





# Cardiovascular risk associated with allopurinol vs. benzbromarone in patients with gout

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## Aims

With the high prevalence of gout and associated cardiovascular (CV) diseases, information on the comparative CV safety of individual urate-lowering drugs becomes increasingly important. However, few studies examined the CV risk of uricosuric agents. We compared CV risk among patients with gout who initiated allopurinol vs. benzbromarone.

## Methods and results

Using the Korean National Health Insurance claims data (2002–17), we conducted a cohort study of 124 434 gout patients who initiated either allopurinol ( $n = 103\,695$ ) or benzbromarone ( $n = 20\,739$ ), matched on propensity score at a 5:1 ratio. The primary outcome was a composite CV endpoint of myocardial infarction, stroke/transient ischaemic attack, or coronary revascularization. To account for competing risk of death, we used cause-specific hazard models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the outcomes comparing allopurinol initiators with benzbromarone. Over a mean follow-up of 1.16 years, 2258 patients developed a composite CV event. The incidence rate of the composite CV event was higher in allopurinol initiators (1.81 per 100 person-years) than benzbromarone (1.61 per 100 person-years) with a HR of 1.22 (95% CI 1.05–1.41). The HR for all-cause mortality was 1.66 (95% CI 1.43–1.93) among allopurinol initiators compared with benzbromarone.

## Conclusion

In this large population-based cohort of gout patients, allopurinol was associated with an increased risk of composite CV events and all-cause mortality compared to benzbromarone. Benzbromarone may reduce CV risk and mortality in patients with gout, although more studies are necessary to confirm our findings and to advance our understanding of the underlying mechanisms.

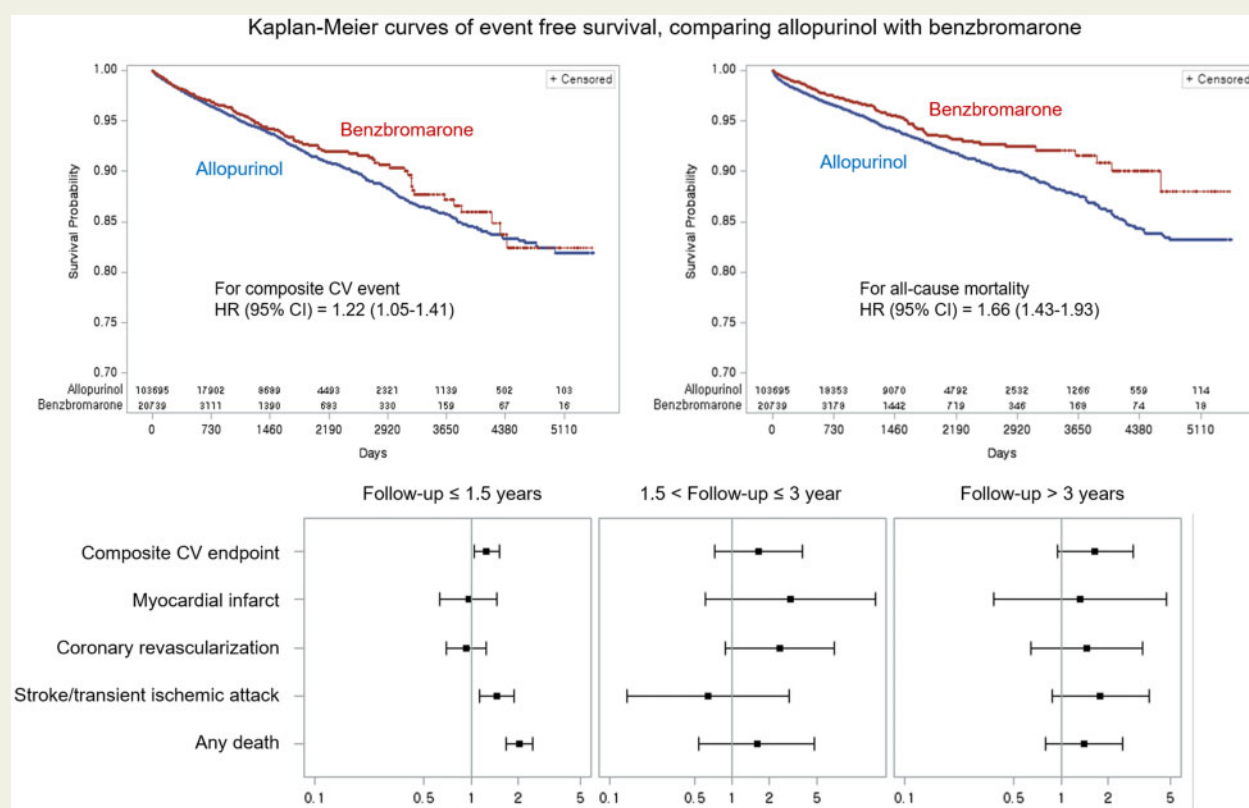
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## Graphical Abstract



Allopurinol, compared to benzbromarone, was associated with a higher risk of cardiovascular events and all-cause mortality among patients with gout.

## Keywords

Gout • Hyperuricaemia • Cardiovascular risk • Allopurinol • Benzbromarone

## Introduction

Cardiovascular (CV) disease is the global leading cause of death, with an estimated 17.9 million people who died of CV disease in 2016, representing 31% of all global deaths.<sup>1</sup> A total of 85% of these CV deaths were due to myocardial infarction (MI) and stroke and one-third of them occurred prematurely under the age of 70 years.<sup>1</sup> Moreover, CV mortality has been the top health issue not only among high income countries<sup>2,3</sup> but also among middle-to-low income countries.<sup>4</sup> Due to the potential disabilities associated with these CV conditions, CV disease causes immense health and economic burden.

Gout is the most common inflammatory arthritis in adults, caused by monosodium urate (MSU) crystal deposits in the joints and soft tissues.<sup>5</sup> It affects up to 4% of the US population and 1–4% of Western Europeans.<sup>5,6</sup> Patients with gout show an increased risk of CV morbidity and mortality associated with ischaemic heart disease, stroke, and/or heart failure.<sup>7</sup> In a health professionals follow-up study, the adjusted risk of CV death and fatal coronary heart disease was

estimated to increase by 38% and 55%, respectively, among men with history of gout compared with men without.<sup>8</sup> However, it is still debated whether such association is causal or simply a residual confounding by traditional CV risk factors highly prevalent in patients with gout. The causal scenario suggests that the mechanisms are likely multifactorial involving hyperuricaemia, xanthine oxidase (XO) activation, oxidative stress, and chronic inflammation.<sup>7,9</sup> The finding that the key cytokine of inflammation is IL-1 $\beta$  in both gout and atherosclerosis may also support causal relationship of gout and CV disease.<sup>10</sup> However, the exact mechanism is not fully understood.

In the context of high prevalence of gout and associated CV outcomes, there has been a need for information on the comparative CV safety of individual urate-lowering drugs. Under such backgrounds, a number of studies have focused on the CV effects of XO inhibitors such as allopurinol and febuxostat because of their capability to suppress both XO activity and hyperuricaemia and to reduce oxidative stress.<sup>9</sup> However, two recent randomized controlled trials (RCTs) comparing allopurinol and febuxostat, the CARES (Cardiovascular Safety of Febuxostat and Allopurinol in Patients with

Gout and CV Morbidities) and FAST (Long-term Cardiovascular Safety of Febuxostat Compared with Allopurinol in Patients with Gout), raised a question on CV benefits of XO inhibition, showing no relationship between CV risk and the potency of individual XO inhibitors,<sup>11,12</sup> and suggested that individual urate lowering drugs may have different CV effects.<sup>13</sup>

Unlike XO inhibitors, data on CV effects of uricosuric agents have been sparse. A recent large Medicare study reported a decreased risk of CV events and all-cause mortality associated with probenecid compared to allopurinol,<sup>14</sup> possibly through other mechanisms than urate-lowering action. Benzbromarone is another uricosuric agent inhibiting a renal tubular transporter, URAT-1.<sup>15</sup> It shows high efficacy and safety in general even for patients with chronic kidney disease<sup>16,17</sup> but was not approved in the USA and withdrawn from some European countries based on several hepatotoxicity reports. However, withdrawal decision of the drug has often been questioned based on the risk estimated <1:17 000.<sup>18–20</sup> Currently, it is still actively used in Asia including South Korea, some countries of Europe, and South America to treat gout. The 2016 EULAR guideline for gout management recommends to use benzbromarone alone or in combination with allopurinol when the initial treatment with allopurinol is not effective enough to lower serum urate (SU) levels.<sup>21</sup>

Benzbromarone exhibits pleiotropic actions beyond urate-lowering effect.<sup>22–27</sup> For example, benzbromarone enhanced insulin sensitivity and led to decreased inflammatory cytokine secretion from immune cells among patients with heart failure<sup>22</sup> or gout patients.<sup>23</sup> Also, direct radical scavenging activity of benzbromarone protected endothelial cells treated with uric acids.<sup>24,25</sup> Recently, a unique vascular effect of benzbromarone was reported that reverses vasoconstriction and pulmonary vascular remodelling in animal models of pulmonary arterial hypertension via at least two different mechanisms.<sup>26,27</sup> However, CV data of benzbromarone are scanty among gout patients.

In this study, we compared the CV risk between new users of allopurinol and benzbromarone among patients with gout using a nationally representative health insurance claims data in South Korea.

## Methods

### Data source

We conducted a cohort study on gout patients who initiated allopurinol or benzbromarone using the 2002–2017 Korea National Health Insurance Service (KNHIS) database. KNHIS is a universal and mandatory health insurance service that provides comprehensive medical care coverage of the entire Korean population.<sup>28</sup> The database contains longitudinal patient data including demographics, International Classification of Diseases Tenth Revision (ICD-10) diagnosis codes, procedures, pharmacy dispensing records, and type of medical utilization (outpatient, inpatient, or emergency department). This study complies with the Declaration of Helsinki, and the Institutional Review Board of the Seoul National University Bundang Hospital approved the study protocol (X-1905/543-902). Informed consent was waived based on fully de-identified database.

### Study cohort

Eligible patients were those who had ICD-10 diagnosis codes for gout and dispensed any of gout-related medications (i.e. colchicine,

allopurinol, febuxostat, benzbromarone, or probenecid). In Korea, allopurinol and benzbromarone have been equivalently available to treat gout. However, physicians may prefer using allopurinol over uricosuric agents as the first-line treatment, based on the international guidelines.<sup>21</sup> To avoid confounding by indication associated with different gout severity and duration, we only included incident new users of either allopurinol or benzbromarone devoid of any urate-lowering drugs during a 365-day period (= baseline period) before the first dispensing of the study drug (= index date), excluding prevalent new users who initiated allopurinol or benzbromarone as a 2nd-line treatment.

### Outcomes

The primary outcome of interest was a composite CV endpoint of hospitalized MI, stroke/transient ischaemic attack (TIA), or coronary revascularization. Secondary outcomes were individual components of the primary outcome, CV mortality, and all-cause mortality. MI and stroke/TIA were defined using inpatient ICD-10 diagnosis codes (MI I21.xx; stroke/TIA I60.xx, I61.xx, I63.xx, I64.xx, and G45.x). Coronary revascularization was identified using inpatient procedural codes. These algorithms were validated to have positive predictive values of >80% to detect corresponding CV outcomes from the claims data.<sup>29–31</sup> CV mortality was defined as deaths associated with ICD-10 codes of I20–I25 (ischaemic heart diseases) or I60–I69 (cerebrovascular diseases). Non-CV mortality was defined as deaths associated with any ICD-10 do except I00–I99 (diseases of the circulatory system). To identify CV and non-CV deaths, Korea national mortality data (<https://kosis.kr/statisticsList>) were linked to the KNHIS database.

### Covariates

We assessed variables potentially associated with CV outcomes and gout severity during the baseline period. These variables included index year, demographics, pre-existing CV conditions, traditional CV risk factors (i.e. hypertension, dyslipidemia, diabetes, peripheral vascular disease, renal diseases), gout medications (i.e. colchicine, non-steroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, and steroids), other comorbidities and medications, and healthcare utilization factors (i.e. hospitalization, emergency department visits, and the use of laboratory or diagnostic tests). We calculated the Charlson–Deyo comorbidity index score to further balance comorbidities.<sup>32</sup>

### Statistical analysis

To control for >60 baseline potential confounders, we used propensity score (PS) matching. To estimate a PS, we constructed a multivariable logistic regression model that included all baseline covariates listed in *Table 1*. Nearest neighbour matching for allopurinol vs benzbromarone initiators was done with a 5:1 ratio with the maximum calliper of 0.025 on the PS scale. Covariate balance after PS matching was considered achieved with absolute standardized differences of <0.1 between the two treatment groups.<sup>33</sup>

For the primary as-treated analysis, follow-up started from the day after the index date and ended on the earliest date of the following censoring events: outcome occurrence, study drug discontinuation, drug switching, end of database, or death. Study drug discontinuation was defined as no dispensing record within 90 days of the last dispensing date plus days of supply, in which case censoring occurred after a 30-day grace period from the last dispensing date plus days of supply. Adding or switching to different urate-lowering agents resulted in immediate censoring. Drug adherence was calculated using a proportion of days covered (PDC) defined as the sum of days of supply divided by the total days of follow-up. For the secondary 1-year intention-to-treat (ITT) analysis,

**Table 1** Baseline characteristics of gout patients before and after 5:1 propensity-score matching

	Before PS matching		s.d.	After PS matching		s.d.
	Allopurinol	Benzbromarone		Allopurinol	Benzbromarone	
N	788 176	20 739		103 695	20 739	
Demographics						
Age, years	57.3 ± 13.0	57.1 ± 13.0	0.010	57.0 ± 12.8	57.1 ± 13.0	0.013
Male sex	81.5	80.8	0.018	80.9	80.8	0.002
Index year						
			0.12			0.02
2003	5.34	6.56		6.92	6.56	
2004	5.10	6.43		6.67	6.43	
2005	5.53	4.93		5.06	4.93	
2006	5.93	4.97		4.91	4.97	
2007	6.22	5.76		5.68	5.76	
2008	6.33	6.47		6.45	6.47	
2009	6.51	7.02		6.90	7.02	
2010	6.95	7.45		7.47	7.45	
2011	7.04	7.70		7.56	7.70	
2012	7.39	7.67		7.52	7.67	
2013	7.60	7.87		7.71	7.87	
2014	7.93	7.58		7.74	7.58	
2015	8.47	7.57		7.52	7.57	
2016	7.95	6.99		6.91	6.99	
2017	5.73	5.02		5.00	5.02	
Cardiovascular comorbidities						
Angina pectoris	11.38	11.37	<.001	11.05	11.37	0.01
Atrial fibrillation	3.29	4.16	0.046	4.14	4.16	0.001
Myocardial infarction	1.80	1.89	0.006	1.82	1.89	0.005
Stroke/TIA	7.38	7.10	0.011	7.06	7.10	0.002
Heart failure	5.72	5.65	0.003	5.46	5.65	0.008
Hypertension	49.30	53.10	0.076	52.35	53.10	0.015
VTE	1.38	1.31	0.006	1.30	1.31	0.001
PVD	10.87	10.73	0.005	10.43	10.73	0.01
Other comorbidities						
CKD	9.22	13.06	0.122	13.32	13.06	0.008
Malignancy	7.36	5.95	0.057	5.94	5.95	<0.001
Hyperlipidaemia	36.57	43.45	0.141	42.80	43.45	0.013
Liver disease	31.88	33.90	0.043	33.10	33.90	0.017
COPD	18.72	17.78	0.024	17.52	17.78	0.007
Asthma	11.94	11.97	<.001	11.62	11.97	0.011
Diabetes	26.44	27.91	0.033	27.32	27.91	0.013
Renal stone	2.54	2.36	0.012	2.38	2.36	<0.001
Obesity	0.11	0.15	0.010	0.14	0.15	0.003
Sleep apnea	0.18	0.19	0.003	0.19	0.19	0.001
Smoking	0.05	0.01	0.021	0.02	0.01	<0.001
Alcoholism	5.91	5.30	0.026	5.27	5.30	0.001
Comorbidity score	1.51 ± 1.83	1.62 ± 1.81	0.063	1.60 ± 1.88	1.62 ± 1.81	0.012
Gout-related medications						
Colchicine	15.16	17.83	0.072	17.62	17.83	0.006
Any NSAIDs	70.57	68.91	0.036	68.62	68.91	0.006
Naproxen	8.95	9.61	0.023	9.62	9.61	<0.001
COXIBs	3.73	4.04	0.016	3.96	4.04	0.004
Opioids	15.23	15.13	0.003	15.01	15.13	0.003
Any steroid use	51.74	54.94	0.064	54.18	54.94	0.015

Continued

**Table 1** Continued

	Before PS matching		s.d.	After PS matching		s.d.
	Allopurinol	Benzbromarone		Allopurinol	Benzbromarone	
Cumulative steroid dose, <sup>a</sup> mg	151.23 ± 585.81	207.69 ± 663.36	0.09	207.87 ± 855.94	207.69 ± 663.36	<0.001
Recent steroid use <sup>b</sup>	29.36	33.17	0.082	32.53	33.17	0.014
Recent cumulative steroid dose, <sup>a,b</sup> mg	45.90 ± 243.45	59.55 ± 248.87	0.055	60.02 ± 327.14	59.55 ± 248.87	0.002
Other medications, %						
ACEI or ARBs	36.32	39.03	0.056	38.52	39.03	0.01
Beta-blockers	22.11	24.56	0.058	24.45	24.56	0.003
Calcium channel blocker	33.38	35.51	0.045	34.86	35.51	0.014
Any diuretics	31.28	32.48	0.026	31.88	32.48	0.013
Loop diuretics	11.62	11.61	<.001	11.42	11.61	0.006
Nitrate	3.43	3.73	0.016	3.67	3.73	0.003
Insulin	5.50	5.92	0.018	5.84	5.92	0.003
Oral hypoglycaemic drugs	13.84	14.13	0.008	13.79	14.13	0.01
Anticoagulants	5.28	6.06	0.034	6.07	6.06	<0.001
Antiplatelets	24.75	25.32	0.013	24.85	25.32	0.011
Thrombolytic agents	0.17	0.18	0.003	0.20	0.18	0.004
Statins	21.48	25.57	0.097	25.19	25.57	0.009
Other lipid-lowering agents	4.23	5.52	0.060	5.51	5.52	<0.001
Healthcare utilization pattern						
Hospitalization	23.22	21.95	0.030	21.51	21.95	0.011
ER visits	15.54	14.94	0.017	14.64	14.94	0.008
ECG order	36.23	35.64	0.012	34.94	35.64	0.015
Echocardiogram order	0.55	0.70	0.019	0.75	0.70	0.006
HbA1C order	19.84	21.13	0.032	20.55	21.13	0.014
Lipid/cholesterol test order	53.19	61.50	0.169	60.49	61.50	0.021
Serum creatinine test order	54.61	62.07	0.152	61.15	62.07	0.019
Uric acid test order	61.64	65.79	0.086	64.83	65.79	0.02

Data are presented as either % for binary variables or mean ± standard deviation for continuous variables.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; COPD, chronic pulmonary obstructive disease; COXIB, cyclooxygenase-2 inhibitor; ECG, electrocardiogram; ER, emergency room; HbA1C, glycated haemoglobin; NSAID, non-steroidal anti-inflammatory drug; PS, propensity score; PVD, peripheral vascular disease; s.d., standardized difference; TIA, transient ischaemic attack; VTE, venous thromboembolism.

<sup>a</sup>Prednisone-equivalent dose.

<sup>b</sup>Within 3 months prior to index date.

patients contributed to person-time in their exposure group for a maximum of 365 days regardless of treatment discontinuation or switching during the follow-up period.

Incidence rates (IRs) and 95% confidence intervals (CIs) were calculated for the primary and secondary outcomes among the PS-matched study cohort. To estimate hazard ratios (HRs) and 95% CIs for the primary and secondary outcomes, we performed a cause-specific hazard model comparing allopurinol vs. benzbromarone, to account for the competing risk of death.<sup>34</sup> When CV mortality risk was compared, we accounted for non-CV mortality as a competing risk. For follow-up time stratified analysis, we first sorted PS-matched study participants into three groups according to their follow-up time ( $\leq 1.5$ ,  $> 1.5$  and  $\leq 3$ , and  $> 3$  years), then ran a matched set stratified cause-specific hazard model within three individual groups.<sup>35</sup> Proportional hazards assumption was tested by including the interaction term between exposure and follow-up time and was not violated in any of the models.<sup>36</sup> All analyses were completed using SAS 9.4 (SAS Institute) software.

## Subgroup analysis

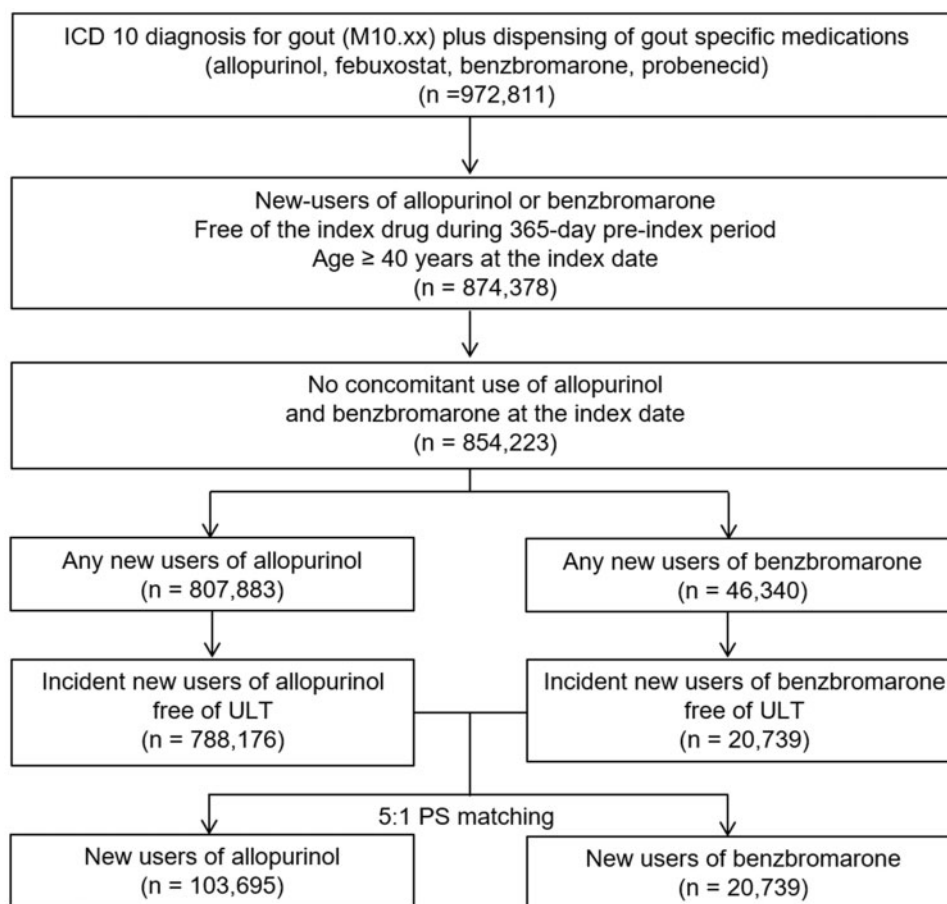
We performed a subgroup analysis on those at high risk of CV events. The high CV risk group included men aged  $\geq 50$  years and women aged  $\geq 55$  years who had at least one of diagnoses of angina, MI, stroke/TIA, peripheral vascular disease, or diabetes during the 1-year pre-index period.<sup>11</sup>

## Estimation of number needed to treat

We calculated the number needed to treat (NNT) with the benzbromarone instead of allopurinol for one additional patient to benefit, using HRs and survival probabilities at different time points up to 2 years of follow-up.<sup>37</sup> We specifically looked at NNT at 1-year follow-up based on the mean follow-up time of 1.16 years.

## Liver safety

Among ICD-10 K00–K77 codes (diseases of liver), hospitalized toxic liver disease (K71) and hepatic failure (K72) were examined during the as-treated follow-up. We also examined liver transplantation and deaths



**Figure 1** Study cohort selection process.

associated with K00–K77 in the two study groups. We also assessed the presence of viral hepatitis (B15–19).

## Results

### Baseline characteristics of study participants

Figure 1 summarizes our study cohort selection process. We identified 788 176 (97.6%) incident new users from 807 883 allopurinol initiators, and 20 739 (44.8%) from 46 340 benzbromarone initiators. Their PS distributions showed an excellent overlap (Supplementary material online, Figure S1).

As expected from their good PS overlap, the two treatment groups showed a relatively balanced covariate distribution even before PS matching with the standardized difference values of <0.1 for most of the covariates (Table 1). However, CV comorbidities were slightly more prevalent among benzbromarone users than allopurinol: atrial fibrillation (4.2% vs. 3.3%), hypertension (53.1% vs. 49.3%), chronic kidney disease (13.1% vs. 9.2%), dyslipidemia (43.5% vs. 36.6%), and diabetes (27.9% vs. 26.4%). Benzbromarone users also had higher cumulative steroid doses than allopurinol users. The

Charlson–Deyo comorbidity score ( $\pm$  standard deviation, SD) was  $1.62 \pm 1.81$  and  $1.51 \pm 1.83$ , for benzbromarone and allopurinol users, respectively. Laboratory testing for lipid levels (61.5% vs. 53.2%), renal function (62.1% vs. 54.6%), and uric acid levels (65.8% vs. 61.6%) was more frequently done among benzbromarone users.

After 5:1 PS-matching, we included 103 695 new users of allopurinol and 20 739 new users of benzbromarone. The mean index age was 57 years and 81% were male. All the baseline covariates including CV risk factors were well-balanced with standardized differences of <0.1 (Table 1). The overall mean follow-up (SD) for the primary outcome was 1.16 (2.00) years with 1.18 (2.03) years among allopurinol initiators and 1.03 (1.82) years among benzbromarone initiators.

### Allopurinol and benzbromarone usage pattern

The distribution of the index dose of the study drugs and their maximum daily dose among the PS-matched cohort are shown in Supplementary material online, Table S1. The most common daily index dose of allopurinol was 300 mg (38.5%), followed by 200 mg (31.8%), and 100 mg or less (26.0%). The



**Table 2** Incidence rates and hazard ratios of the primary and secondary outcomes comparing allopurinol with benzbromarone initiators: 5:1 propensity score matched analysis

	Allopurinol (n = 103 695)			Benzbromarone (Ref) (n = 20 739)			HR <sup>b</sup> (95% CI)
	Events	PY	IR <sup>a</sup> (95% CI)	Events	PY	IR <sup>a</sup> (95% CI)	
As-treated analysis							
Primary outcome							
Composite CV endpoint	2215	122 628	1.81 (1.73–1.88)	343	21 313	1.61 (1.44–1.78)	1.22 (1.05–1.41)
Secondary outcomes							
MI	343	125 565	0.27 (0.24–0.30)	60	21 672	0.28 (0.21–0.35)	1.05 (0.75–1.48)
Coronary revascularization	931	124 365	0.75 (0.70–0.80)	146	21 545	0.68 (0.57–0.79)	1.10 (0.88–1.38)
Stroke/TIA	1255	124 401	1.01 (0.95–1.07)	193	21 505	0.90 (0.77–1.02)	1.27 (1.04–1.55)
Any death	2330	126 095	1.85 (1.77–1.92)	276	21 729	1.27 (1.12–1.42)	1.66 (1.43–1.93)
365 days ITT analysis							
Primary outcome							
Composite CV endpoint	1852	94 760	1.95 (1.87–2.04)	305	17 423	1.75 (1.55–1.95)	1.13 (1.00–1.28)
Secondary outcomes							
MI	267	95 540	0.28 (0.25–0.31)	54	17 537	0.31 (0.23–0.39)	0.92 (0.68–1.23)
Coronary revascularization	664	95 329	0.70 (0.64–0.75)	122	17 508	0.70 (0.57–0.82)	1.00 (0.83–1.22)
Stroke/TIA	1117	95 115	1.17 (1.11–1.24)	175	17 480	1.00 (0.85–1.15)	1.18 (1.01–1.39)
Any death	3009	95 654	3.15 (3.03–3.26)	288	17 560	1.64 (1.45–1.83)	1.96 (1.73–2.21)

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; IR, incidence rate; ITT, intention-to-treat; MI, myocardial infarction; PY, person-years; TIA, transient ischaemic attack.

<sup>a</sup>Per 100 person-years.

<sup>b</sup>All HRs were estimated by cause-specific hazard model.

index daily doses of benzbromarone were 50 mg (46.5%), 100 mg (27.1%), and 150 mg (21.0%). The mean (SD) index dose was 221 (102) mg/day for allopurinol and 84 (42) mg/day for benzbromarone, and the mean maximal dose was 248 (139) mg/day and 88 (51) mg/day. The mean PDC (SD) of the study drugs was 0.74 (0.34) for allopurinol and 0.82 (0.29) for benzbromarone.

### Comparative CV risk between allopurinol vs. benzbromarone initiators

Since we found that the risk of all-cause-mortality was significantly higher among allopurinol vs. benzbromarone users (Table 2), we performed a cause-specific hazard analysis for all of our non-fatal CV outcomes accounting for the competing risk of death. In our primary as-treated analysis, the IR per 100 person-years for the composite CV endpoint was 1.81 in allopurinol users and 1.61 in benzbromarone users. Consequently, the risk of composite CV endpoints was 22% higher among allopurinol users than benzbromarone (PS-matched HR 1.22, 95% CI 1.05–1.41) (Table 2 and Figure 2A). The PS-matched HRs (95% CI) for the secondary CV outcomes showed overall the same direction as for the primary outcome but without statistical significance. The PS-matched HR (95% CI) of all-cause mortality was 1.66 (1.43–1.93) (Table 2 and Figure 2B).

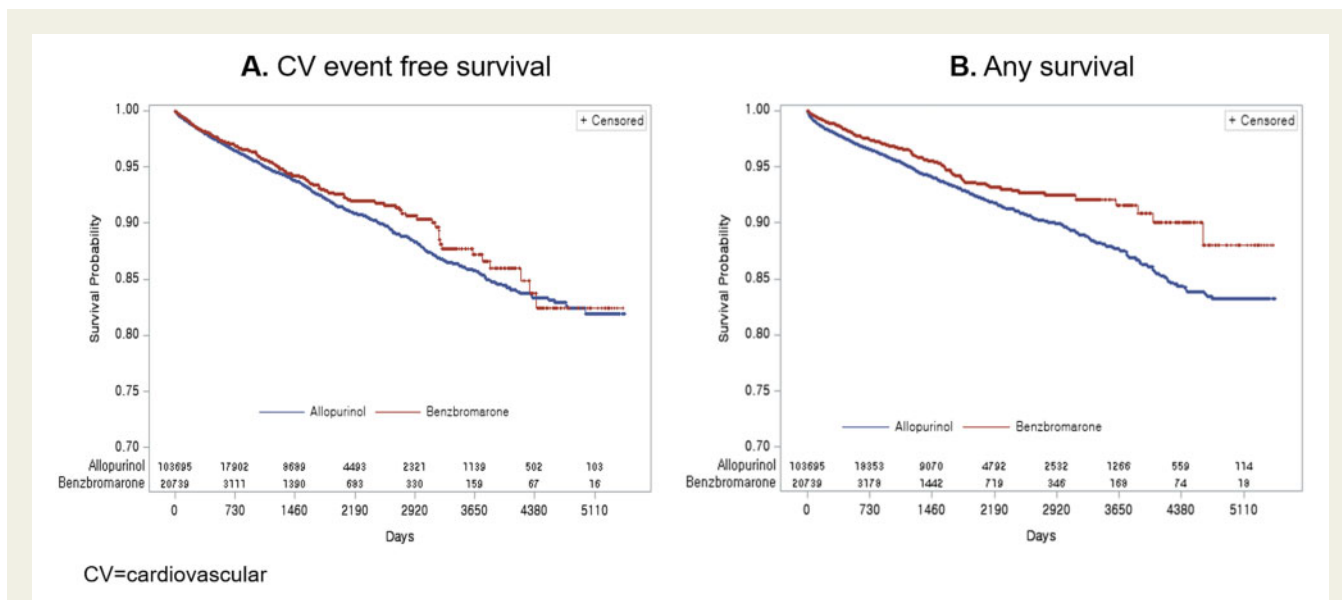
In our secondary ITT approach, the PS-matched HRs (95% CI) was 1.13 (1.00–1.28) and 1.96 (1.73–2.21) for the composite CV endpoint and all-cause mortality, respectively (Table 2).

### Follow-up time stratified analysis

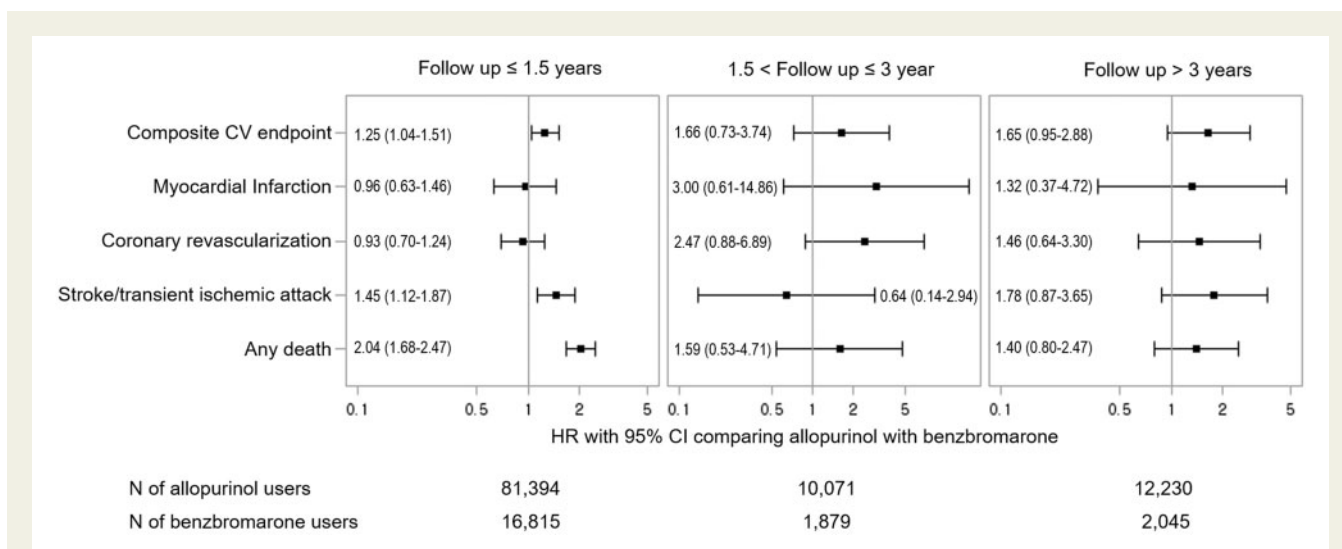
We performed a follow-up time stratified analysis to address whether a longer follow-up time among allopurinol users than benzbromarone would have led to a bias. Study participants were sorted into three groups according to their follow-up times:  $\leq 1.5$ ,  $1 <$  to  $\leq 3$ , and  $> 3$  years. As shown in Figure 3, elevated risk of the composite CV endpoint and all-cause mortality among allopurinol users was consistently observed across all three groups. The PS-matched HR (95% CI) for the composite CV endpoint was 1.25 (1.04–1.15) for  $\leq 1.5$  years, 1.66 (0.73–3.74) for  $1 <$  to  $\leq 3$  years, and 1.65 (0.95–2.88) for  $> 3$  years. The PS-matched HR (95% CI) for death was 2.04 (1.68–2.47), 1.59 (0.53–4.71), and 1.40 (0.8–2.47), respectively, for the individual follow-time periods.

### Cardiovascular and non-cardiovascular mortality

We further explored whether the causes of death were different between the two treatment groups and compared their risk of CV and non-CV mortality. During the as-treated follow-up, 2330 and 276 deaths occurred in allopurinol and benzbromarone users, respectively (Table 2), where the causes of death were available except for 24 (1.03%) allopurinol users (Supplementary material online, Table S2). The overall distribution of causes of death was similar between the two treatment groups in terms of order of frequency. The top 5 causes were diseases of the circulatory system (ICD-10 codes of I00–I99, 28.5%), neoplasm (C00–D48, 27.2%), diseases of the genitourinary system (N00–N99, 10.2%), endocrine/nutritional/metabolic



**Figure 2** Kaplan–Meier curves for the composite cardiovascular endpoint (A) and all-cause mortality (B).



**Figure 3** Follow-up time stratified analysis.

diseases (E00–E90, 8.6%), and injury/poisoning (S00–T98, 8.2%). Notably, the number of deaths among allopurinol users was disproportionately higher than among benzbromarone users exceeding the matching ratio of 5:1 for almost all causes, indicating that the mortality reduction with benzbromarone came from both CV and non-CV causes.

The IR of CV death was numerically higher among allopurinol users than benzbromarone (0.29–0.31 vs. 0.25 per 100 person-years) (Supplementary material online, Table S3). Also, the Kaplan-Meier curves diverged in favour of benzbromarone (Supplementary material online, Figure S2). However, the cause-specific analysis estimated the CV mortality risk as comparable, with a PS-matched HR (95% CI)

of 0.95 (0.67–1.35) when 24 missing causes were treated as non-CV, and of 1.03 (0.73–1.47) when treated as CV: the HR over the study period seemed driven by the early non-divergent period due to patient drop-outs in the late divergent period.<sup>38</sup>

Regarding non-CV mortality, the PS-matched HR (95% CI) was 2.10 (1.73–2.54) treating 24 missing causes as non-CV and 2.07 (1.71–2.50) treating them as CV deaths.

### Subgroup analyses for gout patients at high CV risk

We identified 28 095 allopurinol users and 5619 benzbromarone users at high risk of CV disease (see the Methods section for the



**Table 3** Subgroup analysis among patients with high cardiovascular risk at baseline: 5:1 propensity score matched analysis

	Allopurinol (n = 28 095)			Benzbromarone (Ref) (n = 5619)			HR <sup>b</sup> (95% CI)
	Events	PY	IR <sup>a</sup> (95% CI)	Events	PY	IR <sup>a</sup> (95% CI)	
Primary outcome							
Composite CV endpoint	1238	33 060	3.75 (3.54–3.95)	222	6029	3.68 (3.20–4.17)	1.08 (0.90–1.29)
Secondary outcomes							
MI	204	34 407	0.59 (0.51–0.67)	41	6266	0.65 (0.45–0.86)	0.72 (0.48–1.10)
Coronary revascularization	542	33 806	1.60 (1.47–1.74)	104	6165	1.69 (1.36–2.01)	0.96 (0.74–1.25)
Stroke or TIA	672	33 899	1.98 (1.83–2.13)	115	6171	1.86 (1.52–2.20)	1.15 (0.90–1.47)
Any death	1308	34 636	3.78 (3.57–3.98)	182	6301	2.89 (2.47–3.31)	1.37 (1.14–1.65)

CI, confidence interval; CV, cardiovascular; HRs, hazard ratios; IR, incidence rate; MI, myocardial infarction; PY, person-years; TIA, transient ischaemic attack.

<sup>a</sup>Per 100 person-years.

<sup>b</sup>All HRs were estimated by the cause-specific hazard model.

definition of the high-risk subgroup and [Supplementary material online, Table S4](#) for their PS-matched covariate distribution), with a mean age of 67.3 years and 72% male. The IR of composite CV endpoint was 3.75 and 3.68 per 100 person-years for allopurinol and benzbromarone users, respectively, with a PS-matched HR (95% CI) of 1.08 (0.90–1.29) adjusting for competing risk of death ([Table 3](#)). We found a higher risk of all-cause mortality (PS-matched HR 1.37, 95% CI 1.14–1.65) among allopurinol users compared to benzbromarone.

### Covariate distribution analysis during post-index 180 days

Lastly, we wanted to make sure that a higher risk of the composite CV endpoint and all-cause mortality was not due to a disruption of covariate balance soon after the index date. We looked at covariate distributions in the two groups during post-index 180 days and found that standardized differences were <0.1 for all covariates except for hospitalization (22.8% in allopurinol users vs. 16.1% in benzbromarone users) and ECG testing ordered (28.7% in allopurinol users vs. 23.5% in benzbromarone users) ([Supplementary material online, Table S5](#)). The 180-day cumulative steroid dose (167.53 vs. 139.50 mg of prednisolone equivalent dose) was numerically higher among allopurinol users than benzbromarone.

### NNT at 1 year of follow-up

While this study cannot prove the causality, [Supplementary material online, Table S6](#) shows the NNT with benzbromarone instead of allopurinol to prevent one additional patient from having the composite CV endpoint or all-cause death. The NNT was 277 patients for the composite CV event and 115 for all-cause death at 1-year follow-up.

### Liver safety

The maximal daily dose of allopurinol was 300 mg or less in >93% of the users while that of benzbromarone 150 mg or less in >99% ([Supplementary material online, Table S1](#)). During the as-treated follow-up, there were no hospitalizations associated with toxic liver disease or hepatic failure in the primary position. Among hospitalizations with such diagnoses in the secondary position, three

discontinued the index drug, all of whom were allopurinol users. Three cases ( $n=2$  for allopurinol,  $n=1$  benzbromarone) of liver transplantation had chronic underlying liver diseases before the transplantation. There were 46 hepatic deaths ( $n=40$  for allopurinol,  $n=6$  for benzbromarone) ([Supplementary material online, Table S7](#)): benzbromarone users died of either alcoholic liver disease ( $n=2$ ) or hepatitis B associated liver cirrhosis ( $n=4$ ) prior to death.

Taken together, there were no serious or fatal hepatic adverse events attributable to benzbromarone within a dose range of  $\leq 150$  mg/day.

## Discussion

In this large population-based cohort study, we found a 22% increased risk of CV events and 66% of all-cause mortality, associated with the use of allopurinol compared to benzbromarone, which would correspond to a 1-year NNT with benzbromarone of 277 patients for the composite CV event and 115 for all-cause mortality. The follow-up stratified analysis showed the difference in the risk of non-fatal CV events and all-cause mortality was relatively consistent across all follow-up periods. The IR of CV mortality was numerically higher among allopurinol users than benzbromarone. In our subgroup analysis of high CV risk patients, we found no difference in the risk of non-fatal CV events but increased risk of all-cause mortality among allopurinol vs. benzbromarone users ([Graphical abstract](#)). To the best of our knowledge, this is the first study that directly compared CV effect of allopurinol vs. benzbromarone among patients with gout.

Similar to benzbromarone that exhibits pleiotropic effects,<sup>22–27</sup> allopurinol has shown effects of scavenging oxygen radicals,<sup>39</sup> improving insulin sensitivity,<sup>40</sup> and anti-inflammatory actions.<sup>40</sup> XO inhibitors lower not only SU levels but also XO activity, both of which lead to NO depletion.<sup>9</sup> Due to this reason, XO inhibitors have long been the primary pharmacologic candidate to modulate CV risk, based on their theoretically greater blockade of oxidative stress compared to that of uricosuric agents. However, most gout patients are under-excretors rather than over-producers of uric acids.<sup>41</sup> Consistent with this, genome-wide association studies revealed that

the genetic determinants for hyperuricaemia and/or gout are primarily linked to disturbed urate excretion.<sup>42</sup> Therefore, the role of intracellular XO activity regarding the increased CV risk among gout patients is less compelling than hyperuricaemia itself.

The urate-lowering efficacy of 100 mg/day benzbromarone is known to be superior to that of 300 mg/day allopurinol,<sup>43</sup> and 300–380 mg/day allopurinol has a similar efficacy with 75–80 mg/day benzbromarone.<sup>44,45</sup> Based on the known equipotent dose of the two drugs, dosage use patterns, and PDC of the two drugs, it is likely that a higher proportion of the benzbromarone group achieved target SU levels <6.0 mg/dL during follow-up compared to the allopurinol group. Although the previous CARES and FAST trials do not necessarily link a greater urate-lowering efficacy or lower average SU levels with a better CV outcome,<sup>11,12</sup> it is still worth to discuss whether successful urate-lowering therapy (ULT) might relate to better CV outcomes. The majority of CARES participants achieved target SU levels of <6 mg/dL (61–75% of febuxostat users vs. 50–75% of allopurinol users), with similar proportions of target-achieving patients between the two groups except for the first 2 weeks. Likewise, all of FAST participants achieved the target SU levels through a lead-in phase. Moreover, these trials did not include a placebo group. Therefore, data are far limited even with the CARES and FAST trials regarding whether ULT itself is effective in reducing CV risk. The beneficial effects associated with benzbromarone vs. allopurinol in our study may, in fact, be due to more effective urate-lowering treatment with benzbromarone. An ongoing large RCT comparing allopurinol (600 mg/day) vs. usual care, the ALL-HEART study, is awaited to provide relevant information to this question in the future.

In addition to the upper bound of target SU levels, another important aspect of ULT would be the optimal lower bound, based on the J-shaped relationship between SU and CV events.<sup>9</sup> Because the curve inflection typically occurs at SU levels around 4–5 mg/dL,<sup>9</sup> profound uric acid decrease below such a level could be rather detrimental. Considering the doses used by the majority of our PS-matched cohort (100–300 mg/day allopurinol, 50–150 mg/day benzbromarone),<sup>11,43</sup> patients who experienced hazardously low SU levels were likely infrequent in our study unlike the CARES and FAST.

In the recent US cohort study of elderly Medicare enrollees (mean 76 years of age, 54% male) that compared CV effect of XO inhibitor vs. uricosuric agent, Kim *et al.*<sup>13</sup> found an increased risk of non-fatal CV events and all-cause mortality associated with allopurinol use vs. probenecid. The baseline comorbidity of study participants was higher (mean comorbidity score of 2.4) than ours and 28% had CV disease already. The CV benefits with probenecid is thought to derive from the direct and potent actions of probenecid on vascular and inflammatory process than urate-lowering effect.<sup>46–49</sup> Similar to probenecid, benzbromarone also exhibits diverse CV actions.<sup>22–27,50,51</sup> Among non-renal cells, vascular endothelial and smooth muscle cells are those that express urate transporters: benzbromarone prevented the activation of proliferative and inflammatory pathways induced by intracellularly transported soluble uric acids in these cells.<sup>50,51</sup> Selective inhibition of phosphatase-transactivator protein EYA by benzbromarone (or its metabolites) substantially reversed vascular remodelling in a rat model of pulmonary arterial hypertension.<sup>26</sup> In addition, benzbromarone selectively inhibits Ca<sup>2+</sup>-activated Cl<sup>-</sup> anion channel, TMEM16A, reversing vasoconstriction and vascular remodelling in animal models of pulmonary arterial

hypertension.<sup>27</sup> These unique CV actions of benzbromarone, together with its excellent urate-lowering effect compared to allopurinol, might be related to the CV result of our study. Taken together, it is worth to examine in future studies whether uricosuric agents as a class are favoured over XO inhibitors in terms of CV outcomes.

The null finding in the high-risk subgroup is likely in line with the current window of opportunity concept for ULT.<sup>52</sup> ULT was only effective in lowering blood pressure during the acute phase but not after a prolonged period of hyperuricaemia, at which stage, permanent structural vascular alteration occurred. Similarly, RCTs showed that ULT (both XO inhibitors and uricosurics) was associated with reduced blood pressure among adolescents but not among adults.<sup>53–55</sup> Alternatively, the CV effect of allopurinol vs. benzbromarone was relatively small as observed with the NNT and, thus, could have disappeared in a high-risk subgroup in whom the CV outcome was largely determined by the severity of their own CV disease at baseline.

In this study, we unexpectedly found that allopurinol was associated with two-fold greater risk of non-CV mortality compared to benzbromarone. Because our PS model was primarily designed to serve CV outcomes, concerns for residual or unmeasured confounding exist with non-CV outcomes. Nevertheless, growing evidence suggests that soluble uric acids induce adverse pathways in a wide spectrum of cell types (e.g. vascular, adipose, endocrine, and immune) when intracellularly transported via urate transporters.<sup>50,51,56–59</sup> Coupled with the finding that majority of hyperuricaemia develops by insufficient urate excretion than overproduction, one can postulate that benzbromarone, compared to allopurinol, would provide intrinsic benefits by inhibiting adverse cellular response from tissues that express urate transporters. Until the present, no other studies have directly compared the effect of benzbromarone with allopurinol on the risk of cause-specific mortality. While our results need to be confirmed, our study highlights a need for an RCT of benzbromarone on CV events and all-cause mortality among gout patients.

When we investigated serious or fatal liver diseases that occurred during benzbromarone treatment, we could find none attributable to the drug in our patients, who used a dose of ≤150 mg/day benzbromarone in >99% of cases.

This study has several important strengths. First, rigorous pharmacoepidemiologic methods were used including only the incident new users and adopting active comparator design to minimize confounding by indication.<sup>60</sup> We also performed extensive adjustment for ≥60 covariates using PS matching. To further account for competing risk of death, we used a cause-specific model to estimate the HR. In addition, we performed a follow-up time stratified analysis to avoid bias due to different follow-up times between the two treatment groups. Second, this study provides high generalizability based on the nationally representative database used. Third, our analyses on secondary outcomes and also ITT analyses showed overall consistent results as with the primary analyses. Fourth, we looked at covariate balance during the post-index period to ensure that the balance was overall preserved during the follow-up. Finally, we utilized previously validated claims-based algorithms to define CV outcomes to minimize misclassification bias.<sup>29–31</sup>

There are limitations in this study. First, our cohort study is inevitably subject to residual or unmeasured confounding, despite our rigorous efforts for confounding adjustment. Although we have

balanced proxies of gout severity, direct test results on SU levels, renal functions, or the severity of CV risk factors including hypertension, chronic kidney disease, or heart failure were not ascertainable from the claims data. However, benzbromarone initiators showed a higher prevalence of CV risk factors and greater comorbidity index at baseline (Table 1), thus any residual confounding was likely to render our results in favour of allopurinol than benzbromarone. Nevertheless, the concern of residual or unmeasured confounding is still present. In particular, those with highly advanced kidney disease could have been more frequently included in the allopurinol group. Second, we could not provide the mechanism to support reduced risk of all-cause mortality associated with benzbromarone use than allopurinol.

In conclusion, in this large population-based cohort study, we found that allopurinol use was associated with an increased risk of non-fatal CV events and all-cause mortality compared to benzbromarone. Benzbromarone may reduce CV risk and mortality in patients with gout, although more studies are necessary to confirm our findings and advance the understanding of the biological mechanisms.

## Supplementary material

Supplementary material is available at *European Heart Journal* online.

## Declaration of Helsinki

The authors state that their study complies with the Declaration of Helsinki, that the locally appointed ethics committee has approved the research protocol and that informed consent has been waived for the use of de-identified database.

**Conflict of interest:** S.C.K. has received research support to Brigham and Women's Hospital from Pfizer, AbbVie, Roche, and Bristol-Myers Squibb for unrelated studies.

## Data availability

The data underlying this article are available in the article and in its Supplementary material online.

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