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Allopurinol, Febuxostat, and Nonuse of Xanthine Oxidoreductase Inhibitor Treatment in Patients Receiving Hemodialysis: A Longitudinal Analysis

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Rationale & Objective: Allopurinol and febuxostat, which are xanthine oxidoreductase inhibitors, have been widely used as uric acid-lowering medications. However, evidence regarding their cardiovascular effects in hemodialysis is insufficient. This study compared the effects of allopurinol and febuxostat on mortality and cardiovascular outcomes in patients receiving hemodialysis.

Study Design: A retrospective observational cohort study.

Setting & Participants: Data of 6,791 patients who had no history of topiroxostat usage and underwent maintenance hemodialysis between March 2016 and March 2019 at Yokohama Daiichi Hospital, Zenjinkai, and its affiliated dialysis clinics in Japan's Kanagawa and Tokyo metropolitan areas were collected.

Exposure: Allopurinol, febuxostat, and nontreatment.

Outcomes: All-cause mortality, cardiovascular disease (CVD) events, heart failure (HF), acute myocardial infarction (AMI), and stroke.

Analytical Approach: For the main analyses, marginal structural Cox proportional hazards models were used to estimate HRs adjusted for time-varying confounding and selection bias because of censoring.

Results: Allopurinol and febuxostat showed significantly better survival than nontreatment for all-cause mortality (HR, 0.40; 95% CI, 0.30-0.54 and HR, 0.49; 95% CI, 0.38-0.63, respectively), without significant difference between allopurinol and febuxostat. Allopurinol showed significantly better survival than nontreatment, whereas febuxostat did not for CVD events (HR, 0.89; 95% CI, 0.84-0.95 and HR, 1.01; 95% CI, 0.96-1.07, respectively), HF (HR, 0.71; 95% CI, 0.56-0.90 and HR, 1.03; 95% CI, 0.87-1.21, respectively), and AMI (HR, 0.48; 95% CI, 0.25-0.91 and HR, 0.76; 95% CI, 0.49-1.19, respectively). No comparisons showed significant results for stroke.

Limitations: The ratio of renal or intestinal excretion of uric acid and uremic toxins could not be elucidated, and we could not investigate gene polymorphism because of the large number of cases.

Conclusions: Allopurinol and febuxostat improved survival for all-cause mortality. Allopurinol and not febuxostat reduced the risk of CVD events, HF, and AMI.

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Accumulated evidence has shown that xanthine oxidoreductase plays an important role in the pathogenesis of cardiovascular and kidney diseases.[1,2]

Our previous study, conducted using the aristolochic acid nephropathy model, suggested that xanthine oxidoreductase inhibition could ameliorate tissue oxidative stress and inflammation.[3] In the preceding study, we hypothesized that xanthine oxidoreductase inhibition might affect the prognosis of patients receiving hemodialysis, leading to improved outcomes within 3 years.[4] Febuxostat is a strong adenosine triphosphate-binding cassette transporter G2 (ABCG2) inhibitor with a 10-fold higher inhibitory effect than topiroxostat and allopurinol that leads to the accumulation of uremic toxins by decreasing excretion from the intestine, particularly in patients with chronic kidney disease (CKD) with a reduced ability to excrete uremic toxins.[5]

The importance of gene polymorphism of ABCG2 (Q126X or Q141K) has recently been recognized.[6-8] Functional ABCG2 has been associated with accelerated estimated glomerular filtration rate decline in patients with asymptomatic hyperuricemia with CKD when compared with fully functional ABCG2.[9] The Food and Drug Administration (https://www.fda.gov/media/120418/download) issued a "Boxed Warning for increased risk of death with febuxostat"[10] according to the randomized clinical trial (RCT) of febuxostat and allopurinol performed in the Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial, which indicated that febuxostat results in higher cardiovascular (hazard ratio [HR], 1.34) and all-cause (HR, 1.23) mortality rates.[11] Febuxostat is a strong ABCG2 blocker,[5] which implies that it inhibits the excretion of uremic toxins and uric acid from the kidney or intestine despite strong xanthine oxidoreductase inhibition.

In an open-label RCT conducted in the European Union comparing allopurinol and febuxostat, the febuxostat group was noninferior to the allopurinol group regarding

PLAIN LANGUAGE SUMMARY

Uric acid-lowering therapy has been used to prevent gout attacks and protect organs by reducing inflammation by lowering uric acid levels. However, uric acid-lowering medications have recently been found to have a side effect of inhibiting a channel responsible for excreting toxins, such as adenosine triphosphate-binding cassette transporter G2; the effects of medications with a strong inhibitory effect, such as febuxostat, are currently under investigation. Patients with kidney failure or dialysis excrete toxins through feces from their intestines in addition to removing toxins through dialysis. If uric acid-lowering medications suppress the channels responsible for intestinal toxin excretion, could this lead to the development of heart failure or stroke? This study investigated this question.

cardiovascular disease (CVD)-related deaths.[12] Another Austrian nationwide study reported that the outcome of febuxostat was inferior to that of allopurinol (HR, 0.58),[13] and this issue remains controversial.

Therefore, this study aimed to compare the effects of allopurinol and febuxostat on all-cause mortality and cardiovascular outcomes in patients receiving hemodialysis using marginal structural Cox proportional hazards models (MSMs).[14–18] To our knowledge, this is the first study to evaluate the respective effects of allopurinol and febuxostat compared with those of nontreatment on cardiovascular outcomes in patients receiving hemodialysis, particularly in those with deteriorated kidney function and residual intestine excretion channels.

METHODS

Study Participants

This retrospective cohort study used laboratory and clinical data of 6,791 patients who had no history of topiroxostat usage as of March 2016 and underwent hemodialysis at Yokohama Daiichi Hospital, Zenjinkai, and its affiliated dialysis clinics located in the Kanagawa and Tokyo metropolitan areas of Japan. The follow-up was performed for 3 years, from April 2016 to March 2019, with March 2016 as the baseline.

Exposure

The time-varying treatment variables were allopurinol, febuxostat, and nontreatment. Allopurinol and febuxostat, which are xanthine oxidoreductase inhibitors, were defined based on their prescription status each month, and nontreatment was defined if neither of the medications was prescribed for each month. At baseline, 5,156, 775, and 860 patients received nontreatment, allopurinol, and febuxostat, respectively (Tables 1 and 2); however, in some cases, these statuses were switched during the follow-up period through a change in medications, discontinuation of treatment, or restart of treatment.

Outcomes

Outcomes were all-cause mortality, CVD events, heart failure (HF), acute myocardial infarction (AMI), and stroke. Data on all-cause mortality were obtained from medical records. Furthermore, data on CVD events and HF were derived from the claims data system, STEPII (SJ Medical), with *International Classification of Diseases* (ICD)-10 codes I-00 to I-99 and I-20–23 for AMI, I-50 for HF, and I-60–69 for stroke.

Covariates

Time-fixed covariates included age, sex, diabetes mellitus, and comorbidity data. Comorbidity data were extracted from insurance claims and classified according to ICD-10 codes.[19,20] Time-varying covariates included laboratory, concomitant medication, and vital sign data. Tables 1 and 2 present the time-fixed and time-varying covariates at baseline. Laboratory and vital sign data were averaged by month. Figure S1 presents the relationship among covariates, treatments, censoring, and outcomes. All data were derived from the STEPII dialysis data system.

Statistical Analyses

Descriptive data are presented as mean and standard deviation for continuous variables and as numbers and percentages (%) for categorical variables.

Excluding patients with missing data have been shown to reduce efficiency and generally introduce bias.[21] Therefore, to handle missing data on covariates (Table S1), we performed multiple imputation (MI)[22] with a fully conditional specification method[23] using the treatment, covariates, and outcomes for each month and created 10 imputed data sets. To confirm the validity of the MI, we calculated the fraction of missing information,[24] which takes values between 0 and 1. A fraction of missing information close to 0 suggests that MI is valid even if the missing percentage is large, provided the information to describe the missing mechanism is sufficient.[24]

We estimated the stabilized inverse probability weights (IPWs), which were the product of the stabilized inverse probability of treatment weights (IPTWs) to adjust for time-varying confounding and stabilized inverse probability of censoring weights (IPCWs) to adjust for selection bias due to censoring.[17] We fitted 2 pooled polytomous logistic models with treatment as the response variable to estimate the denominator and numerator of IPTWs and 2 pooled logistic models with censoring as the response variable to estimate the denominator and numerator of IPCWs for each of the 10 datasets separately. Previous treatment and covariates were the explanatory variables in the 2 models to estimate the denominator, whereas previous treatment was the explanatory variable in the 2

Table 1. Baseline Characteristics of Patients Undergoing Dialysis

	Nontreatment (n = 5,156)		Allopurinol (n = 775)		Febuxostat (n = 860)		
Demographic Data (Categorical)	**No.**	%	**No.**	%	**No.**	%	***P***
Sex (male)	3,372	65	545	70	640	74	<0.001
DM	2,116	41	242	31	353	41	<0.001
Baseline hyperuricemia	991	19	744	96	802	93	<0.001
Demographic data (Continuous)	Mean	SD	Mean	SD	Mean	SD	
Age (y)	68	13	65	12	64	13	<0.001
Dialysis duration (d)	220	216	266	213	133	173	<0.001
Body weight pre (kg)	59.8	13.7	62.9	14.5	65.9	15.9	<0.001
Body weight post (kg)	57.4	13.2	60.3	14.0	63.3	15.3	<0.001
Delta body weight (kg/HD)	−0.8	0.5	−0.8	0.4	−0.8	0.4	<0.001
sBP start (mm Hg)	154	22	151	22	152	21	0.01
dBP start (mm Hg)	79	13	80	14	81	13	0.09
HR start (bpm)	74	12	76	12	76	12	<0.001
BMI (kg/m²)	21.9	3.9	22.6	4.2	23.6	4.5	<0.001
Comorbidity data	No.	%	No.	%	No.	%	
Infectious diseases	2,463	49	424	55	361	43	<0.001
Viral and fungal infections	2,028	40	298	39	307	36	0.1
Malignant neoplasms	1,444	29	254	33	205	24	<0.001
Anemia	4,764	94	753	98	820	97	<0.001
Endocrine metabolic	4,847	96	760	99	831	98	<0.001
Mental disorders	856	17	120	16	106	13	0.005
Nervous system	2,801	55	421	55	397	47	<0.001
Eye ear adnexa	1,767	35	290	38	248	29	<0.001
Circulatory system	4,813	95	753	98	825	97	<0.001
Respiratory system	4,067	80	699	91	662	78	<0.001
Digestive system	4,559	90	729	95	758	89	<0.001
Skin subcutaneous tissue	3,979	79	640	83	619	73	<0.001
Musculoskeletal connective tissue	3,981	79	660	86	628	74	0.2
Genitourinary	4,859	96	760	99	830	98	<0.001

Note: Descriptive data are presented as mean and standard deviation (SD) for continuous variables and as number (No.) and percentage (%) for categorical variables.
Abbreviations: BMI, body mass index; Body weight pre, before dialysis; Body weight post, post dialysis; Delta body weight, body weight loss during dialysis session; DM, diabetes mellitus; dBP start, diastolic blood pressure just at dialysis start; HR start, heart rate just at dialysis start; sBP start, systolic blood pressure just at dialysis start.

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Table 2. Baseline Laboratory Data and Concomitant Medications of Patients Undergoing Dialysis

	Nontreatment (n = 5,156)		Allopurinol (n = 775)		Febuxostat (n = 860)		
Laboratory Data	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	***P***
Hb (g/dL)	10.8	1	10.8	1	10.9	1	<0.001
BUN pre (mg/dL)	63.9	14.3	67.6	14.1	68.6	14.9	<0.001
BUN post (mg/dL)	19.6	6.4	20.4	6.2	23	7.5	<0.001
Cr pre (g/dL)	10.17	2.67	11.38	2.71	10.67	3.09	<0.001
Cr post (g/dL)	3.84	1.27	4.28	1.34	4.32	1.5	<0.001
K (mmol/L)	4.7	0.7	4.8	0.7	4.7	0.7	0.009
P (mg/dL)	5.3	1.3	5.4	1.3	5.5	1.3	<0.001
UA pre (mg/dL)	7.5	1.3	7	1.3	5.5	1.6	<0.001
UA post (mg/dL)	2.1	0.6	1.9	0.5	1.6	0.7	<0.001
Na pre (mEq/L)	139.2	2.8	139.4	2.9	139.4	2.6	0.04
Na post (mEq/L)	139	1.6	138.9	1.7	138.8	1.7	0.002
Fe (μg/dL)	73.5	28.1	72.4	27.6	74.5	29.3	0.4
Ferritin (ng/mL)	104	133	92	88	107	175	0.01
TP (g/mL)	6.9	0.5	6.9	0.5	6.9	0.5	0.06
Alb (g/mL)	3.6	0.4	3.6	0.3	3.6	0.4	<0.001
Glu (mg/dL)	130.6	46.9	124.4	48.1	130.6	46.3	<0.001
Tcho (mg/dL)	156.8	35.2	159	32.5	158	32.4	0.7
HDL (mg/dL)	50.8	16.5	50.6	17.2	48.5	17.8	0.2
LDL (mg/dL)	82.5	27.6	83.5	25.2	83.1	27.2	0.9
CRP (mg/L)	0.5	1.3	0.4	0.9	0.4	0.9	0.07
iPTH (pg/mL)	248.4	208.5	269.9	222.7	225.6	166.8	0.02
β2MG (mg/dL)	27.1	6.7	31	7.4	27.6	8.1	0.001
Kt/V	1.5	0.5	1.5	0.3	1.3	0.3	<0.001
NPCR (g/kg/day)	0.9	0.2	0.9	0.2	0.9	0.2	<0.001
CGR (%)	95.2	32.7	104.2	23.6	92	30.2	<0.001
Concomitant medication data	No.	%	No.	%	No.	%	
AHT α	523	10	78	10	80	9	0.7
AHT αβ	532	10	84	11	90	10	0.9
AHT ACE	184	4	26	3	29	3	0.9
AHT ARB	1,509	29	233	30	280	33	0.1
AHT β	274	5	37	5	49	6	0.7
AHT CaA	2,323	45	340	44	414	48	0.2
AHT renin	15	0	10	1	1	0	<0.001
AHT other	178	3	41	5	26	3	0.02
Calcimimetics	1,399	27	294	38	227	26	<0.001
ESA	3,353	65	483	62	556	65	0.3
Iron iv	1,137	22	163	21	157	18	0.04
Iron oral	69	1	16	2	33	4	<0.001
Phosphate binder	3,592	70	658	85	682	79	<0.001
Phosphate binder iron	600	12	88	11	151	18	<0.001
DM po	1,118	22	130	17	206	24	0.001
Insulin	53	1	5	1	10	1	0.5
Warfarin	291	6	34	4	41	5	0.2
Anticoagulant	53	1	8	1	7	1	0.8
Antiplatelet	2,325	45	352	45	372	43	0.6
Dialysate Ca	3,107	60	508	66	552	64	0.001

Note: Descriptive data are presented as mean and standard deviation (SD) for continuous variables and as number (No.) and percentage (%) for categorical variables. Abbreviations: α, α blocker; ACE, angiotensin converting enzyme inhibitor; AHT, anti-hypertensive agents; Alb, albumin; ARB, angiotensin receptor blocker; β, β blocker; β2MG, beta-2 microglobulin; BUN, blood urea nitrogen; CGR; creatinine generation rate; Cr, creatinine; CRP, C- reactive protein; Dialysate Ca, dialysate calcium concentration >2.75 mEq/L; ESA, erythropoiesis-stimulating agent; Fe, iron; Ferritin; Hb, hemoglobin; HDL, high-density lipoprotein; iPTH, intact parathyroid hormone; Iron iv, iron intravenous injection; Iron Oral, iron oral intake; LDL, low-density lipoprotein; Na, sodium; NPCR, normalized protein catabolic rate; K, potassium; Kt/V, urea adequacy measure scales dialysis dose; Other, anti-hypertensive agents; P, phosphate; Renin, renin inhibiter; Tcho, total cholesterol; TP, total protein; UA, uric acid.

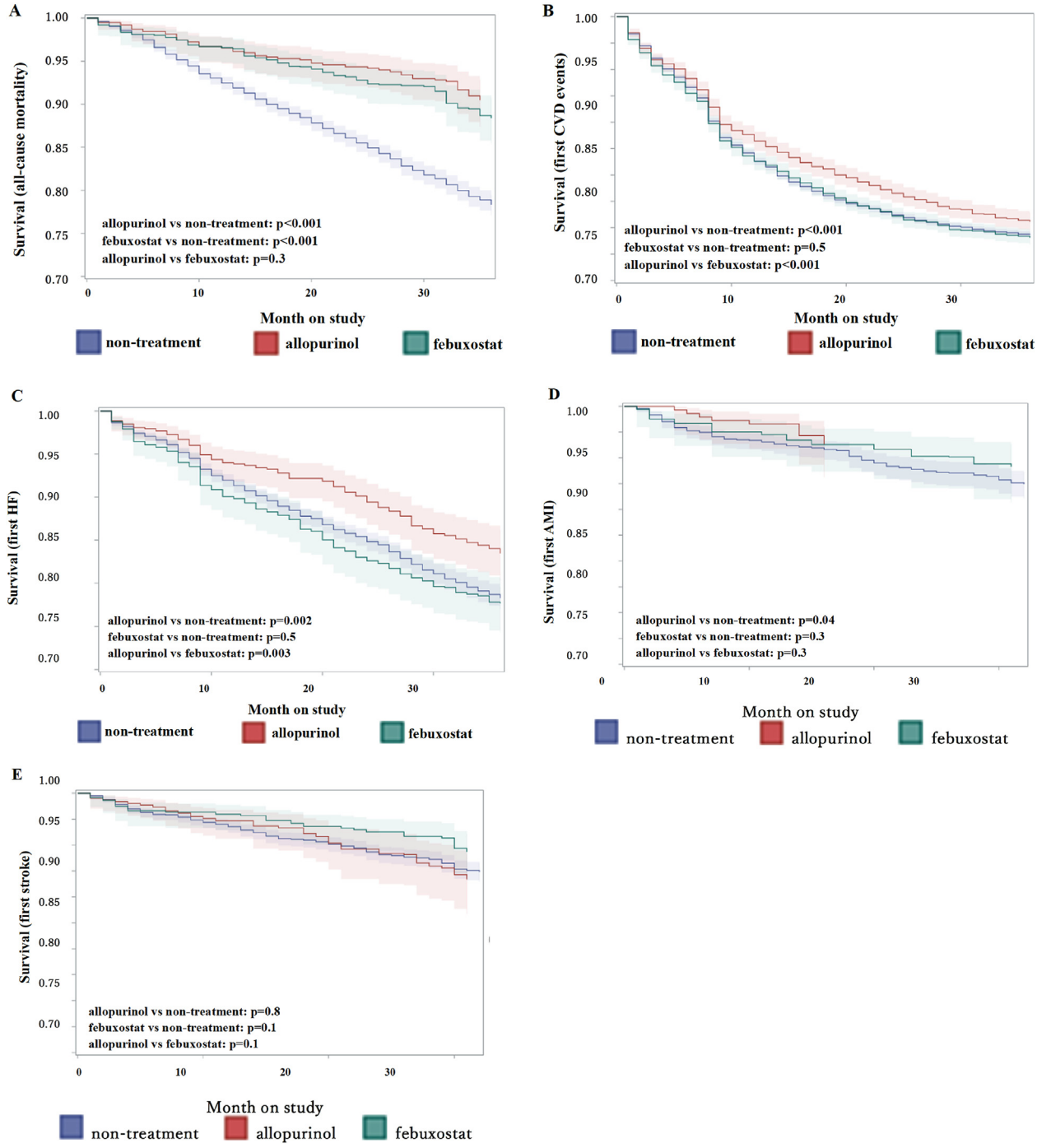

Figure 1. Adjusted survival curves with stabilized inverse probability weights (IPWs) for all-cause mortality and cardiovascular disease (CVD) events. (A) all-cause mortality; (B) first CVD events; (C) first heart failure (HF); (D) first AMI; and (E) first stroke.

models to estimate the numerator. All 4 models included time-dependent intercepts with natural cubic splines and 4 knots on months 7, 13, 21, and 28, corresponding to the 5th, 35th, 65th, and 95th percentiles, respectively.[18,25] To prevent unstable estimation because of patients with extreme weights, we truncated IPWs by resetting the value of weights greater (lower) than the 99th (1st) percentile to the value of the 99th (1st) percentile[26] for each of the 10 data sets separately. The formulas of IPW and pooled (polytomous) logistic models used for the estimation of IPW are provided in Item S1.

We created adjusted survival curves with IPWs[27] that were extensions of those in the time-fixed case[28] to the time-dependent case to compare survival among the allopurinol, febuxostat, and nontreatment. Adjusted survival curves were drawn using 1 of the 10 datasets

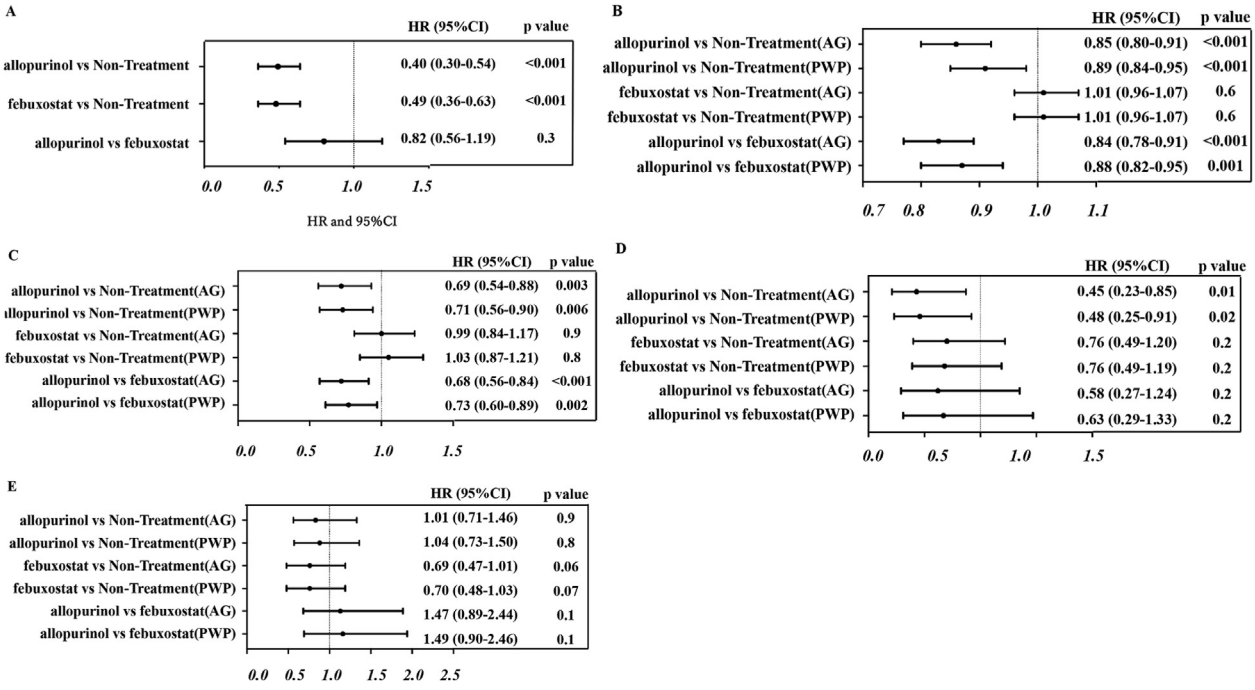

Figure 2. Results of marginal structural Cox proportional hazards models (MSMs) for all-cause mortality and cardiovascular disease (CVD) events. (A) all-cause mortality; (B) CVD events; (C) heart failure (HF); (D) AMI; and (E) stroke. allopurinol; febuxostat; HR, hazard ratio; LCL, 95% lower confidence limit; UCL, 95% upper confidence limit; AG, the Andersen and Gill model; PWP, the Prentice, Williams, and Peterson total time model; CI, confidence interval.

for each outcome as follows: all-cause mortality, first CVD events, first HF, first AMI, and first stroke.

For the main analyses, we used MSMs to estimate the respective treatment effect of allopurinol and febuxostat compared with that of nontreatment and the difference between them for each of the 5 outcomes (all-cause mortality, CVD events, HF, AMI, and stroke) (Fig S1). All-cause mortality was analyzed using a Cox proportional hazards model (Cox model) weighted by IPWs. CVD events, HF, AMI, and stroke, which were recurrent events, were analyzed using the Andersen and Gill (AG)[29] and the Prentice, Williams, and Peterson (PWP) total time[30] models weighted by IPWs. The AG model generalizes the Cox model to allow for recurrent events, whereas the PWP total time model stratifies the AG model by the event sequence to allow for differences in baseline hazards between the sequential events.[31] For each of the 9 models, we analyzed 10 data sets separately and obtained estimates of HRs and 95% confidence intervals (CIs) by combining 10 results.[22] The formulas for MSMs are provided in Item S1.

We fitted conventional and time-dependent Cox models for additional analyses to compare with MSMs (Tables S5 and S6). Furthermore, for sensitivity analysis, we performed MSM analyses for 2,537 patients who had a history of hyperuricemia at baseline.

Two-sided P values of <0.05 were considered indicative of statistical significance. All analyses were conducted using SAS version 9.4 (SAS Institute Inc).

Statement of Ethics

This study protocol was approved by the ethical committee of Yokohama City University (approval number: B200700018) and performed in accordance with the principles of the Declaration of Helsinki. Owing to the deidentified nature of patient records, informed consent was obtained through an opt-out method on the website of the Zenjinkai-Group (https://www.zenjinkai-group.jp/zenjinkai/privacypolicy/) according to the ethical guidelines for medical and health research involving human subjects in Japan.

RESULTS

Tables 1 and 2 summarize the baseline characteristics of patients. Table S2 presents the results of pooled polytomous logistic regression for the denominator of IPTWs and pooled logistic regression for the denominator of IPCWs. Figure S2 and Table S3 show the distribution of IPWs, which are the products of IPTWs and IPCWs, before and after truncation. The variance of IPWs increased over time both before and after truncation (Fig S2A and B). The variance was greater before truncation than after truncation.

Figure 1A shows the adjusted survival curves for all-cause mortality. Allopurinol and febuxostat were associated with significantly better survival than nontreatment (both $P < 0.001$), whereas febuxostat was associated with less favorable survival than allopurinol, without a

significant difference (P = 0.3). Allopurinol was associated with significantly better survival than febuxostat and nontreatment for first CVD events (both P < 0.001) and first HF (P = 0.002 and P = 0.003), without a significant difference between febuxostat and nontreatment (both P = 0.5; Fig 1B and C). Allopurinol was associated with significantly better survival than nontreatment for the first AMI (P = 0.04), whereas other comparisons did not show significant results (Fig 1D). None of the comparisons showed significant results for the first stroke (Fig 1E). Figure S3 shows the nonadjusted survival curves.

Figure 2A shows the MSM results for all-cause mortality. Both allopurinol and febuxostat were associated with significantly better survival than nontreatment (HR, 0.40; 95% CI, 0.30-0.54 and HR, 0.49; 95% CI, 0.36-0.63, respectively), without a significant difference between allopurinol and febuxostat (HR, 0.82; 95% CI, 0.56-1.19). Figure 2B shows the MSM results for CVD events. Allopurinol was associated with significantly better survival than nontreatment in the AG and PWP models (HR, 0.85; 95% CI, 0.80-0.91 and HR, 0.89; 95% CI, 0.84-0.95, respectively) but not febuxostat (both HR, 1.01; 95% CI, 0.96-1.07). Furthermore, allopurinol was associated with significantly better survival than febuxostat in the AG and PWP models (HR, 0.84; 95% CI, 0.78-0.91 and HR, 0.88; 95% CI, 0.82-0.95, respectively). Figure 2C shows the MSM results for HF. Allopurinol was associated with significantly better survival than nontreatment in the AG and PWP models (HR, 0.69; 95% CI, 0.54-0.88 and HR, 0.71; 95% CI, 0.56-0.90, respectively) but not febuxostat (HR, 0.99; 95% CI, 084-1.17 and HR, 1.03; 95% CI, 0.87-1.21, respectively). Furthermore, allopurinol was associated with significantly better survival than febuxostat in the AG and PWP models (HR, 0.68; 95% CI, 0.56-0.84 and HR, 0.73; 95% CI, 0.60-0.89, respectively). Figure 2D shows the MSM results for AMI. Allopurinol was associated with significantly better survival than nontreatment in the AG and PWP models (HR, 0.45; 95% CI, 0.23-0.85 and HR, 0.48; 95% CI, 0.25-0.91, respectively) but not febuxostat (HR, 0.76; 95% CI, 0.49-1.20 and HR, 0.76; 95% CI, 0.49-1.19, respectively). For stroke, none of the comparisons showed significant results (Fig 2E). The fraction of missing information was close to 0 for all parameters of MSMs (Table S4). The MSM results in patients with a history of hyperuricemia at baseline (Fig S4) were similar to those in all patients (Fig 2). Tables S5 and S6 present the results of conventional and time-dependent Cox models.

DISCUSSION

In an observational patients receiving hemodialysis cohort using marginal structural models, use of the xanthine oxidoreductase inhibitors allopurinol and febuxostat was associated with improved survival, allopurinol but not febuxostat was associated with a lower risk of CVD, HF, and myocardial infarction events, and neither allopurinol nor febuxostat were associated with a reduction in stroke events. These results could be influenced by the unique characteristics of patients undergoing dialysis, whose mechanisms for eliminating uric acid and uremic substances are constrained to the intestinal tract or dialysis sessions. Various controversies exist regarding the therapeutic efficacy of uric acid-lowering treatments for patients receiving hemodialysis.[32] However, it is also inferred to be important to further maintain the function of the excretory pathway of uric acid and uremic toxins through the ABCG2 channel.

Besides the uric acid-lowering effect, the better survival associated with xanthine oxidoreductase inhibitors against all-cause mortality is suspected to be due to the following mechanisms: preservation of cell energy through the adenosine triphosphate salvage cycle[33] and the anti-inflammatory effect of xanthine oxidoreductase inhibitors.[34] Based on these reports, xanthine oxidoreductase inhibition may improve prognoses by reducing oxidative stress rather than lowering uric acid levels. Therefore, in our preceding study, we hypothesized that xanthine oxidoreductase inhibition might affect the prognosis of patients receiving hemodialysis, and the results showed that treatment with xanthine oxidoreductase inhibitors was associated with improved all-cause mortality in these patients.[4] However, the effect of xanthine oxidoreductase inhibition on cardiovascular outcomes, including CVD events, HF, and AMI, has not been determined. In addition, analyzing whether the treatment efficacy differed among inhibitors was necessary. In our previous animal study, xanthine oxidoreductase activity was elevated in an aristolochic acid-induced kidney insufficiency mouse model.[3] In this model, xanthine oxidoreductase activity was persistently increased in the renal tissue. The results suggested that the increase in xanthine oxidoreductase activity is associated with the progression of kidney damage, specifically fibrosis. Therefore, we hypothesized that chronic inflammation in CKD status results in the elevation of xanthine oxidoreductase levels, and xanthine oxidoreductase inhibition exerts its effect against inflammation.

In our previous animal study, xanthine oxidoreductase inhibition was associated with tissue damage-preventive effects, mainly by alleviating xanthine oxidoreductase-induced oxidative stress.[35] Besides reducing oxidative stress, xanthine oxidoreductase was associated with a salvaging effect, implying that it simultaneously prevents oxidative stress, salvages circulating metabolites, and improves energy status.[36] In clinical settings, recently developed febuxostat and topiroxostat are excreted from the intestine and are available to patients with CKD to prevent oxidative stress and improve energy status.[37]

Allopurinol reduced the risk of CVD events, HF, and AMI compared with nontreatment, whereas febuxostat did not. This result suggests that febuxostat inhibited the excretion of uremic toxins through the ABCG2 channel from the intestine, resulting in an increased incidence of

CVD events due to uremic toxin accumulation. ABCG2 activity can vary extensively because of known genetic polymorphisms or coincidental use of medications.[38-40] However, in addition to lowering uric acid concentrations through xanthine oxidoreductase inhibition, which is the primary therapeutic target, maintaining the function of the excretory pathway of uric acid and uremic toxins via the ABCG2 channel may also play a significant role. Miyata et al[5] demonstrated that febuxostat strongly inhibited urate transport through ABCG2 compared with other medications, including pyrazinecarboxylic acid, salicylic acid, allopurinol, mizoribine, and ribavirin, in vitro (human embryonic kidney cell-derived 293A cells), and in vivo. The calculated half maximal inhibitory concentration value for inhibiting the ABCG2-mediated urate transport activity was 1/10 for febuxostat when compared with that for topiroxostat.[5] In addition, the study indicated that febuxostat strongly inhibits ABCG2 in the kidneys and intestine. In a previous study, the transporters in the basal membrane were identified as the organic anion transporter 1 and organic anion transporter 3,[41] whereas the transporter of uremic toxins in the apical membrane had been unknown. Taniguchi et al[42] indicated that ABCG2 was present in the small intestines, liver, and kidneys and that ABCG2 mediated the excretion of uremic toxins in a mouse adenine CKD model. In the study, a large amount of uremic toxins was excreted from the intestines and livers in patients with CKD, which was identified as a compensatory mechanism in a mouse model. In humans, Ohashi et al[43] estimated that ~650 or 500 mg of uric acid was produced daily in male or female participants undergoing hemodialysis, with 60% of uric acid excreted through ABCG2 in the extra-renal pathway. The ABCG2 dysfunction strongly contributes to an accumulation of uric acid; further extrarenal urate excretion capacity can expand with kidney function decline, and the extra-renal pathway is particularly important for the outcomes of uric acid and uremic toxin homeostasis in patients with kidney dysfunction.[42,43] Clinically, probenecid, benzbromarone, and dotinurad, a more recent medication, are the recommended uricosuric medications for patients with CKD.[44] Furthermore, the newly developed febuxostat and topiroxostat have become widely used for CKD. However, febuxostat is a coadministered medication for breast cancer. In breast cancer, ABCG2 mediates the excretion of anticancer medications, resulting in reduced effectiveness.[38,39] Therefore, to prevent this, febuxostat has been used as a coadministered medication to inhibit ABCG2 function,[40] and it has stronger inhibitory effects on ABCG2 than allopurinol, topiroxostat, and other medications.[5] The ABCG2 has been recognized as a breast cancer-releasing protein that is widely distributed in the small intestines, breasts, kidneys, and kidney tissues[38,45] and mediates the excretion of uric acid and uremic toxins from the apical side of epithelial cells.

Furthermore, many recent clinical investigations have been reported[13] regarding the differences in treatment outcomes between allopurinol and febuxostat. The ABCG2 is the main transporter of urate and uremic toxins in humans,[45] and accumulated uremic toxins can lead to higher risks of CVD events. Therefore, not inhibiting ABCG2 function in patients with CKD who have reduced kidney function may be important to prevent the increased risk of CVD events. According to the CARES study,[11] cardiovascular and all-cause mortality rates were higher in the febuxostat group than in the allopurinol group. However, the study had no control group; therefore, the effect of both medications compared with that of nontreatment remains unelucidated.

Furthermore, the febuxostat group had a high frequency of dropouts; we investigated our cohort of all longitudinal observational steps to explore characteristics. The mean uric acid levels before dialysis were 7.42, 6.99, and 5.56 in the nontreatment, allopurinol, and febuxostat groups, respectively. In addition, the mean treatment durations in all observational steps were 28.45 ± 12.66 and 25.91 ± 13.07 months for allopurinol and febuxostat prescriptions, respectively. These patients were well-compliant, and withdrawal rates were suggested to be slightly higher for febuxostat than allopurinol. Therefore, the uric acid-lowering and suggested xanthine oxidoreductase inhibitory effects appeared to be stronger in the febuxostat group than in the allopurinol group, as supported by literature on CKD. O'Dell et al[46] suggest a withdrawal rate of 20.1% in a veteran cohort that includes individuals with stage III CKD, higher than that observed in the CARES trial, where the withdrawal rate was <50%. Despite this difference, both allopurinol-treated and febuxostat-treated participants demonstrated noninferiority, with 80% of participants achieving the mean target urate level.

The Stop Gout study[46] also demonstrated noninferiority against febuxostat, without substantial differences between febuxostat and allopurinol for all-cause mortality and CVD events. As this study specifically focused on individuals with stage III CKD, we speculate that the reason for this noninferiority in terms of CVD events could be attributed to the kidneys maintaining an excretion pathway for uremic toxins, unlike in the case of patients undergoing dialysis, where excretion is primarily restricted to intestinal pathways.

Another study compared the survival efficacy of febuxostat and allopurinol for all-cause mortality and CVD events, besides the uric acid-lowering effect, using Austrian national data of 20,000 adult patients with hyperuricemia observed for 5 years and indicated that 7,767 febuxostat-treated patients had relatively more events than allopurinol-treated patients.[13] In that study, the estimated HR of allopurinol was relatively lower than that of febuxostat (0.6) in terms of ischemic heart disease, stroke, and all-cause mortality, with significant differences. However, the study had no control group. Therefore, to clarify this problem, our study compared the effects of febuxostat and allopurinol with those of nontreatment

after adjusting for time-varying confounding and selection bias due to censoring.

Notably, to our knowledge, this study is the first to elucidate the differences in the effect of allopurinol and febuxostat on CVD outcomes in patients undergoing hemodialysis. In patients with end-stage kidney disease, particularly those undergoing dialysis, the reduced excretory capacity of uremic toxins through the gut may majorly contribute to the increased risks of CVD events, even more than the inhibitory effect on xanthine oxidoreductase. Therefore, we recommend a urate transporter 1 inhibitor for patients with slightly impaired kidney function.[44] Regarding the ineffectiveness for preventing cerebral hemorrhage, there is a diverse range of backgrounds associated with the onset of cerebral hemorrhage.

This study has some limitations. First, the ratio of renal or intestinal excretion of uric acid and uremic toxins was not investigated in this study. However, according to Ohashi et al's[43] uric acid pool model, the ratio of intestinal excretion is expected to increase through intestinal ABCG2, which can mediate the excretion of ~60% of the daily uric acid turnover in patients undergoing hemodialysis. The renal excretion of uric acid or uremic toxins through ABCG2 may be reduced using the ABCG2 blocker febuxostat rather than allopurinol. Second, we could not investigate the gene polymorphism of ABCG2 because of the large number of cases that probably influenced the results. Finally, this was not an RCT. However, this study had high validity when compared with previous studies that did not properly account for time-varying confounding.[47] Although several previous studies have used MSMs in the field of CKD,[48] this is a novel study that applied MSMs to examine the current research hypothesis.

In conclusion, allopurinol and febuxostat had stronger xanthine oxidoreductase inhibitory effects than nontreatment. However, febuxostat was not inferior to allopurinol in terms of all-cause mortality. The involvement of ABCG2 is considered a possibility, although conclusive evidence is yet to be established. Therefore, further investigations that do not affect gut excretion should be conducted.

SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Fig S1: Directed acyclic graph (DAG) illustrating time-varying confounding and selection bias due to censoring.

Fig S2: Boxplots of the log-transformed stabilized inverse probability weights (IPWs).

Fig S3: Nonadjusted survival curves

Fig S4: Results of marginal structural Cox proportional hazards models (MSMs) in patients with a history of hyperuricemia at baseline

Item S1: Formulas for stabilized inverse probability weight (IPW) estimation of marginal structural Cox proportional hazards models (MSMs)

Table S1: Number of Missing Data on Covariates for Each Month

Table S2: Results of Models for Estimating the Denominator of Stabilized Inverse Probability Weights (IPWs)

Table S3: Distribution of Inverse Probability Weights (IPWs) for Each Month

Table S4: Fraction of Missing Information (FMI) of Marginal Structural Cox Proportional Hazards Models (MSMs)

Table S5: Results of Cox Proportional Hazards Models

Table S6: Results of Time-Dependent Cox Proportional Hazards Models

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