dialysis therapy were not included. The eGFR was calculated from the serum creatinine level and age by the following equation[10]: $eGFR = 194 \times Age^{-0.287} \times sCr^{-1.094}$ ($\times 0.739$ for females).

After more than 4 weeks of run-in period, the patients were given Alp (50, 100 mg once daily or 100 mg twice daily) or Tpx (20, 40 or 80 mg twice daily) for 3 to 6 months according to a randomized crossover design. The xanthine oxidase inhibitor having been taking, if any, was stopped before starting on the study drugs. The sequence of treatment periods with Alp and Tpx was randomized. The titrations of study drugs were left to the discretion of attending physicians within the above-indicated doses.

Office blood pressure was measured with a sphygmomanometer in the sitting position after resting for at least 20 min at each visit every 4 weeks. After overnight fasting blood samples were collected at rest in the sitting position for more than 20 minutes on the final day of each treatment period. In addition to the routine blood chemistry and blood cell counts, plasma high-sensitivity C-reactive protein (HSCRP), a marker of inflammation, was measured by a highly sensitive sandwich ELISA and plasma B-type natriuretic peptide (BNP) was assayed using chemiluminescent enzyme immunoassay.

As circulating markers of oxidative stress, derivatives of reactive oxygen metabolite (d-ROM) and biological antioxidant potential (BAP) were determined in the serum stored at −80℃ and thawed only once before examination using autoanalyzer, FRAS4 (Wismerll, Tokyo, Japan)[11]. The d-ROM was measured by colorimetry of oxidized chromogen, N,N-diethyl-p-phenylenediamine and expressed in units of U. CARR[12]. The BAP was measured as antioxidants that reduce ferric ion (Fe^{3+}) to ferrous iron (Fe^{2+}) and expressed in μmol/L[13].

Casual urine samples were collected on the final day of each treatment period. Urinary albumin was measured by an immunoturbidimetric method and corrected using the urinary creatinine level. Urinary concentration of L-FABP was measured by enzyme-linked immunosorbent assay (ELISA), and the value was expressed as a ratio to the urinary creatinine concentration measured by colorimetry[14].

The study protocol was in accordance with the recommendations of the World Medical Association for biomedical research involving human subjects and

Table 1 Baseline characteristics of the study subjects

Age, years	64.7±14.3
	66 (27–85)
Gender, male/female	25/10
Body mass index, kg/m^2	24.0±4.1
Systolic blood pressure, mmHg	126.4±13.4
Diastolic blood pressure, mmHg	77.6±7.7
Heart rate, bpm	73.7±13.1
Serum creatinine, mg/dL	1.75±0.99
	1.42 (0.75–4.46)
eGFR, mL/min/1.73 m^2	40.9±20.8
	40.3 (9.1–78.3)
Urinary albumin, mg/gCr	766±1192
	1.42 (0.75–4.46)
Renal disease	
Chronic glomerulonephritis	19 (54.3%)
Nephrosclerosis	8 (22.9%)
Diabetic kidney disease	3 (8.6%)
Complications	
Hypertension	24 (68.6%)
Diabetes mellitus	8 (22.9%)
Dyslipidemia	18 (51.4%)
Cardiovascular disease	6 (17.1%)

Data are the mean±SD and median (min–max), eGFR : estimated glomerular filtration rate.

Table 2 Medications concurrently given with the xanthine oxidase inhibitor in study subjects.

Drug	Number of subjects (%)
Antihypertensive drug	32 (91.4%)
Diuretic	7 (20.0%)
β-blocker	1 (2.9%)
α-blocker	3 (8.6%)
Calcium channel blocker	19 (54.3%)
ACE inhibitor	3 (8.6%)
ARB	27 (77.1%)
Direct renin inhibitor	1 (2.9%)
Oral hypoglycemic agent	5 (14.3%)
DPP-4 inhibitor	4 (11.4%)
SGLT-2 inhibitor	4 (11.4%)
Other	1 (2.9%)
Lipid-lowering drug	17 (48.6%)
Statin	11 (31.4%)
Other	8 (22.9%)
Antiplatelet drug	16 (45.7%)
Anticoagulant	1 (2.9%)
Antianginal drug	2 (5.7%)
Carbon adsorbent	2 (5.7%)
Vitamin D	4 (11.4%)
Steroid	2 (5.7%)

ARB : Angiotenisn II receptor blocker, DPP-4 : dipeptidyl peptidase-4, SGLT-2 : sodium-glucose transporter-2.

was approved by the institutional review board (R-8-2). Informed consent was obtained from all subjects after explaining the study objective and design.

Clinical data were expressed as means±standard deviations (SD). Values between the 2 periods were compared by paired t-test, however, Wilcoxon signed-rank test was applied for the data with skewed distribution such as urinary albumin, L-FABP, BNP and HSCRP. Comparisons between the values at more than two time points were performed using one-way ANOVA for repeated measures followed by Tukey's method for post-hoc multiple comparisons. A P value of less than 0.05 was considered to be statistically significant.

RESULTS

All the 35 patients enrolled showed good adherence to the therapy and fulfilled the whole study periods. The average doses of Alp and Tpx given at the end of each treatment period was 87±36 mg and 64±34 mg, respectively. Table 1 shows the background characteristics of these 35 patients. The average age was 64.7 years (29 to 85) and 71.4% were men. Although the averaged blood pressure (BP) level was within normal range, 5 patients (14.3%) had systolic BP≥140 mmHg and/or diastolic BP≥90 mmHg and 21 patients (60.0%) had systolic BP≥130 mmHg and/or diastolic BP≥80 mmHg. In other words, 30 patients (85.7%) had BP lower than140/90 mmHg and of which 14 patients (40.0%) had BP lower than 130/80 mmHg. The body mass index was in overweight range (≥25 kg/m^2) in 12 patients (34.3%). As to the GFR stage of CKD, 5 (14.3%), 10 (28.6%), 8 (22.9%), 7 (20.0%) and 5 (14.3%) patients were classified as G2 (60–89 mL/min/1.73 m^2), G3a$^{45\sim59)}$, G3b$^{30\sim44)}$, G4$^{15\sim29)}$ and G5 (<15), respectively. On the other hand, the albuminuria stage, 11 (31.4%), 10 (28.6%) and 14 (40.0%) patients showed A1 (<30 mg/gCr), A2 (30–299) and A3 (≥300) level albuminuria, respectively. Chronic glomerulonephritis was most frequent as causative renal disease followed by nephrosclerosis. In addition, a considerable number of

Table 3 Office blood pressure, heart rate and body weight at the ends of allopurinol and topiroxostat therapy periods.

	Before	Allopurinol	Topiroxostat
Systolic BP, mmHg	126.4±13.4	126.8±11.3	122.1±13.0†
Diastolic BP, mmHg	77.6±7.7	77.9±7.8	76.7±8.6
Heart rate, bpm	73.7±13.1	74.7±11.8	75.3±13.0
Body weight, kg	64.3±14.4	64.2±14.2	64.4±14.3

Data are the mean±SD. BP：blood pressure, †$p<0.005$.

Table 4 Laboratory data at the ends of allopurinol and topiroxostat therapy periods.

Variable	Allopurinol	Topiroxostat	P value
Blood cell counts			
White blood cell, $\times10^3/mm^3$	6.43±1.50	6.23±1.38	0.275
Red blood cells, $\times10^6/mm^3$	41 3±75	424±73	0.133
Blood hemoglobin, g/dL	13.0±2.1	13.0±2.7	0.162
Hematocrit, %	39.1±5.7	39.6±8.3	0.319
Platelet, $\times10^4/mm^3$	21.3±6.5	21.9±6.6	0.107
Blood chemistry			
Aspartate transaminase, U/L	24±10	23±7	0.429
Alanine transaminase, U/L	22±15	23±15	0.59
Total protein, g/dL	7.1±0.5	7.1±0.6	0.775
Albumin, g/dL	4.0±0.3	4.0±0.3	0.738
Creatinine, mg/dL	1.93±1.24	1.72±0.97	0.002
Uric acid, mg/dL	6.4±1.1	5.8±1.0	<0.001
Na, mEq/L	140.2±2.1	140.6±1.4	0.303
K, mEq/L	4.7±0.5	4.7±0.5	0.438
Hemoglobin A1c, %	6.0±0.5	6.0±0.5	0.636
HDL-Chol, mg/dL	53±19	54±19	0.642
LDL-Chol, mg/dL	102±28	113±32	0.008
Triglycerides, mg/dL	192±112	171±103	0.158

Data are the mean±SD. HDL：high-density lipoprotein, LDL：low-density lipoprotein.

patients had lifestyle-related diseases other than hyperuricemia such as hypertension and dyslipidemia.

Table 2 lists the drugs concurrently taken with Alp or Tpx by study subjects during the study periods. Most patients were under antihypertensive drug therapy and angiotenisn II receptor blockers (ARB) were most frequently used followed by calcium channel blockers. In addition to these antihypertensive drugs, a considerable numbers of patients were taking lipid-lowering drugs such as statin and antiplatelet drugs.

The changes in office BP, heart rate and body weight of study subjects during the study periods were presented in Table 3. Body weight was not significantly changed throughout the study periods. The systolic BP was significantly lower in the period given Tpx than the run-in period, while the change was insignificant in the period given Alp. There were no significant differences in the diastolic BP or the heart rate between the run-in period, of the Alp period and the Tpx period.

Table 4 shows the data of routine blood cell counts and blood chemistry at the end of each treatment period. The blood hemoglobin concentration and hematocrit as well as white blood cell and platelet counts were not significantly different between the Alp and the Tpx periods. Serum uric acid and creatinine were significantly lower in the Tpx period than in the Alp period. There were no significant differences in serum liver enzymes, proteins, electrolytes, and an index of glucose metabolism. As to the serum lipid

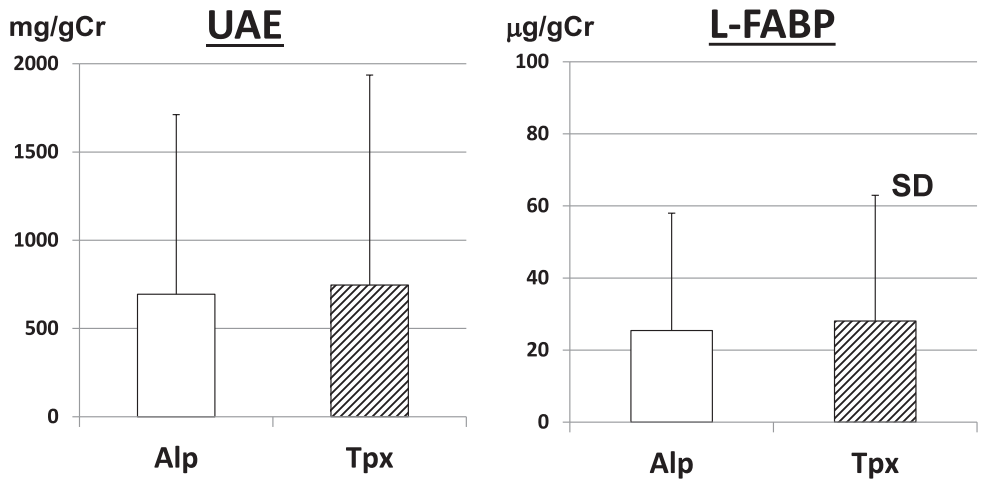

Figure 1 Urinary Excretions of Albumin (UAE) and Liver-type Fatty Acid Binding Protein (L-FABP) at the end of period given allopurinol (Alp) or topiroxostat (Tpx).

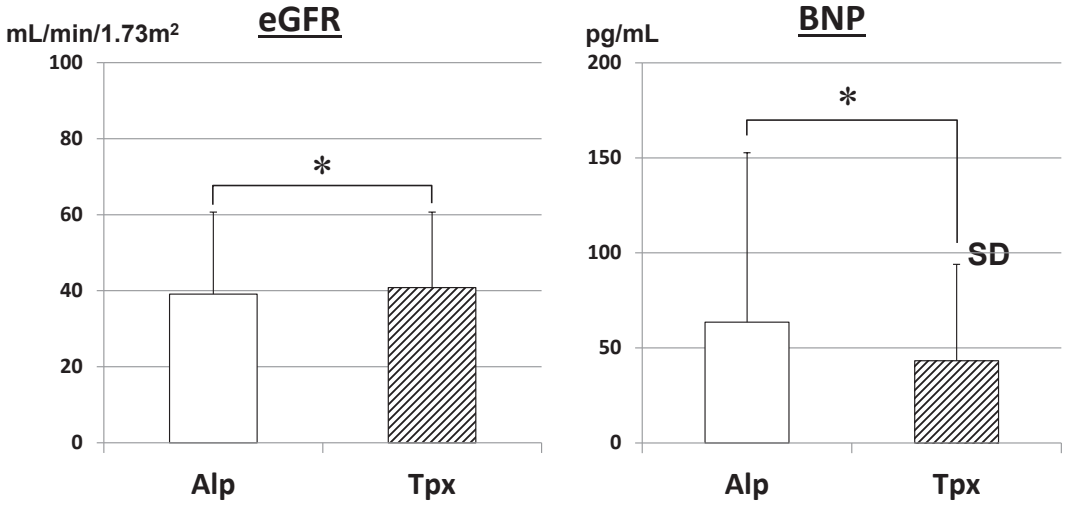

Figure 2 Estimated Glomerular Filtration Rate (eGFR) and Plasma Brain Natriuretic Peptide (BNP) at the end of period given allopurinol (Alp) or topiroxostat (Tpx). *$p<0.05$

profile, serum LDL-cholesterol was significantly lower in the Alp period than in the Tpx period, however, serum HDL-cholesterol or triglycerides were not significantly different between the two treatment periods.

Figure 1 shows urinary excretions of albumin (left panel) and L-FABP (right panel) at the end of period given Alp or Tpx. Significant differences were not observed in these parameters of renal injury between the two xanthine oxidase inhibitors. Figure 2 presents eGFR (left panel) and plasma BNP (right panel) in the Alp and the Tpx periods. As expected from the difference in serum creatinine described above, eGFR was significantly higher in the Tpx period than in the Alp period (40.8 ± 19.8 vs. 39.0 ± 21.5, $p = 0.034$). Furthermore, plasma BNP was significantly lower in the Tpx period than in the Alp period.

Circulating markers of oxidative stress and inflammation are indicated in Figure 3. The metabolites of free radical-providing molecules, d-ROM, was significantly lower in the Tpx period than in the Alp period, while the biological antioxidant capacity, BAP, was not significantly different. The effects on plasma HSCRP, an inflammatory marker, did not significantly differ between the two xanthine oxidase inhibitors.

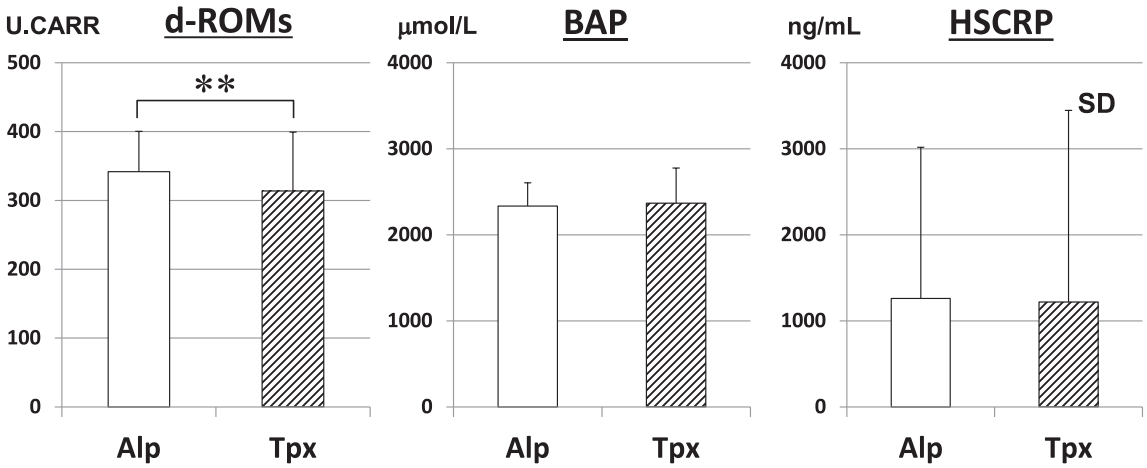

Figure 3 Serum Reactive Oxygen Metabolites (d-ROMs), Biological Antioxidant Potential (BAP) and High-Sensitivity C-Reactive Protein (HSCRP) at the end of period given allopurinol (Alp) or topiroxostat (Tpx). **p<0.01.

DISCUSSION

Hyperuricemia is generally recognized as a risk factor for cardiovascular diseases such as hypertension, stroke and coronary artery disease[15~22] and has also shown to be associated with the incidence of CKD and the progression of renal dysfunction in patients with CKD[23~27]. As the urinary excretion of uric acid is impaired in patients with decreased function, serum uric acid level is expected to increase in these patients and it seems unclear if hyperuricemia contributes to the pathogenesis of renal injuries or is only a marker of reduced renal function[28~30]. However, it has been reported that the incidence of CKD increased with increasing serum uric acid level even in subjects with estimated glomerular filtration rate (eGFR) higher than 60 mL/min/1.73 m^2 at baseline during the following 10 years[31]. In addition, the pharmacological treatment of hyperuricemia with allopurinol has been shown to reduce the incidence of cardiovascular events and delay further deterioration of renal function in CKD patients[32,33]. Therefore, it is speculated that the increased circulating levels of uric acid plays a role in the progression of renal and cardiovascular organ injuries.

As the antihyperuricemic effect of uricosuric drugs lessened by the existence of reduced renal function, Alp has been frequently used to inhibit uric acid production and improve hyperuricemia in CKD patients. However, Alp sometimes causes severe adverse effects such as bone marrow suppression and toxic epidermal necrosis and the risk is increased in CKD patients because of oxypurinol, a metabolite of Alp, is mainly excreted into urine and the blood concentration of this toxic metabolite is increased by renal dysfunction[34,35]. As compared with Alp, the newer XOi such as febuxostat and Tpx are excreted not only into urine but also metabolized in the liver and they can be used without reducing doses even in patients with reduced renal function[36,37]. Moreover, febuxostat and Tpx inhibit the activity of xanthine oxidase more selectively and more strongly than Alp in molecular bases[38], and these newer XOi have been shown to decrease serum uric acid more potently than Alp in patients with gout and hyperuricemia[39,40]. In this study, the serum uric acid was lower in the period given Tpx than in the period given Alp and no side effects were observed throughout the study periods. Therefore, it is thought that Tpx is more potent than Alp in lowering serum uric acid in hyperuricemic CKD patients without increasing the risk of adverse effects.

It is assumed that the cardiovascular diseases and renal dysfunction develop based on the progression of arteriosclerosis which is promoted by aging, smoking and lifestyle-related diseases such as diabetes, hypertension, dyslipidemia, and hyperuricemia. As for the risks of arteriosclerosis other than hyperuricemia, sys-

tolic BP was significantly decreased at the end of the period given Tpx in this study, while the BP was not significantly changed by Alp as compared with in the run-in period. So far several studies have shown that uric acid-lowering therapy by XOi reduced BP in patients with hyperuricemia[41~44]. The results of meta-analyses also indicate that XOi treatment significantly reduces BP in hyperuricemic patients including CKD[45,46]. Several possibilities have been surmised as to the mechanism by which XOi lowers BP such as inhibition of renin-angiotensin system, improvement of endothelial function and promotion of natriuresis[47~49]. Considering that Tpx but not Alp reduced BP in this study, such hypotensive effect as well as the hypouricemic effect may be more likely exhibited by Tpx than Alp. It is speculated that this BP reduction by XOi could contribute to the inhibition of cardiovascular diseases and the alleviation of renal dysfunction observed in the earlier clinical studies[50,51].

As to the effects of XOi on renal parameters, it has been reported that Tpx reduces albuminuria in CKD patients[52]. In the present study, eGFR was higher in Tpx than in Alp, however, urinary albumin excretion was not significantly different between Tpx and Alp. It has been also suggested that the antialbuminuric effect of Tpx is dose-dependent[53]. Considering that the dose of Tpx ranged from 40 to 160 mg and the average dose was 87mg, this dose may not have been sufficient to exhibit significant reduction in urinary albumin excretion in the current study.

On the other hand, Alp rather than Tpx is thought to have exerted preferable effects on serum lipid profile because serum LDL-cholesterol was lower in the Alp period than in the Tpx period. Alp has been shown to reduce serum LDL-cholesterol in some earlier studies with small number of patients[54,55], but the mechanism by which Alp works is unclear. Although the restoration of lipoprotein lipase activity suppressed by uric acid may promote the metabolism of LDL[56], the serum uric acid was more prominently lowered by Tpx than Alp. In addition, the significant effects of Alp on serum lipids were not consistently observed in other clinical studies[57], and the results of comprehensive meta-analysis could not indicate significant effects of uric acid normalization by Alp on serum lipid levels[58]. Therefore, the clinical significance of the influence of Alp on serum lipids seems elusive.

In addition to these traditional risk factors of arteriosclerosis, nontraditional factors such as inflammation and oxidative stress are thought to participate in the etiology and pathogenesis of vascular injuries[59~62]. It is assumed that arteriosclerotic and atherosclerotic lesions are initiated by functional disorder of the vascular endothelium and oxidative stress and inflammation are thought to participate in the etiology and pathogenesis of endothelial dysfunction[63]. The epidemiological studies have indicated that the existence of endothelial dysfunction and arterial stiffening is predictive of the incidence of cardiovascular events[64~67]. It has been shown that the endothelial dysfunction takes place from the early stage of CKD and is deeply involved in the development of cardiovascular disorders[68,69]. Considering that the serum d-ROM was lower in the Tpx period than in the Alp period in this study, Tpx may have advantage over Alp in reducing the oxidative stress and preventing the progression of vascular injuries in hyperuricemic CKD patients.

Thus, Tpx reduced systolic BP and alleviated oxidative stress, while serum LDL-cholesterol was lowered in the Alp period. Collectively thinking, Tpx rather than Alp seems more likely to be effective in improving cardiovascular and renal outcomes considering that the renal dysfunction was less prominent in the Tpx period than in the Alp period of the current study. Furthermore, in this study Tpx lowered plasma BNP compared with Alp in the study subjects. Circulating BNP is produced mainly in the cardiac ventricles and increases by pressure and volume load to the heart. Therefore, the reduced BP by Tpx may have contributed to the reductions in ventricular load and BNP production during the period given Tpx. In addition, higher GFR in Tpx than in Alp may have promoted the renal clearance of BNP resulting in lowered plasma BNP. As plasma BNP is supposed to be a predictive factor of the prognosis of cardiac diseases[70~72], it is speculated that the decreased BNP by Tpx may be associated with cardiovascular and renal protection in the long-term treatment of hyperuricemia in CKD patients. However, further evaluations and validations by long-term prospective studies are needed considering that all-cause and cardiovascular mortalities were

higher in patients with gout and cardiovascular comorbidities given febuxostat, another newer XOi as potent as Tpx in lowering serum uric acid, than those given Alp in CARES study[73].

In conclusion, this study demonstrated that Tpx is more effective in lowering serum uric acid than Alp in hyperuricemic CKD patients. Tpx also lowered BP, reduced plasma BNP, alleviated oxidative stress and improved renal function, while Alp lowered serum LDL-cholesterol. Taken these results together use of, Tpx seems to be advantageous over the use of Alp in the long-term management of hyperuricemia in CKD patients in terms of preventing cardiovascular and renal disorders.

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