MANAGEMENT OF RENAL FAILURE IN THE CONTEXT OF HYPERURICEMIC HEART DISEASE THROUGH DRUG METABOLISM: A COMPARATIVE ANALYSIS OF FEBUXOSTAT AND TOPIROXOSTAT

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ANNOTATION: *Hyperuricemia is one of the major risk factors for the development of chronic kidney failure and aggravates its progression. In this sub-analytical TROFEO study investigating chronic kidney failure, patients with hyperuricemia who underwent cardiovascular surgery and had an estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 m² were selected, and the effects of two xanthine oxidase enzyme inhibitors — febuxostat and topiroxostat — were compared. Forty-two patients were treated with febuxostat and thirty-nine with topiroxostat. The primary outcome of the study was the serum uric acid level, which febuxostat maintained below the clinically relevant threshold of 6.0 mg/dL. Secondary outcomes — creatinine, glomerular filtration rate, cystatin-C, and oxidized lipoproteins — showed favorable changes in the febuxostat group. No significant differences were found in urine albumin and lipid profile parameters. Based on these findings, febuxostat is evaluated as a superior therapeutic agent for the stable control of uric acid metabolism and preservation of renal function in patients with chronic kidney failure.*

KEYWORDS: *TROFEO study, hyperuricemia, chronic kidney failure, xanthine oxidase-reductase inhibitors, febuxostat, topiroxostat, uric acid*

INTRODUCTION: Hyperuricemia is a metabolic disorder that poses a risk of developing both early-stage renal disease and chronic kidney disease. Xanthine oxidase-reductase inhibitors are used worldwide for the treatment of hyperuricemia. In recent years, scientific data have been published regarding the efficacy of new agents in this drug class — febuxostat and topiroxostat. Previous observations have shown that febuxostat reduces serum uric acid levels faster than allopurinol, has stronger

renoprotective properties, and exhibits superior antioxidant and anti-inflammatory effects. These findings were demonstrated in the NU-FLASH study, which directly compared allopurinol and febuxostat.

Additionally, the TROFEO (Trial of Febuxostat and Topiroxostat for Hyperuricemia with Cardiovascular Disease) study was conducted to compare febuxostat and topiroxostat, involving 55 patients who underwent cardiovascular surgery and had complications due to hyperuricemia. The study was designed as a prospective cross-over trial. The primary evaluation criterion was serum uric acid level. Secondary indicators included: serum creatinine, estimated glomerular filtration rate (eGFR), urinary albumin level, cystatin C concentration, oxidized low-density lipoprotein (oxLDL), the ratio of eicosapentaenoic acid to arachidonic acid, total cholesterol, triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (HDL), cholesterol in remnant-like particles, high-sensitivity C-reactive protein, B-type natriuretic peptide, as well as drug-related adverse events.

The results of this study showed that febuxostat reduced uric acid levels more rapidly and effectively than topiroxostat, and demonstrated superior antioxidant properties. However, in that study, the two drugs were not compared specifically among patients with chronic kidney disease. Therefore, this article presents the sub-analysis of the TROFEO study — the TROFEO chronic kidney disease study — conducted among the subgroup of patients with chronic kidney disease who had undergone cardiovascular surgery. Patients with chronic kidney disease following cardiovascular surgery are considered a high-risk group, and the study was specifically conducted in such high-risk patients.

MATERIALS AND METHODS: This article presents a sub-analysis conducted among patients with an estimated glomerular filtration rate (eGFR) of 60 milliliters per minute per 1.73 square meters or lower, selected from participants in the TROFEO study on chronic kidney disease. The TROFEO study was conducted among outpatients with cardiovascular disease and hyperuricemia, in whom serum uric acid levels were controlled at 6 milligrams per deciliter or lower through treatment with allopurinol or febuxostat.

Patients were randomly assigned to groups using the envelope method: the first group received febuxostat for 6 months, and the second group received topiroxostat. After 6 months, the medications were switched, and treatment was continued with the alternate drug for another 6 months. Baseline data were collected before the medication switch, and follow-up was conducted for 6 months after the switch.

The primary evaluation criterion was serum uric acid level after treatment. Secondary indicators included: serum creatinine, estimated glomerular filtration rate, urinary albumin, cystatin C, oxidized low-density lipoprotein, the ratio of eicosapentaenoic acid to arachidonic acid, total cholesterol, triglycerides, low-density lipoprotein (LDL), high-

density lipoprotein (HDL), cholesterol in remnant-like particles, high-sensitivity C-reactive protein, B-type natriuretic peptide, and drug-related adverse effects.

Serum uric acid, creatinine, eGFR, total cholesterol, triglycerides, LDL, HDL, and their ratios were measured before treatment and monthly thereafter. Urinary albumin, cystatin C, oxidized LDL, the EPA/AA ratio, and B-type natriuretic peptide were evaluated before treatment and at 3 and 6 months.

Measurement results were expressed as mean values with standard error. Two-way analysis of variance was used to compare parameters between groups. A p-value of less than 0.05 was considered statistically significant.

RESULTS: A total of 55 patients participated in the TROFEO study. Among them, 42 patients were evaluated in the febuxostat group and 39 patients in the topiroxostat group within the TROFEO CKD sub-analysis.

Patient characteristics

	Febuxostat	**Toxpiroxostat**
Number	42	39
Age (years)	70.0 ± 8.0	70.8 ± 7.3
Gender (male: female)	31:11	28:11
Basic disease		
Ischemic heart disease	17 (41%)	17 (44%)
Valvular disease	15 (36%)	12 (31%)
Aortic disease	9 (21%)	9 (23%)
Others	1 (2%)	1 (2%)
Risk factors		
Diabetes mellitus	15 (36%)	15 (38%)
Hypertension	35 (83%)	32 (82%)
Dyslipidemia	29 (69%)	26 (67%)
Cerebrovascular disease	3 (7%)	3 (8%)
Obesity	5 (12%)	5 (13%)
Smoking	13 (31%)	13 (33%)
Chronic kidney disease		
G3a	11	15
G3b	22	19
G4	9	5
Medication		
ARB	24 (57%)	21 (54%)
ACE inhibitor	4 (10%)	4 (10%)
Renin inhibitor	4 (10%)	4 (10%)
Aldosterone blocker	23 (55%)	20 (51%)
Calcium antagonist	17 (41%)	17 (44%)

Beta-blocker	30 (71%)	28 (72%)
Statin	29 (69%)	26 (67%)
Furosemide	21 (50%)	21 (54%)
Febuxostat	16 (38%)	38 (97%)
Toxpiroxostat	25 (60%)	0 (0%)
Allopurinol	1 (2%)	1 (3%)

Primary outcome: Before and after treatment, there was no significant difference in serum uric acid (SUA) levels between the two groups. However, during the treatment period, SUA levels in the febuxostat group remained below 6.0 mg/dL, whereas in the topiroxostat group, 7 patients exceeded this threshold. This outcome was significantly higher in the topiroxostat group ($p = 0.004$). The mean initial dose of febuxostat was 17.3 ± 10.5 mg and remained unchanged during the 6-month period. In contrast, the initial dose of topiroxostat was 63.1 ± 37.4 mg, which was gradually increased during the 6 months of observation to 74.4 ± 43.3 mg.

Secondary outcomes: renal function parameters: There were no significant differences in serum creatinine (SCr) and estimated glomerular filtration rate (eGFR) at baseline. However, after 6 months, patients in the febuxostat group had lower SCr levels ($p = 0.043$) and higher eGFR ($p = 0.041$). Urinary albumin levels showed no significant differences between groups before treatment or at 3 and 6 months (3 months: $p = 0.354$, 6 months: $p = 0.313$). Cystatin C levels were similar at baseline but significantly lower in the febuxostat group after 6 months ($p = 0.011$).

Oxidative Stress Marker (oxidized low-density lipoprotein – Ox-LDL): No differences were observed at baseline. However, Ox-LDL levels were lower in the febuxostat group compared to the topiroxostat group at both 3 months ($p = 0.038$) and 6 months ($p = 0.048$).

Lipid and Fatty Acid Parameters: There were no significant differences between groups in total cholesterol, triglycerides (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), LDL/HDL ratio (L/H), remnant-like particle cholesterol, and the eicosapentaenoic acid/arachidonic acid (EPA/AA) ratio before or after treatment.

Inflammation Marker (high-sensitivity C-reactive protein – hs-CRP): No significant differences were found between the groups before or after treatment.

BNP (B-type natriuretic peptide): No significant differences in BNP levels were observed before or after treatment.

According to the data obtained in this study, serum creatinine (SCr), estimated glomerular filtration rate (eGFR), cystatin-C, and oxidized low-density lipoprotein (Ox-LDL) levels indicated that febuxostat has a stronger renoprotective and antioxidant effect compared to topiroxostat. The nephroprotective properties of xanthine oxidoreductase inhibitors (XOR-Is)—including allopurinol, febuxostat, and topiroxostat—have been previously reported in patients with chronic kidney disease (CKD).

In a meta-analysis conducted by Pisano et al., XOR-Is were evaluated as agents that slow the progression of CKD. In a study by Shibagaki, treatment with febuxostat resulted in increased eGFR and reduced proteinuria in patients with stage 3b–5 CKD. Similarly, in a 5-year observational study by Whelton, febuxostat improved eGFR inversely proportional to serum uric acid (s-UA): for every 1 mg/dL reduction in s-UA, a 1 mL/min increase in eGFR was predicted.

Cystatin-C, a sensitive marker of renal function, is not influenced by diet, muscle mass, or physical activity. There are no other studies specifically investigating uric acid control in patients with hyperuricemic CKD treated with XOR-Is, but this 6-month follow-up demonstrated that febuxostat lowered s-UA levels more effectively than topiroxostat, with additional benefits in SCr and eGFR levels.

While no significant difference in urinary albumin levels was observed between the groups, the febuxostat group showed numerically lower values. In some stage 3 CKD patients, allopurinol was switched to febuxostat, and after 3 months, s-UA levels significantly decreased, though the overall difference between groups was not statistically significant.

In animal studies, febuxostat was shown to dose-dependently reduce urinary protein and oxidative stress markers in a model of cisplatin-induced acute kidney injury. In a clinical trial by Hosoya, treatment with topiroxostat significantly decreased urinary albumin levels. The ETUDE study also showed that in diabetic nephropathy, high-dose topiroxostat (160 mg/day) significantly reduced albuminuria compared to a low dose (40 mg/day).

In a study by Nakamura, topiroxostat reduced both urinary albumin and plasma XOR levels in a dose-dependent manner in mice, whereas febuxostat did not exhibit a similar dose relationship. Furthermore, in another clinical study involving 13 CKD patients, switching from febuxostat to topiroxostat led to a significant decrease in urinary protein.

Apart from this study, there are no other direct comparative clinical trials between febuxostat and topiroxostat, making it difficult to draw definitive conclusions about which agent has stronger nephroprotective effects. However, the renal protective effects of XOR-Is have been supported by multiple studies.

CONCLUSION: According to the results of the additional study conducted within the framework of the Trial of Febuxostat and Topiroxostat for Hyperuricemia with Cardiovascular Disease (TROFEO) focused on chronic kidney failure, among the drugs that block the activity of the enzyme xanthine oxidase, febuxostat demonstrated a stronger nephroprotective and antioxidant effect compared to topiroxostat. This superiority was especially evident among patients diagnosed with both chronic kidney failure and cardiovascular diseases complicated by hyperuricemia. Throughout the study, the level of uric acid in the blood of patients treated with febuxostat consistently remained below 6.0 milligrams per deciliter, while in the group of patients treated with

topiroxostat, this indicator exceeded the threshold in seven individuals. This confirms the clinical efficacy of febuxostat in controlling serum uric acid levels.

The laboratory parameters used to evaluate renal function — serum creatinine concentration, estimated glomerular filtration rate, and cystatin-C levels — showed significant improvement in the group receiving febuxostat. A decrease in cystatin-C reflects a sensitive and stable improvement in renal function. Moreover, the reduction in oxidized low-density lipoprotein levels indicates febuxostat's potent antioxidant activity in the body.

At the same time, no statistically significant differences were observed between the two groups in urinary protein levels, inflammatory markers, or lipid metabolism indicators, such as total cholesterol, triglycerides, low-density lipoproteins, and high-density lipoproteins. This suggests that both drugs possess similar effects in terms of certain metabolic characteristics.

Based on the findings of this analysis and authorial evaluation, febuxostat can be recommended as the preferred therapeutic agent for long-term treatment in patients with chronic kidney failure, especially in those with concomitant cardiovascular diseases and hyperuricemia. Nevertheless, it remains appropriate to conduct further long-term and large-scale clinical trials to better elucidate the potential renal outcomes of topiroxostat therapy, particularly at higher doses and in various pathological contexts.

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