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Original article

Comparison of benzbromarone and allopurinol on the risk of chronic kidney disease in people with asymptomatic hyperuricemia

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ABSTRACT

Objective: The objective of the study was to compare the relative effects of benzbromarone and allopurinol on the risk of developing chronic kidney disease in persons with asymptomatic hyperuricemia.
Methods: A retrospective cohort study was conducted to analyze a 2003–2015 national database including all claims data of 2 million beneficiaries in Taiwan. Asymptomatic hyperuricemia was defined as follows: persons using urate-lowering drugs who never developed gout flares. The benzbromarone group included persons ages 20–84 that had asymptomatic hyperuricemia and received benzbromarone alone. The allopurinol group included persons ages 20–84 that had asymptomatic hyperuricemia and received allopurinol alone. The maximum follow-up time was set as 5 years in this study. The main outcome was defined as follows: persons were newly diagnosed with chronic kidney disease. A Cox proportional hazards regression analysis was performed to test the association between variables and the risk of chronic kidney disease.
Results: After propensity score matching, 9107 persons in the benzbromarone group and 4554 persons in the allopurinol group were eligible for the study. Approximately 71% of the study subjects were males. The mean age was 56 years old. The incidence rate of chronic kidney disease was lower in the benzbromarone group than in the allopurinol group (1.18 versus 1.99/per 100 person-years, incidence ratio = 0.60, and 95% confidence interval = 0.52–0.68).The Cox proportional hazards regression analysis disclosed that after adjusting for co-variables, there was a decreased risk of developing chronic kidney disease in the benzbromarone group as compared with the allopurinol group (hazard ratio = 0.59, 95% confidence interval = 0.52–0.67 and $P<0.001$).
Conclusions: The use of benzbromarone is associated with a lower hazard of developing chronic kidney disease as compared to allopurinol use among persons ages 20–84 with asymptomatic hyperuricemia. More studies are needed to confirm our findings.

1. Introduction

The distribution of chronic kidney disease (CKD) varies worldwide due to differences in study populations, study regions, and diagnostic criteria. Cockwell et al. wrote that the global prevalence of CKD in 2017 was about 9.1% and nearly 700 million persons suffered from chronic kidney disease. [1] One systemic review by Liyanage et al. reported that based on the definition of CKD as the estimated glomerular filtration rate (eGFR)<60 mL/min/per 1.73 m^2, the prevalence of CKD in Asia ranged from 7.0% to 34.3% and the prevalence of advanced CKD (eGFR<30 mL/min/per 1.73 m^2) ranged from 0.1% to 17.0%. [2] In Liyanage et al's report, the prevalence of CKD in Taiwan ranged from 7.4% to 22.6%. [2] Lai et al. wrote that the incidence of CKD requiring dialysis increased by 19% and the prevalence of CKD requiring dialysis increased by 26.6% in Taiwan during the period of 2010–2018. [3]

Data have been accumulating on the link between hyperuricemia

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and chronic kidney disease, even if the cause-effect relationship has not been demonstrated. Obermayr et al. reported that as a reference of serum uric acid level<7.0 mg/dL, when the serum level of uric acid was within 7.0–8.9 mg/dL, the probability of chronic kidney disease was increased 74% (odds ratio{OR}=1.74 and 95% confidence interval {CI}=1.45–2.09); when the serum level of uric acid was ≧9.0 mg/dL, the risk of chronic kidney disease was increased 2.1 folds (OR = 3.12 and 95%CI = 2.29–4.25). [4] Yu et al. reported that as a reference of no gout, the risk of chronic kidney disease needing long-time renal replacement therapy was increased 57% among those with gout (hazard ratio{HR}= 1.57 and 95%CI =1.38–1.79). [5] Bellomoet al reported that as the serum level of uric acid increased 1.0 mg/dL, the probability of eGFR reduction was increased 13% (HR = 1.13 and 95%CI = 1.04–1.39). [6]

The above observations raise questions and they also inspire efforts to find answers. The causal link between hyperuricemia and CKD remains unclear. Further research is suggested to investigate whether an increase of serum uric acid causes CKD or a decrease in glomerular filtration rate causes hyperuricemia, or whether there are common risk pathways between both. Till now, the exact mechanism by which hyperuricemia is associated with an increased risk of CKD is not fully understood, but it is thought to be related to three possible mechanisms, including endothelial dysfunction, [7–9] activation of the renin-angiotensin system, [10–13] and inflammation-fibrosis. [14–18] But clarifying the underlying mechanisms is not the scope of the present study. In theory, lowering serum uric acid can protect the kidneys away from the damage caused by serum uric acid. Therefore, use of urate-lowering agents may reduce the risk of CKD. Epidemiological studies have revealed contrary results about the relation between urate-lowering agents and the risk of chronic kidney disease. That is, some showed benefits and some showed no benefit. [19–21]

In Taiwan, about 92% of urate-lowering prescriptions were allopurinol and benzbromarone. [22] Previous studies in Taiwan have revealed that the use of benzbromarone could decrease the risk of the first gout flare and the probability of developing type 2 diabetes mellitus among persons having asymptomatic hyperuricemia when compared with use of allopurinol, [22,23] but the risk of CKD has not yet been clarified between use of benzbromarone and use of allopurinol. Therefore, we did an observational cohort study to compare the relative effects of benzbromarone and allopurinol on the probability of CKD among persons having asymptomatic hyperuricemia.

2. Methods

2.1. Study design and data source

One retrospective cohort research was designed to analyze a 2003–2015 National Health Insurance Research Database (NHIRD) in Taiwan. This database contains medical records of 2 million beneficiaries, including information on outpatient, inpatient, emergency and use of medications.

2.2. Research subjects

The definition of asymptomatic hyperuricemia was as follows: persons using urate-lowering drugs who never developed gout flares. Only those persons who had the prescription duration of uric acid-lowering medications ≥ 30 days were included in this study. An index date was set as the first prescription dispensing date of urate-lowering drugs. The benzbromarone group included persons ages 20–84 that had asymptomatic hyperuricemia and received benzbromarone alone. The allopurinol group included persons ages 20–84 that had asymptomatic hyperuricemia and received allopurinol alone.

2.3. Exclusion criteria

The following conditions must be excluded:

(1) Persons who had a history of CKD before the index day must be excluded.
(2) Persons suffering from gout-related diseases before the index day and during the cohort must be excluded.
(3) Persons having any cancer prior to the index day and during the cohort must be excluded.
(4) Persons who alternately received various uric acid-lowering drugs during the cohort must be excluded.

Fig. 1 demonstrates the flow diagram of the process of selecting study subjects.

2.4. Medications and comorbidities of the study

Uric acid-lowering drugs currently on the Taiwan market are as follows: allopurinol, febuxostat, benzbromarone, sulfinpyrazone as well as probenecid. Comorbidities were included in the study only if they were diagnosed within 1 year before the index date, including cerebrovascular disease, chronic obstructive pulmonary disease (COPD), coronary artery disease, diabetes mellitus, hyperlipidemia as well as hypertension. These comorbidities could be considered as confounding factors of the study.

2.5. Major outcome

The maximum follow-up time since the index date was set as 5 years in this study. The definition of the major outcome was set as follows: persons were newly diagnosed with CKD (based on International Classification of Diseases 9th Revision Clinical Modification, ICD-9 codes 581–583, 585–587 as well as 588.8–588.9). In order to increase the accuracy of disease diagnosis, the diagnosis codes of chronic kidney disease and comorbidities must have appeared ≧3 times in outpatients or ≧1 time in inpatients.

2.6. Statistical analyses

Both benzbromarone and allopurinol groups were paired using the propensity score generated by the logistic regression model according to sex, age and comorbidities. Both benzbromarone and allopurinol groups were paired with 2:1. Continuous data were shown as mean ± standard deviation and a *t*-test had been applied to test the differences among continuous variables. Categorical data were shown as numbers with percentage and a Chi-square test had been performed to examine the differences among category variables. A Kaplan-Meier curve was applied to present the cumulative incidence of CKD for the group of benzbromarone use and the group of allopurinol use during the 5-year follow-up time. The log-rank test had been performed to examine whether there was a difference in the cumulative incidence of CKD for both benzbromarone and allopurinol groups. An incidence density of CKD was estimated based on person-years for the group of benzbromarone use and the group of allopurinol use. The Kolmogorov-type supremum test was used to evaluate the assumption of proportional hazards. It was not violated. A Cox proportional hazards regression analysis was conducted to test the relation between variables and the risk of CKD. The cumulative defined daily dose of benzbromarone use and allopurinol use during the follow-up period were estimated to explore the risk of the development of CKD between these two drugs. The hazard ratio was used to measure the association strength. A statistical significance was addressed as a 95% confidence interval which did not include the null or a *P* value less than 0.05. The SAS software was used in all analyses (version 9.4 for Windows; SAS Institute Inc., Cary, NC, USA).

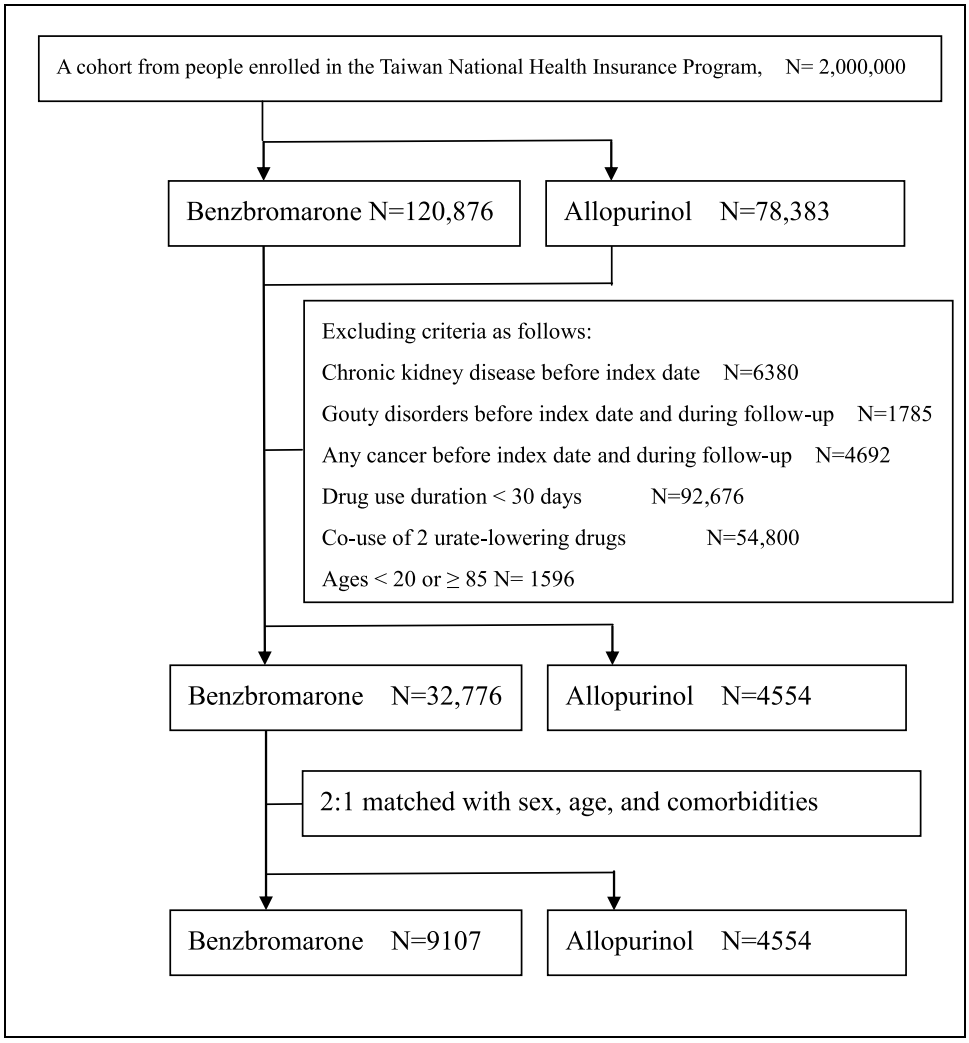

Fig. 1. Flowchart showing selection process of study subjects.

3. Results

3.1. Baseline data of study subjects

In Table 1, after propensity score matching, 9107 benzbromarone users and 4554 allopurinol users were suitable for the study. Approximately 71% of the study subjects were males. The mean age was 56 years old. The mean time from the index date to developing CKD was the same for benzbromarone users as allopurinol users (mean time 2.1 years and $P = 0.402$). The cumulative defined daily dose is larger for benzbromarone users than allopurinol users (median, 107.0 versus 89.3), with reaching statistical significance ($P = 0.002$).

3.2. Incidence density of chronic kidney disease

The overall incidence density of CKD for benzbromarone users was 1.18/per 100 person-years. The overall incidence density of CKD for allopurinol users was 1.99/per 100 person-years. The incidence ratio was 0.60, with a statistical significance (95% confidence interval = 0.52–0.68, Table 2). When we performed stratification by sex, the incidence density of CKD seemed to be lower for benzbromarone users than allopurinol users in both sexes. When we performed stratification by age, the incidence density of CKD was lower for the benzbromarone users than the allopurinol users in the three age groups. The highest incidence density of CKD was found among allopurinol users ages 65–84 (3.27 per 100 person-years).

A Kaplan-Meier curve revealed that the cumulative incidence of chronic kidney disease seemed to be lower for the group of benzbromarone use than the group of allopurinol use during the 5-year follow-up period, with a statistical significance ($P<0.001$, Fig. 2).

3.3. Risk of chronic kidney disease associated with medications and comorbidities

In Table 3, a Cox proportional hazards regression analysis disclosed that after adjusting for co-variables, there was a decreased risk of CKD for benzbromarone users when compared with allopurinol users (hazard ratio = 0.59, 95% confidence interval = 0.52–0.67, and $P<0.001$).

3.4. Risk of chronic kidney disease associated with cumulative defined daily dose of benzbromarone use and allopurinol use

We performed a stratified analysis by cumulative defined daily dose of benzbromarone use and allopurinol use in Table 4. After adjusting for co-variables, the adjusted HR of CKD was 0.43 in the group of Q1 cumulative defined daily dose of benzbromarone use versus Q1 cumulative defined daily dose of allopurinol use (95% CI = 0.31–0.59). The adjusted HR of CKD was 0.51 in the group of Q2 cumulative defined daily dose (95% CI = 0.38–0.69). The adjusted HR of CKD was 0.72 in the group of Q3 cumulative defined daily dose (95% CI = 0.56–0.92). The adjusted

Table 1
Baseline information of study subjects.

	Benzbromarone group *N*=9107		Allopurinol group *N*=4554		
Variable	n	(%)	n	(%)	*P* value*
Sex					0.997
Male	6483	71.2	3242	71.2	
Female	2624	28.8	1312	28.8	
Age group (years)					0.747
20–39	1442	15.8	737	16.2	
40–64	4807	52.8	2414	53.0	
65–84	2858	31.4	1403	30.8	
Mean age ± SD †	55.8 ± 15.1		55.6 ± 15.1		0.478
The period from index date to new-onset of chronic kidney disease (years)					
Mean ± SD †	2.1 ± 1.4		2.1 ± 1.4		0.402
Cumulative defined daily dose					
Median (Q1,Q3) ††	107.0 (46.0–271.0)		89.3 (47.3–234.0)		0.002
Baseline comorbidities					
Cerebrovascular disease	707	7.8	394	8.7	0.072
Chronic obstructive pulmonary disease	591	6.5	333	7.3	0.071
Coronary artery disease	1235	13.6	637	14.0	0.494
Diabetes mellitus	1876	20.6	945	20.8	0.837
Hyperlipidemia	2081	22.9	1071	23.5	0.383
Hypertension	4572	50.2	2244	49.3	0.307

SD: standard deviation.
Q1: Quarter 1; Q3: Quarter 3.
*Chi-square test.
†*t*-test comparing benzbromarone group and allopurinol group.
††Wilcoxon rank-sum test comparing benzbromarone group and allopurinol group.

HR of CKD was 0.63 in the group of Q4 cumulative defined daily dose (95% CI = 0.51–0.78). All reached statistical significance ($P<0.05$). These results indicate regardless of the cumulative defined daily dose, benzbromarone provides a protective effect on renal function compared to allopurinol.

4. Discussion

We noted that the benzbromarone users seemed to have a lower incidence rate of CKD than the allopurinol users (Table 2). After adjustment for co-variables, the risk of CKD was decreased 41% among persons with asymptomatic hyperuricemia using benzbromarone when compared to persons with asymptomatic hyperuricemia using allopurinol (Table 3). Regardless of the cumulative defined daily dose, benzbromarone provides a protective effect on renal function compared to allopurinol (Table 4).

We reviewed the relevant literature to answer whether the different effects of the two uric acid-lowering treatments on serum uric acid levels lead to a different renal protection or a direct effect of these two drugs on the kidney, or both. One meta-analysis by Bose et al. revealed that after analyzing 5 studies, no significant difference could be found in the change of eGFR between the baseline status and post-treatment status for the allopurinol group and the control group (mean difference of eGFR 3.1 mL/min/1.73 m^2, 95%CI −0.9~7.1 and $P = 0.13$). [19] The authors commented that due to the inclusion of inadequate studies, it was unable to recommend allopurinol use to slow the decline of eGFR among persons with hyperuricemia. [19] However, another meta-analysis by Kanji et al. revealed that among persons with baseline chronic kidney disease (stage 3–5), the allopurinol group could maintain a higher eGFR than the control group (mean difference of eGFR 3.2 mL/min/1.73 m^2, 95%CI = 0.16–6.2 and $P = 0.039$). [20] The authors commented that among persons comorbid with hyperuricemia and CKD, allopurinol use might have some benefits in protecting renal function. [20] However, based on the above two meta-analyses, the efficacy of allopurinol on the risk of CKD remains unsettled.

Benzbromarone is one of the uricosuric medications, and it is commonly used to treat hyperuricemia. Benzbromarone can inhibit urate transporter 1 (URAT1) which is located at the kidney's proximal tubule. [24,25] Inhibition of URAT1 can reduce the reabsorption of urinary uric acid and further promote the elimination of urinary uric acid via urine. [24,25] Then the serum level of uric acid is reduced.

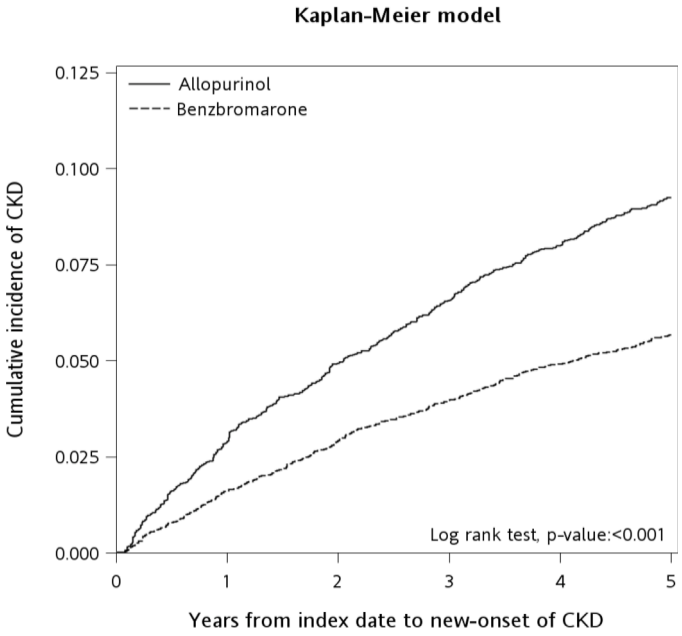

Fig. 2. Kaplan-Meier curve showing that the cumulative incidence of chronic kidney disease (CKD) was lower in the benzbromarone group than the allopurinol group during the 5-year follow-up period (P<0.001).

Table 2
Incidence density of chronic kidney disease between benzbromarone and allopurinol groups.

	Benzbromarone				Allopurinol				
Variable	N	Event	Person-years	Incidence rate*	N	Event	Person-years	Incidence rate*	Incidence rate ratio(95% CI)†
All	9107	517	43,715	1.18	4554	421	21,204	1.99	0.60(0.52–0.68)
Sex									
Male	6483	347	31,176	1.11	3242	276	15,178	1.82	0.61(0.52–0.72)
Female	2624	170	12,539	1.36	1312	145	6026	2.41	0.56(0.45–0.70)
Age group (years)									
20–39	1442	24	7124	0.34	737	25	3610	0.69	0.49(0.28–0.85)
40–64	4807	184	23,425	0.79	2414	192	11,359	1.69	0.46(0.38–0.57)
65–84	2858	309	13,166	2.35	1403	204	6235	3.27	0.72(0.60–0.86)

*Incidence rate: 100 person-years.
†Incidence rate ratio: benzbromarone use versus allopurinol use (95%CI).

Table 3
Hazard ratio and 95% confidence interval of chronic kidney disease associated with medications and co-variables.

	Crude			Adjusted†		
Variable	HR	(95%CI)	*P* value	HR	(95%CI)	*P* value
Sex (male vs. female)	0.79	0.69–0.91	0.001	1.20	1.04–1.39	0.011
Age (every one year)	1.05	1.04–1.05	<0.001	1.04	1.03–1.04	<0.001
Benzbromarone use (allopurinol use as a reference)	0.60	0.53–0.68	<0.001	0.59	0.52–0.67	<0.001
Baseline comorbidities (yes vs. no)						
Cerebrovascular disease	1.90	1.58–2.29	<0.001	1.10	0.91–1.33	0.338
Chronic obstructive pulmonary disease	1.46	1.18–1.82	0.001	1.01	0.81–1.26	0.915
Coronary artery disease	1.78	1.52–2.08	<0.001	1.09	0.92–1.28	0.319
Diabetes mellitus	3.16	2.77–3.59	<0.001	2.26	1.97–2.6	<0.001
Hyperlipidemia	1.57	1.37–1.80	<0.001	1.13	0.98–1.3	0.104
Hypertension	2.50	2.17–2.87	<0.001	1.37	1.17–1.61	<0.001

†Adjusting for sex, age, cerebrovascular disease, chronic obstructive pulmonary disease, coronary artery disease, diabetes mellitus, hyperlipidemia and hypertension.

Table 4
Risk of chronic kidney disease associated with cumulative defined daily dose of benzbromarone use and allopurinol use.

	Crude			Adjusted†		
Variable	HR	(95%CI)	*P* value	HR	(95%CI)	*P* value
Benzbromarone Q1 vs allopurinol Q1	0.46	0.33–0.64	<0.001	0.43	0.31–0.59	<0.001
Benzbromarone Q2 vs allopurinol Q2	0.55	0.41–0.74	<0.001	0.51	0.38–0.69	<0.001
Benzbromarone Q3 vs allopurinol Q3	0.72	0.56–0.92	0.008	0.72	0.56–0.92	0.009
Benzbromarone Q4 vs allopurinol Q4	0.61	0.50–0.76	<0.001	0.63	0.51–0.78	<0.001

Q1: Q1: Quarter 1; Q2: Quarter 2; Q3: Quarter 3; Q4: Quarter 4.
†Adjusting for sex, age, cerebrovascular disease, chronic obstructive pulmonary disease, coronary artery disease, diabetes mellitus, hyperlipidemia and hypertension.

While benzbromarone has been shown to be effective in treating hyperuricemia, due to the potential side effect of hepatotoxicity associated with benzbromarone use detected by case reports, [26–29] benzbromarone has been off the market in many countries since 2003. [25,30] However, benzbromarone continues to be used in Taiwan and some other countries. [30,31] So far there is no case report of hepatotoxicity in Taiwan. Although there is not much literature on benzbromarone, some available studies can still be interpreted. Perez-Ruiz et al. reported that among male persons with a history of gout flares receiving standard doses of allopurinol (300 mg/per day) for 6–9 months, 53% of these persons could achieve serum uric acid level<6.0 mg/dL. [32] But 100% of studied persons could achieve a serum level of uric acid<6.0 mg/dL if they were treated with standard doses of benzbromarone (100 mg/per day) for 6–9 months. [32] The creatinine clearance rate was elevated from 116 mL/min to 119 mL/min in the allopurinol group, but without reaching statistical significance. [32] The creatinine clearance rate was elevated from 87 mL/min to 104 mL/min in the benzbromarone group, with a statistical significance. [32] These results indicate that the uric acid-lowering effect is better for benzbromarone use than allopurinol use. Also, benzbromarone can protect renal function. Hanvivadhanakul et al. reported that among persons with normal renal function (serum creatinine level $\leq$ 1.5 mg/dL), the uric acid-lowering effect is better for benzbromarone use than allopurinol use. [33] Stamp et al. reported that among persons with eGFR >60 or eGFR 30–59 mL/min/per 1.73 m^2, the uric acid-lowering effect is better for benzbromarone use than allopurinol use. [34] Obermayr et al's study also demonstrated a dose effect of uric acid on the risk of CKD. [4] It means that the higher the uric acid level, the higher the CKD risk. Based on the above review, regardless of persons with normal renal function or with CKD, benzbromarone has a better effect on lowering serum uric acid than allopurinol. We infer that benzbromarone use may reduce the risk of developing CKD among persons with asymptomatic hyperuricemia. Such an advantage may come from the better effect of benzbromarone on lowering serum uric acid when compared with allopurinol.

Some limitations should be discussed. First, the matching of the 2 study groups should consider the comparable values of serum uric acid on the index date. There was no blood data in the database studied. The study could not evaluate serum uric acid level, serum creatinine level and eGFR before and after drug use. Due to the lack of eGFR data, the stage of CKD could not be determined in the study. Due to no urine data in the database, the study could not evaluate albuminuria at the baseline and all the follow-ups. More research is needed to evaluate whether these data would affect the risk of developing CKD. However, according to the Taiwan's consensus, hyperuricemia is defined as s the serum level of uric acid > 6.8 mg/dL for both adult males and females. [35] The Taiwan's consensus suggests that after dietary control and lifestyle adjustment, and after discussing the benefits and harms of urate-lowering drugs, the urate lowering treatment might be considered in persons with asymptomatic hyperuricemia who do not have the evidence of gouty arthritis, gouty tophi or urolithiasis if he/she still has the serum level of uric acid $\geqq$9 mg/dL and comorbidities or still has the serum level of uric acid $\geqq$10 mg/dL and no evidence of comorbidities. [35] If the above approach is how physicians prescribe the urate-lowering drugs for persons included in our study, then the study findings might only apply to persons who have quite high serum level of uric acid. In addition, persons with the serum level of uric acid $\geqq$9 mg/dL and comorbidities, and persons with the serum level of uric acid $\geqq$10 mg/dL and no evidence of comorbidities, both could have a different susceptibility to develop chronic kidney disease. This potential difference should be considered. The Taiwan's consensus also suggests that patients with renal impairment or urolithiasis should avoid using benzbromarone, if possible. [35] Although persons who had a history of CKD before the index day had been excluded from our study, the potential bias related to benzbromarone use preferentially in persons with better renal function at the baseline should be considered. Second, although the propensity score matching was used for the benzbromarone and allopurinol groups, no information was obtained on many risk factors for eGFR change, including lifestyle differences, use of over-the-counter medications, etc. Residual confounding by these unmeasured factors cannot be ruled out. Third, confounding by indication is a bias frequently found in observational pharmacoepidemiological studies because the treatment assignment in observational studies is not completely randomized and the treatment indication might be associated with the potential risk of future health outcomes. However, benzbromarone and allopurinol are commonly used to lower serum uric acid.

Both drugs have the same indication for treating hyperuricemia. So confounding by indication is less likely. Fourth, the same selection criteria for both benzbromarone and allopurinol groups minimize the possibility of selection bias. Fifth, because there is no untreated group for comparison, the absolute risk of developing CKD related to either benzbromarone or allopurinol is unknown. We could only compare the relative effects of benzbromarone and allopurinol on the risk of developing CKD. However, it is important to note that clinical trials are required to determine whether the use of individual uric acid-lowering agents can reduce the risk of developing CKD among persons having asymptomatic hyperuricemia.

5. Conclusions

The use of benzbromarone is associated with a lower hazard of CKD as compared to allopurinol use among persons ages 20–84 with asymptomatic hyperuricemia. Previous studies also revealed that use of benzbromarone could decrease the probability of the first gout flare and the probability of developing type 2 diabetes mellitus among persons having asymptomatic hyperuricemia as compared with the use of allopurinol. [22,23] However, the causal relationship between hyperuricemia and CKD is not fully understood. More research is needed to fully elucidate the association between use of individual uric acid-lowering agents and the risk of CKD among persons with asymptomatic hyperuricemia.

Key messages

- What is already known about this subject?
- Data have been accumulating on the association between hyperuricemia and chronic kidney disease, even if the cause-effect relationship has not been demonstrated.
- In theory, lowering serum uric acid can protect the kidneys away from damage caused by serum uric acid.
- What does this study add?
- The benzbromarone users seemed to have a lower incidence rate of developing chronic kidney disease than the allopurinol users.
- There was a decreased hazard of developing chronic kidney disease in the benzbromarone group as compared with the allopurinol group.
- How might these findings impact clinical practice or future developments?
- The use of benzbromarone is associated with a lower hazard of developing chronic kidney disease as compared to allopurinol use among persons ages 20–84 with asymptomatic hyperuricemia.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Specific author contributions

Shih-Wei Lai: contributed to the conception of the study, initiated the draft of the study, and approved the final draft. **Shih-Wei Lai and Kuan-Fu Liao:** contributed equally to the study. **Kuan-Fu Liao and Yu-Hung Kuo:** conducted data analysis. **Bing-Fang Hwang and Chiu-Shong Liu:** interpreted analysis results.

Ethical considerations

All methods were carried out in accordance with relevant guidelines and regulations. Insurance reimbursement claims data used in the study were available for public access. Patient identification numbers had been scrambled to ensure confidentiality. Patient-informed consent was not required. The study was approved by the Research Ethics Committee at Taichung Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation in Taiwan (REC109–35).

Data availability statement

The original contributions are included in the study. Further inquiries can be directed to the corresponding author.

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