Comparative Renoprotective Effect of Febuxostat and Allopurinol in Predialysis Stage 5 Chronic Kidney Disease Patients: A Nationwide Database Analysis

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Hyperuricemia has been associated with chronic kidney disease (CKD) progression. The antihyperuricemic febuxostat's potential renoprotective effect has been demonstrated in stage 1–3 CKD. Large-scale studies comparing the renoprotective potential of febuxostat and allopurinol in advanced CKD are lacking. We exclusively selected 6,057 eligible patients with predialysis stage 5 CKD prescribed either febuxostat or allopurinol using the National Health Insurance Research Database in Taiwan during 2012–2015. There were 69.57% of allopurinol users and 42.01% febuxostat users who required long-term dialysis ($P < 0.0001$). The adjusted hazard ratio (HR) of 0.65 (95% confidence interval (CI) 0.60–0.70) indicated near 35% lower hazards of long-term dialysis with febuxostat use. The renal benefit of febuxostat was consistent across most patient subgroups and/or using the propensity score-matched cohort. The adjusted HR was 0.66 (95% CI, 0.61–0.70) for long-term dialysis or death. In conclusion, lower risk of progression to dialysis was observed in predialysis stage 5 CKD febuxostat users without compromising survival.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THIS TOPIC?

☑ Hyperuricemia has been suggested to be an independent risk factor for chronic kidney disease (CKD) and a target for renal function preservation. Allopurinol, an older antihyperuricemic, is associated with adverse cutaneous reactions and dosing difficulty in patients with renal impairment. Febuxostat has been shown to be safe and effective in delaying renal function decline in mild-to-moderate CKD.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ The possible association of febuxostat use and delayed progression to dialysis in advanced CKD remains unknown. Our objective is to compare the renoprotective potential of febuxostat and allopurinol in patients with predialysis stage 5 CKD.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Compared with allopurinol, febuxostat is associated with a 35% risk reduction in progression to dialysis in patients with predialysis stage 5 CKD without compromising survival. The renal benefit associated with febuxostat use is consistent across almost all patient subgroups.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ For patients with predialysis stage 5 CKD, febuxostat seems to be superior to allopurinol as it is associated with delayed need for long-term dialysis.

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Hyperuricemia is often observed in patients with chronic kidney disease (CKD). In a study of patients with predialysis stage 5 CKD (estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73 m^2), 50% of the patients have hyperuricemia.[1] Although it has been suggested that hyperuricemia is an independent risk factor for developing CKD and progression to end-stage renal disease (ESRD), a recent Mendelian randomization study has found no significant causal connection between serum urate level and risk of CKD.[2–4] Conversely, decreased eGFR in CKD may also lead to decreased excretion of uric acid (UA), inevitably resulting in hyperuricemia. Thus, whether hyperuricemia precedes CKD or vice versa remains controversial.

Nonetheless, drugs targeting to decrease serum UA level have emerged as promising therapeutic options for slowing CKD progression for patients with mild-to-moderate CKD (eGFR ≥ 30 mL/min/1.73 m^2).[5,6] One longitudinal study has found that the unfavorable effect of elevated UA trajectories on progression to ESRD is differentially higher among patients with CKD without using urate-lowering agents at baseline.[7] Xanthine oxidase inhibitors (XOis), such as the prototypic allopurinol and the novel febuxostat, are the commonly prescribed agents for patients with concurrent gout and CKD. XOis decrease UA production by inhibiting the conversion of UA precursors (i.e., hypoxanthine and xanthine) to UA. One randomized controlled trial (RCT) has demonstrated that allopurinol decreases serum UA levels in patients with mild-to-moderate CKD and helps preserve kidney function.[8] However, certain pitfalls of allopurinol limit its use. First of all, allopurinol has been associated with severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, especially in individuals with the HLA-B*5801 allele that is often observed in Han Chinese.[9,10] Second, the fact that maximal tolerable doses of allopurinol are not established for varying degrees of renal impairment is also problematic.[11] In fact, the recommended dose adjustment of allopurinol based on renal function often compromises its urate-lowering ability.[12] Thus, febuxostat has emerged as an alternative of interest in the past few years.

Febuxostat is a novel non-purine selective XOi mainly metabolized by the liver and excreted through urinary and fecal routes, which divert the workload from the kidneys.[13] Smaller-scale studies have demonstrated febuxostat's benefit over allopurinol in retarding renal disease progression and dialysis in patients with moderate-to-severe CKD provided that UA levels of ≤ 7 mg/dL are achieved.[14,15] However, recent study results have not reached a consensus regarding the mortality risk of febuxostat and allopurinol. Higher risk of cardiovascular (CV) death and all-cause mortality for febuxostat users suggested by one RCT has not been demonstrated in other cohort studies.[16–18] To our knowledge, large-scale studies investigating febuxostat's renoprotective potential and mortality risk in patients with predialysis stage 5 CKD are lacking. Thus, using our nationwide population-based cohort consisting exclusively of patients with predialysis stage 5 CKD, we aimed to analyze the comparative risk of dialysis and all-cause mortality between febuxostat users and allopurinol users.

RESULTS

Patient characteristics

The study included 6,057 antihyperuricemic users, of whom 2,633 (43.47%) were febuxostat users and 3,424 (56.53%) were allopurinol users. The mean age of febuxostat users and allopurinol users were 67.05 years and 67.23 years, respectively (P = 0.5898; **Table 1**). Both groups were predominantly men, with men accounting for 67.22% among febuxostat users. The most common comorbid conditions for patients in both groups were hypertension, diabetes mellitus, and hyperlipidemia, which accounted for 95.10%, 60.08%, and 59.93% of the febuxostat users, respectively. Comorbidity incidences were comparable between the two groups except for hypertension, diabetes mellitus, and hyperlipidemia.

Outcomes: renal outcome and composite outcome (long-term dialysis or death)

The median follow-up time was 0.72 years (**Table 1**) in our study. Regarding differences between groups, the median follow-up time for febuxostat users and allopurinol users were significantly different (0.79 years vs. 0.61 years; P < 0.0113). The propensity score-matched (PSM) cohort based on all covariates listed in **Table 1** similarly demonstrated significantly longer median follow-up time for febuxostat users compared with allopurinol users (0.79 years vs. 0.62 years; P < 0.0282; **Table S2**).

From 90 days after January 1, 2012, to December 31, 2016, a total of 3,488 patients (57.59%) required long-term dialysis and 4,193 patients (69.23%) died or required dialysis. The incidence of long-term dialysis was higher among allopurinol users (69.57%) compared with only 42.01% among febuxostat users (P < 0.0001; **Table 1**). Survival curves by means of the life-table method were created and analyzed using the log-rank test. Survival curves demonstrated significantly lower chance of requiring long-term dialysis for febuxostat users (P < 0.0001; **Figure 1a**).

The PSM cohort demonstrated that significantly fewer febuxostat users initiated long-term dialysis (43.56% vs. 65.17%, P < 0.0001; **Table S2**) during the follow-up period, supporting febuxostat's better performance in delaying long-term dialysis. Analysis with the multivariate Cox analysis showed that compared with treatment with allopurinol, treatment with febuxostat was associated with significant risk reduction in long-term dialysis both before and after PSM (adjusted hazard ratio (HR), 0.65; 95% confidence interval (CI), 0.60–0.70 vs. adjusted HR, 0.65; 95% CI, 0.60–0.70; **Table 2** and **Table S3**).

For the composite outcome, 52.72% of febuxostat users compared with 81.92% of allopurinol users reached long-term dialysis or death (P < 0.0001; **Table 1**). Survival curves for the composite outcome for febuxostat users and allopurinol users were significantly different (P < 0.0001), with superior survival benefit for febuxostat users (**Figure 1b**). Similarly, significantly fewer febuxostat users compared with allopurinol users reached long-term dialysis or death after PSM (53.64% vs. 80.03%; P < 0.0001; **Table S2**). The multivariate Cox hazards model also found a 34% risk reduction in reaching the composite outcome with febuxostat use compared with allopurinol use in both the pre-PSM and PSM

Table 1 Baseline characteristics of study patients

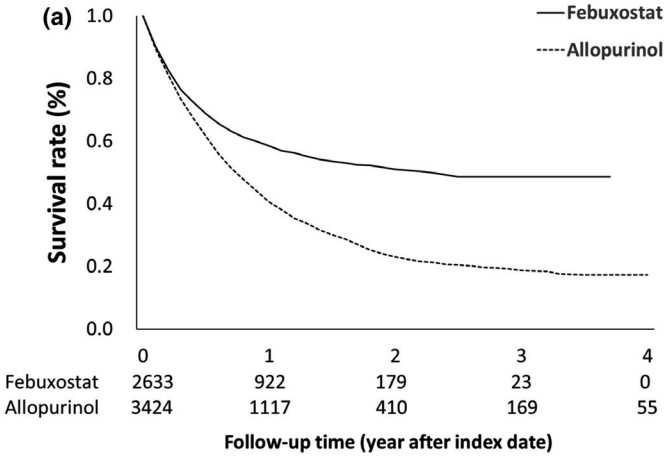
Variables	Febuxostat (*n* = 2,633)	Allopurinol (*n* = 3,424)	*P* value
Age, year, mean (SD)	67.05 (13.47)	67.23 (13.20)	0.5898
Age, no. (%)			0.7097
20–39	88 (3.34)	107 (3.13)	
40–59	615 (23.36)	829 (24.21)	
60–79	1,446 (54.92)	1,838 (53.68)	
Over 80	484 (18.38)	650 (18.98)	
Sex, no. (%)			0.0933
Male	1,770 (67.22)	2,371 (69.25)	
Female	863 (32.78)	1,053 (30.75)	
Place of residence, no. (%)			0.2847
Urban	1,453 (55.18)	1,851 (54.06)	
Suburban	862 (32.74)	1,105 (32.27)	
Rural	311 (11.81)	454 (13.26)	
Unknown	7 (0.27)	14 (0.41)	
Income levels, no. (%)			0.8238
Quintile 1 (lowest)	637 (24.19)	790 (23.07)	
Quintile 2	194 (7.37)	256 (7.48)	
Quintile 3	931 (35.36)	1,240 (36.21)	
Quintile 4	334 (12.69)	421 (12.30)	
Quintile 5 (highest)	537 (20.39)	717 (20.94)	
Occupation, no. (%)			0.0431
Dependents of the insured individuals	954 (36.23)	1,244 (36.33)	
Civil servants, teachers, military personnel, and veterans	240 (9.12)	315 (9.20)	
Nonmanual workers and professionals	290 (11.01)	325 (9.49)	
Manual workers	846 (32.13)	1,196 (34.93)	
Other	303 (11.51)	344 (10.05)	
Comorbidities, no. (%)			
Diabetes mellitus	1,582 (60.08)	1,964 (57.36)	0.0329
Hypertension	2,504 (95.10)	3,298 (96.32)	0.0191
Hyperlipidemia	1,578 (59.93)	1,940 (56.66)	0.0105
Heart failure	786 (29.85)	988 (28.86)	0.3981
Stroke	709 (26.93)	895 (26.14)	0.4906
HBV	110 (4.18)	171 (4.99)	0.1343
HCV	129 (4.90)	159 (4.64)	0.6430
Liver cirrhosis	131 (4.98)	181 (5.29)	0.5874
SLE	20 (0.76)	23 (0.67)	0.6864
Coronary artery disease	1,081 (41.06)	1,436 (41.94)	0.4892
Malignancy	865 (32.85)	1,132 (33.06)	0.8641
Other medication use, no. (%)			
ACEi	428 (16.26)	847 (24.74)	<0.0001
ARB	1,558 (59.17)	2,241 (65.45)	<0.0001
CCB	2,257 (85.72)	3,029 (88.46)	0.0015
Beta-blockers	1,319 (50.09)	1,974 (57.65)	<0.0001
Diuretics	2,061 (78.28)	2,851 (83.27)	<0.0001
Aspirin	1,032 (39.19)	1,680 (49.07)	<0.0001
Other NSAIDs	1,739 (66.05)	2,673 (78.07)	<0.0001

(Continued)

Table 1 (Continued)

Variables	Febuxostat (*n* = 2,633)	Allopurinol (*n* = 3,424)	*P* value
Outcomes, no. (%)			
Long-term dialysis	1,106 (42.01)	2,382 (69.57)	<0.0001
Long-term dialysis or death	1,388 (52.72)	2,805 (81.92)	<0.0001
Follow-up time, year, median (IQR)	0.79 (0.93)	0.61 (0.98)	0.0113

Overall follow-up time, year, median (IQR): 0.72 (0.97).
ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drugs; SLE, systemic lupus erythematosus.



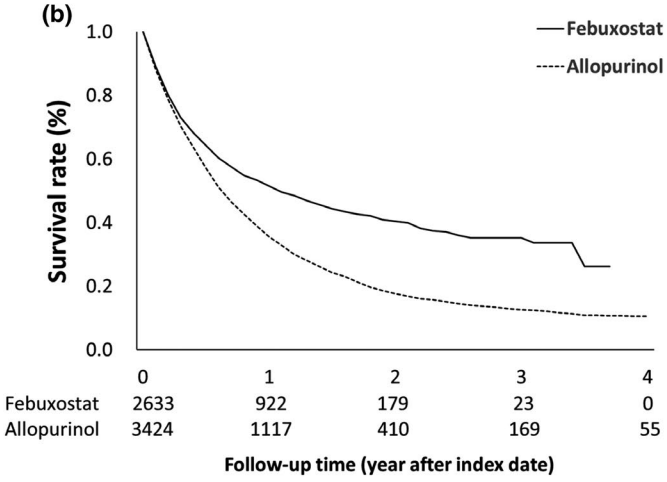


Figure 1 Survival probability of patients with predialysis stage 5 chronic kidney disease. Survival curves were created using the life-table method. (**a**) Long-term dialysis (log-rank test, $P < 0.0001$). (**b**) Long-term dialysis or death (log-rank test, $P < 0.0001$).

cohort (adjusted HR, 0.66; 95% CI, 0.61–0.70 vs. adjusted HR, 0.66; 95% CI, 0.61–0.71; **Table 2** and **Table S3**).

Subgroup analyses

We conducted subgroup analyses to examine whether the benefit of febuxostat in retarding the progression to dialysis would be similarly observed in the selected subgroups (**Figure 2**). Age, sex, comorbidities, and medication use were included for analysis. Consistent reduction in HRs of long-term dialysis in patients with predialysis stage 5 CKD in favor of febuxostat use was observed across most patient subgroups except for those with hepatitis C virus or hepatitis B virus infection or liver cirrhosis.

Risk of adverse effects: Cardiovascular mortality and myopathy

The incidence and comparative risk of CV mortality of the febuxostat users and allopurinol users were analyzed. No statistically significant increase in CV mortality was observed for patients using febuxostat (adjusted HR, 1.06; 95% CI, 0.76–1.50; **Table S4**). Additionally, febuxostat use was associated with lower risk of myopathy (adjusted HR, 0.67; 95% CI, 0.53–0.84; **Table S4**).

DISCUSSION

In our large-scale observational study of exclusively patients with predialysis stage 5 CKD with concurrent gout or hyperuricemia, lower risk of progression to dialysis with febuxostat use compared with allopurinol use is observed. Fewer febuxostat users compared with allopurinol users require long-term dialysis (42.01% vs. 69.57%; $P < 0.0001$). Treatment with febuxostat compared with allopurinol is associated with a 35% risk reduction in long-term dialysis. Additionally, the overall dialysis or death rate is significantly lower among febuxostat users.

Interventional studies, although sparse, have suggested that lowering UA levels in patients with hyperuricemia with CKD is safe and might slow CKD progression.[19] Although some studies have shown allopurinol's renoprotective role in different stages of CKD, an RCT involving 40 patients with IgA nephropathy and CKD stages 1–3 has reported no renoprotective effects.[20–22] The FEATHER trial has found no mitigation of CKD progression in stage 3 CKD, while a single-center study has demonstrated renoprotective effects of febuxostat in a prospective cohort of 48 febuxostat users with stage 3–4 CKD.[23,24] When using allopurinol as a comparison, both the FREED trial and the NU-FLASH trial have demonstrated febuxostat's renoprotective effects in patients whose renal function ranged from normal to stage 4 CKD.[25,26] However, studies on XOis' renoprotective effects in patients with CKD have remained incomplete, largely due to the lack of sufficient data on patients with stage 5 CKD.

For patients with stage 5 CKD, a few studies have suggested that febuxostat's observed association with slowed renal function decline could possibly be extended to this population. In their

Table 2 Risks of study outcomes in patients using febuxostat and allopurinol

Treatment (no. of patients)	No. of events (%)		Incidence rate per 100 patient-years		Study outcome, HR (95% CI)					
					Long-term dialysis		Dialysis or death			
	Long-term dialysis	Dialysis or death	Long-term dialysis	Dialysis or death	Unadjusted	Adjusted	Unadjusted	Adjusted		
Febuxostat (n = 2,633)	1,106 (42.01)	1,388 (52.72)	49.60	62.24	0.59 (0.55–0.64)	0.65 (0.60–0.70)	0.64 (0.60–0.68)	0.66 (0.61–0.70)		
Allopurinol (n = 3,424)	2,382 (69.57)	2,805 (81.92)	76.17	89.70	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)		

The reference category was the use of allopurinol. Multivariate analysis was adjusted for all variables listed in **Table 1**.
CI, confidence interval; HR, hazard ratio.

single-center study of patients with stages 1–5 CKD, Yamaguchi *et al*. have demonstrated that the decline of eGFR could be ameliorated by febuxostat therapy.[27] When compared with allopurinol, Chou *et al*. have found that febuxostat is associated with less eGFR decline in their cohort of 138 febuxostat users (47 of whom have stage 5 CKD).[15] Consistent with the above findings, our data adds evidence to febuxostat's superior renoprotective potential over allopurinol in patients with predialysis stage 5 CKD, as demonstrated by a 35% risk reduction in ESRD requiring dialysis.

For the mortality risk of patients with CKD using febuxostat or allopurinol, results have been inconsistent across different studies. White *et al*. have found that in patients with CV disease, all-cause mortality is higher among febuxostat users than among allopurinol users.[17] On the contrary, Zhang *et al*. have found no statistically significant increase in all-cause mortality for febuxostat users.[18] We have found a risk reduction of 34% in composite outcome (dialysis or death) with febuxostat use, suggesting that survival is not compromised by febuxostat administration. The discrepancy between study results could be related to the inherent differences in the population characteristics. For instance, White *et al*. exclusively selected patients with a history of major CV disease and excluded those with advanced CKD (stage 4–5), whereas Zhang *et al*. exclusively selected patients with gout aged 65 or older. These underlying differences in the patient population make comparisons difficult; thus, the interplay between different comorbid conditions and febuxostat's role in the body warrants further investigation.

There seems to be no consensus on the patient subgroups most likely to benefit from febuxostat use. Yamaguchi *et al*. have suggested that renoprotective effects of febuxostat are significant in male patients, age < 70 years, systolic blood pressure < 130 mmHg, normal cholesterol levels, and absence of diabetes.[27] In our cohort, febuxostat users with comorbid hepatitis B virus/hepatitis C virus infection and liver cirrhosis are the only subgroups with no significant benefit over allopurinol users with regard to dialysis delay. It is possible that the observed nonsignificant benefit of febuxostat in our study is attributed to the small number of patients in these subgroups. A previous study has also suggested that daily febuxostat in patients with Child-Pugh A and B cirrhosis is associated with clinically insignificant lessening of urate-lowering ability.[28] Therefore, future studies with a larger sample size are warranted to investigate and validate whether liver disease is associated with diminished renal benefit of febuxostat.

Although our study does not attempt to extrapolate febuxostat's mechanism of renoprotection, several mechanisms have been proposed. Several RCTs have demonstrated febuxostat's superior urate-lowering efficacy to allopurinol in patients with mild-to-moderate CKD, hinting at the positive correlation between better urate-lowering ability and CKD progression delay.[29,30] On the other hand, studies of rat models have shown that febuxostat may exert renoprotective effects by suppressing oxidative stress to prevent interstitial fibrosis.[31,32] One prospective randomized trial on patients with stage 3 CKD has found that febuxostat improves not only serum UA levels but also levels of urinary protein, L-FABP, albumin, and β2MG.[33] Although a comprehensive mechanism of febuxostat's effect on the human body has not been revealed, our large real-world data nonetheless provides evidence for febuxostat's

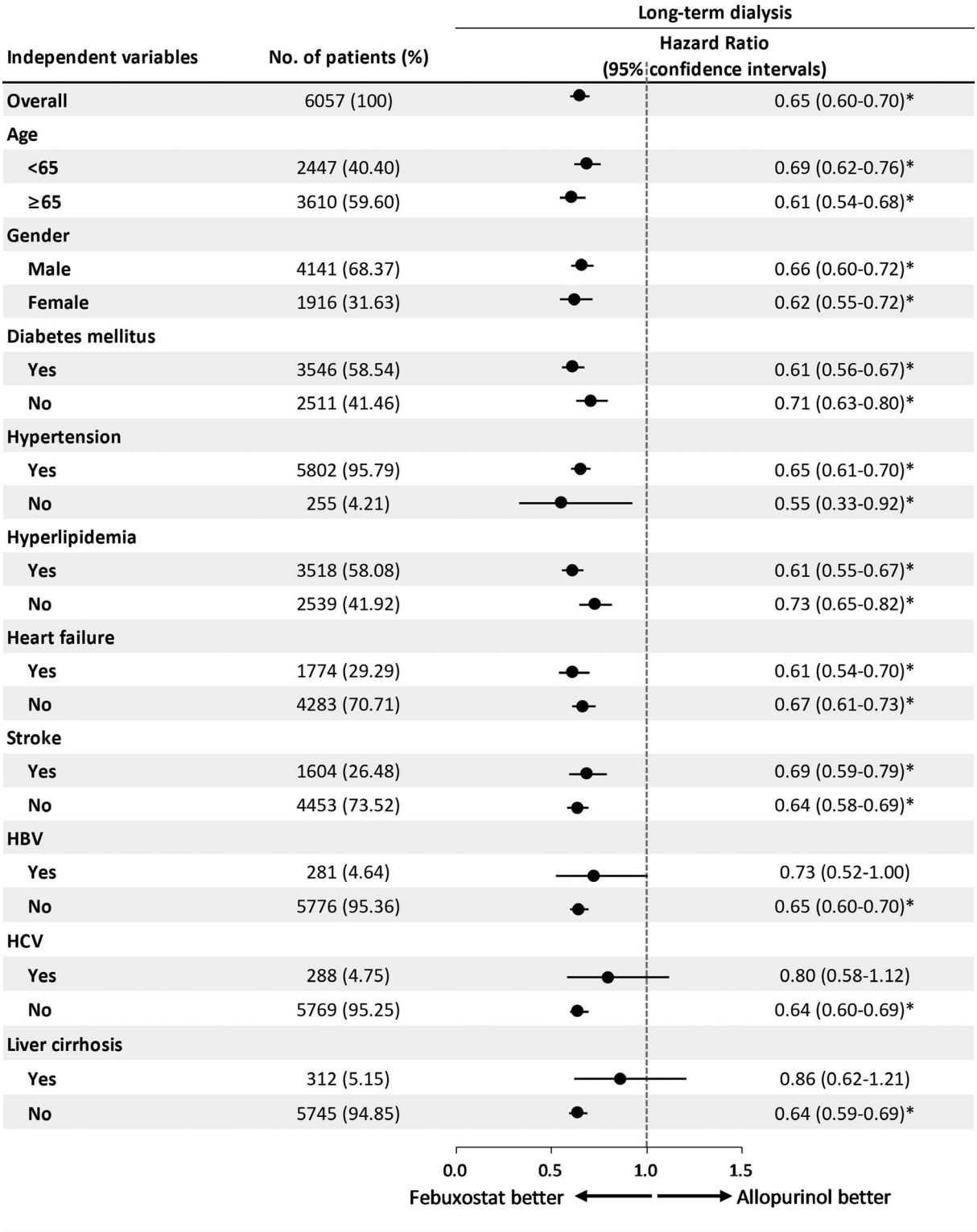


Figure 2 Adjusted hazard ratios of long-term dialysis using the Cox proportional hazards model. Each variable was adjusted for all other variables listed in **Table 1**. ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; HBV, hepatitis B virus; HCV, hepatitis C virus; NSAIDs, nonsteroidal anti-inflammatory drugs; SLE, systemic lupus erythematosus.

superior renoprotective potential over allopurinol in patients with predialysis stage 5 CKD.

Potential adverse effects associated with XOis are important when making clinical decisions. Allopurinol is associated with increased risk of severe hypersensitivity reactions in patients with renal insufficiency, and they seem to occur in a dose-dependent manner.[34–36] Thus, increasing dosage of allopurinol in patients with stage 5 CKD on an economic standpoint may

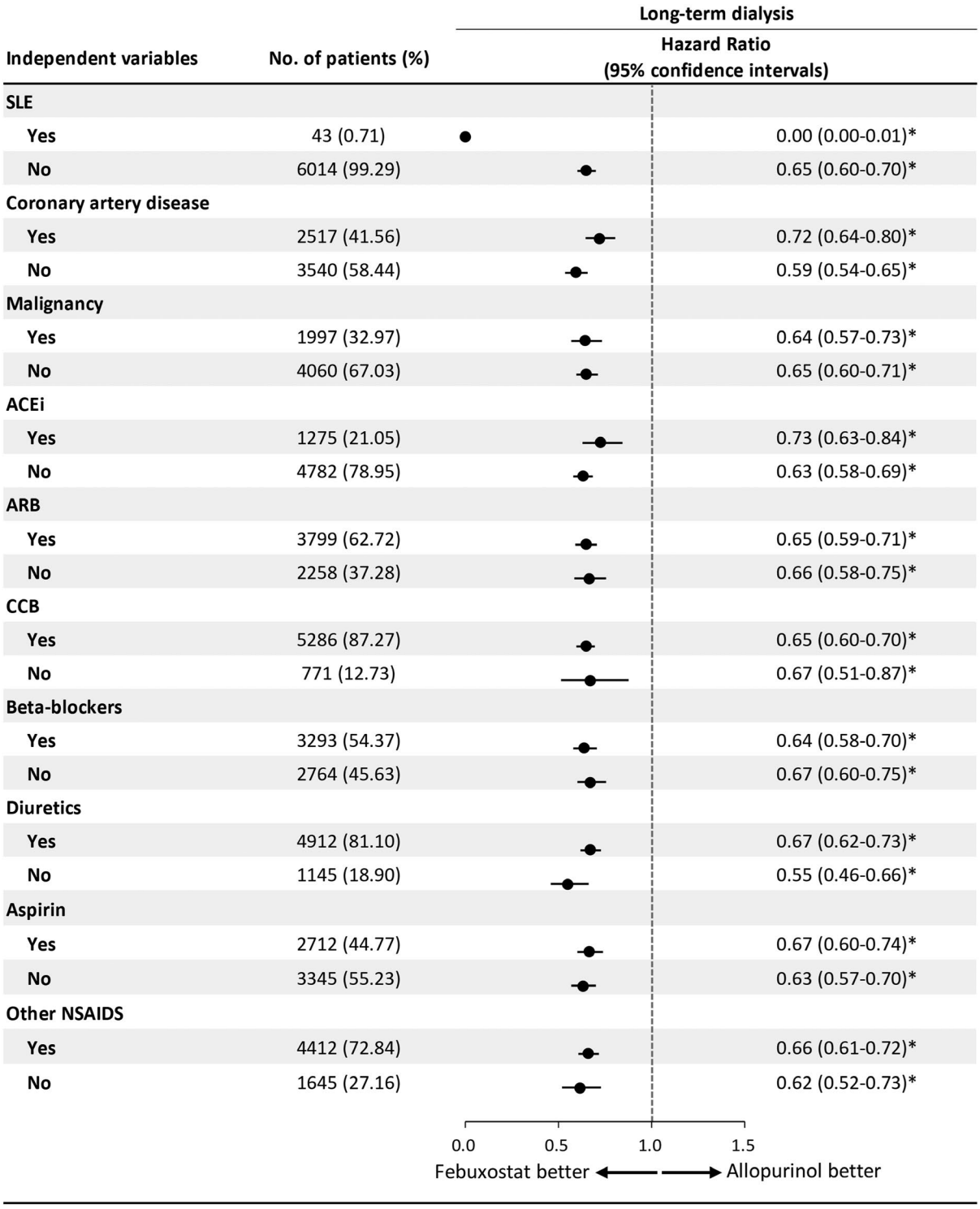


Figure 2 (Continued)

not be ideal. Although less associated with hypersensitivity, one particular concern with febuxostat is that increased CV mortality has been observed in patients with underlying CV disease.[17] However, a recent study has found no significant difference in CV deaths for febuxostat users and allopurinol users, which is consistent with our results.[16] As described, our cohort differs drastically from the former study, which consists only of patients with CV disease, necessitating further research on febuxostat's association with CV death in our target population of patients with stage 5 CKD with or without comorbid CV disease. It has been suggested that low eGFR may be related to higher risk of myopathy in patients using febuxostat, although we have found

that the risk of myopathy is higher among predialysis stage 5 CKD allopurinol users.[37] Thus, there still exists possible setbacks to febuxostat that need to be investigated and balanced with its potential renoprotective effect.

To our knowledge, this is the first large, population-based study reflecting the real-world renal and mortality outcomes of exclusively patients with predialysis stage 5 CKD upon febuxostat use. By selecting patients who survived to the 91st day after erythropoiesis-stimulating agent (ESA) prescription and following them after this exposure time window, we are able to control for survival bias.[38] Our results were further analyzed using subgroup analyses and PSM to adjust for confounding baseline variables. Our study supports that febuxostat use could be extended to patients with predialysis stage 5 CKD with the potential for renoprotection without compromising their survival. Potential limitations are present in our study. First of all, we did not exclude patients with antihyperuricemic exposure prior to first-time ESA prescriptions. However, Japanese studies have found that the switch from allopurinol to febuxostat, many of which were due to hyperuricemia refractory to allopurinol, reduced serum UA levels and slowed the progression of renal disease more than in the group in which allopurinol was continued.[14,39,40] Thus, prior allopurinol exposure is not expected to mask febuxostat's potential renoprotective effect. Second, certain important prognostic factors are not provided by the National Health Insurance Research Database (NHIRD), such as biochemical data (creatinine, UA, etc.) and drug compliance data. Therefore, we could not trace the change in eGFR, UA, or drug usage. However, we believe that consistency in the subgroup analyses ensures the robustness of our results. Third, due to the limitation of the NHIRD, patients with stage 5 predialysis CKD are identified by having an ESA prescription (i.e., concurrent anemia). In addition to the 85% ESA usage rate for patients with predialysis stage 5 CKD in Taiwan, as high as 96.5% of patients with stage 5 CKD in a Korean cohort have concurrent anemia.[41,42] Therefore, our cohort is nonetheless representative of patients with predialysis stage 5 CKD. Finally, because our study is retrospective and observational in design, we could not prove mechanisms or causality. Ideally, prospective, double-blind RCTs should be conducted in the future to confirm febuxostat's renoprotective role.

In conclusion, in our nationwide population-based cohort study, we have found a lower risk of dialysis and dialysis or mortality for febuxostat users with predialysis stage 5 CKD in Taiwan. Our results suggest febuxostat's possible benefit over allopurinol in terms of delayed progression to long-term dialysis without compromising survival. The renoprotective potential of febuxostat is consistent across most patient subgroups. Future studies are necessary to identify and confirm subgroups of patients that are less likely to benefit from febuxostat in patients with predialysis stage 5 CKD.

METHODS

Data source

The present study used data from the NHIRD, which contained complete healthcare utilization data of approximately 24 million persons enrolled under the universal health insurance (the National Health Insurance (NHI)) program in Taiwan and has been demonstrated to be a reliable source for population studies.[43,44] De-identified information kept in the NHIRD included birth date, sex, diagnostic codes, and medication prescriptions. We used the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and ICD-10 to define the diseases (**Table S1**). This study complied with the Declaration of Helsinki and Declaration of Taipei (on ethical considerations regarding health databases and biobanks) of the World Medical Association and was approved (approval serial number: 201800292B1) by the institutional review board at Chang Gung Memorial Hospital, Linkou Branch. Informed consent was waived after de-identifying personal information in the NHIRD.

Design and study participants

The study was designed as a population-based retrospective cohort study. To identify patients with predialysis stage 5 CKD, we selected patients who had at least twice been diagnosed with CKD (ICD-9-CM codes 016.0, 042, 095.4, 189, 223, 236.9, 250.4, 271.4, 274.1, 403, 404, 440.1, 442.1, 446.21, 447.3, 572.4, 580–589, 590–591, 593, 642.1, 646.2, 753, and 984) and at least twice been diagnosed with hyperuricemia (fasting serum urate > 7 mg/dL) or gout (ICD-9-CM codes 274 and 790.6). Additionally, patients enrolled required ESA prescription. In Taiwan, for patients with CKD, ESA were covered by the NHI for serum creatinine > 6 mg/dL and hematocrit ≤ 28% before November 30, 2015, which guaranteed stage 5 CKD status (eGFR < 15 mL/min/1.73 m^2) based on the 4-variable Modification of Diet in Renal Disease Study equation.[45] Since December 1, 2015, the NHI reimbursed ESA prescribed to patients with predialysis stage 5 CKD with a hemoglobin level of < 9 g/dL. In 2012, the rate of ESA use was 85% for patients with advanced stage 5 predialysis CKD in Taiwan.[41] Therefore, the study cohort was representative of patients with predialysis stage 5 CKD. Patients who satisfied the above criteria with a first ESA prescription date between January 1, 2012, and December 31, 2015, were initially selected.

We excluded patients with incomplete demographic data, those younger than 20 years (legal age based on the Civil Code), and those who had received renal replacement therapy before ESA prescription. Because we used prescription information within 90 days after ESA treatment to ascertain antihyperuricemic use, the 91st day after ESA prescription was set as the index date.[38,44] Patients who died or commenced dialysis within 90 days after ESA prescription were also excluded (**Figure 3**). We were able to control for survival bias by selecting patients who survived to the 91st day after ESA prescription and following them after this exposure time window.[38]

A total of 13,204 patients with comorbid predialysis stage 5 CKD and gout or hyperuricemia were initially identified. Patients without allopurinol or febuxostat use (nonusers) or those with prescriptions for both medications on the same day (both-users) were excluded (**Figure 3**). Of the 6,057 patients included in our study, those with febuxostat or allopurinol prescription within 90 days after ESA prescription were categorized as febuxostat users (n = 2,633) or allopurinol users (n = 3,424), respectively, regardless of possible medication change thereafter. All analyses were conducted on an intention-to-treat basis according to the patients' initial assignment.

Other covariates, such as comorbidities, were defined as diseases with at least two outpatient diagnoses or one inpatient diagnosis within 3 years before the index date. In addition, medication use was defined as having any prescription record after the index date.

Renal outcome, composite outcome, and adverse effects

The observation period started on the 91st day after ESA prescription (designated as the index date)[38,44] and ended on the date of death, commencement of long-term dialysis, or December 31, 2016 (the end date of this study), whichever came first. The onset of the renal outcome was defined as the starting date of long-term dialysis, as confirmed by peer

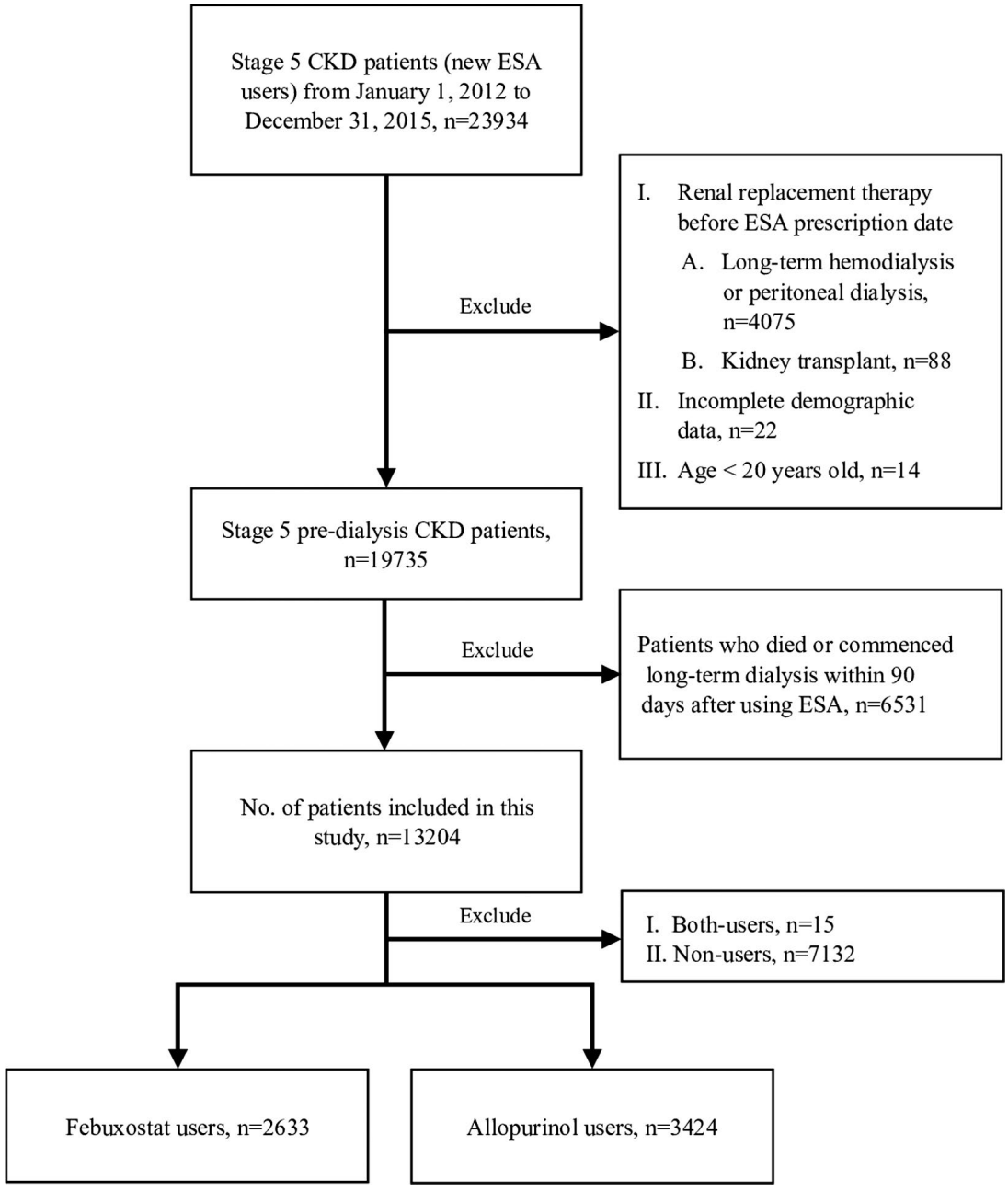


Figure 3 Flowchart of patient selection. CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent.

reviewing of nephrologists. The onset of the composite outcome was defined as the starting date of long-term dialysis or the date of death, whichever occurred first. Adverse effects (cardiovascular mortality and myopathy) were identified by ICD-9-CM and ICD-10 codes, as listed in **Table S1**. CV mortality included patients with corresponding ICD codes as their primary or secondary diagnosis upon death. Myopathy was defined by at least two outpatient diagnoses or one inpatient diagnosis during the observation period.

Statistical analysis

Baseline characteristics of the study groups were compared using the two-sided *t*-test for continuous variables and the χ^2 test for categorical variables. The life-table method was applied to generate survival probability curves, which were compared by the log-rank test. We applied the multivariate Cox proportional hazards model, which adjusted for age, sex, place of residence, income level, occupation, comorbidities, and other medication use to compare febuxostat users' risk of reaching the anticipated outcomes and adverse effects to that of allopurinol users. The proportional hazards assumption was checked and met using the log–log plot. For the long-term dialysis outcome, observations were censored at the date of death or the end of the study. For the composite outcome, observations were censored at the end of the study. The adjusted HRs for long-term dialysis and the composite outcome associated with antihyperuricemic use were analyzed among different subgroups of patients. For sensitivity analysis, PSM was conducted to pair each febuxostat user with an allopurinol user based on the calculated propensity scores from all baseline covariates listed in **Table 1** to adjust for confounders. All *P* values were two-sided, and the significance α level was set at .05. All statistical analyses were performed using SAS version 9.4 (SAS Institute).

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

Table S1. List of ICD-9-CM and ICD-10 Codes.
Table S2. Baseline characteristics of febuxostat users and allopurinol users *after* propensity-score matching.
Table S3. Risks of study outcomes in patients using febuxostat and allopurinol *after* propensity-score matching (using Cox proportional hazards model).
Table S4. Risks of adverse effects.

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CONFLICT OF INTEREST

All authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

Y.S.H., I.W.W., S.H.C., and C.C.L. wrote the manuscript. H.Y.Y., Y.S.H., and S.H.C. designed the research. Y.S.H., W.T.L., and Y.T.H. performed the research. All authors analyzed the data.

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