Comparative cardiovascular risk in users versus non-users of xanthine oxidase inhibitors and febuxostat versus allopurinol users

Chengsheng Ju * [1], Rachel Wing Chuen Lai * [2], Ka Hou Christien Li [2, 3], Joshua Kai Fung Hung [2], Jenny CL Lai [4], Jeffery Ho PhD [5], Yingzhi Liu [6], Man Fung Tsoi [7], Tong Liu MD PhD [8], Bernard Man Yung Cheung MB BChir PhD FRCP [7], Ian Chi Kei Wong PhD [1, 9], Lai Shan Tam MD FRCP [2], Gary Tse PhD FESC FACC FRCP FFPH [8]

[1] School of Pharmacy, University College London, United Kingdom

[2] Laboratory of Cardiovascular Electrophysiology, Li Ka Shing Institute of Health Sciences, Hong Kong, P.R. China

[3] Faculty of Medicine, Newcastle University, Newcastle Upon Tyne, United Kingdom

[4] Department of Pharmacy & Pharmacology, University of Bath, Bath, United Kingdom

[5]Department of Microbiology, Faculty of Medicine, Chinese University of Hong Kong, Hong Kong, P.R. China

[6] Department of Anaesthesia and Intensive Care, Faculty of Medicine, Chinese University of Hong Kong, Hong Kong, P.R. China

[7] Division of Clinical Pharmacology and Therapeutics, Department of Medicine, The University of Hong Kong, Pokfulam, Hong Kong, P.R. China

[8] Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular disease,

Department of Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin, 300211, P.R. China

[9] Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, Hong Kong, P.R. China

* Joint first authors

Correspondence to

Prof. Gary Tse

Professor, Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular disease, Department of Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin, 300211, P.R. China

Email: gary.tse@doctors.org.uk

KEY MESSAGES

- Xanthine oxidase inhibitor users showed similar risks of all-cause mortality and MACE compared to non-users.
- Febuxostat users showed similar MACE and all-cause mortality outcomes compared to allopurinol users.
- Concurrent colchicine use reduced the risk of all-cause mortality and heart failure-related hospitalizations.

ABSTRACT

Background: The aim of this study is to determine major adverse cardiovascular events (MACE) and all-cause mortality comparing between xanthine oxidase inhibitors (XOIs) and non-XOI users, and between allopurinol and febuxostat.

Methods: This is a retrospective cohort study of gout patients prescribed anti-hyperuricemic medications between 2013 and 2017 using a territory-wide administrative database. XOI users were matched 1:1 to XOI non-users using propensity scores. Febuxostat users were matched 1:3 to allopurinol users. Subgroup analyses were conducted based on colchicine use.

Results: Of the 13997 eligible participants, 3607 (25.8%) were XOI users and 10390 (74.2%) were XOI non-users. After propensity score matching, compared to non-users (n = 3607), XOI users (n = 3607) showed similar incidence of MACE (hazard ratio [HR]: 0.997, 95% confidence interval [CI], 0.879-1.131; P>0.05) and all-cause mortality (HR=0.972, 95% CI 0.886-1.065, P=0.539). Febuxostat (n=276) users showed a similar risk of MACE compared to allopurinol users (n=828; HR: 0.672, 95% CI, 0.416-1.085; P=0.104) with a tendency towards a lower risk of heart failure (HF)-related hospitalizations (HR=0.529, 95% CI 0.272-1.029; P=0.061). Concurrent colchicine use reduced the risk for all-cause mortality amongst XOI users (HR=0.671, 95% 0.586-0.768; P<0.001).

Conclusions: In gout patients, XOI users showed similar risk of MACE and all-cause mortality compared to non-users. Compared to allopurinol users, febuxostat users

showed similar MACE and all-cause mortality risks but lower HF-related hospitalizations.

Keywords: Xanthine oxidase inhibitor, allopurinol, febuxostat, gout, cardiovascular risk, myocardial infarction

Introduction

The burden of cardiovascular diseases (CVDs) remain high in the 21st century particularly in low and middle income countries, where around 17 million cardiovascular deaths per year are reported [1]. Healthcare economists have estimated that, over 15 years, CVDs led to loss of 3.76 trillion US dollars, and account for than half of the economic loss due to non-communicable diseases [1]. Previous observational studies have reported a significant association between hyperuricemia or gout and increased risks of cardiovascular morbidities including congestive heart failure, myocardial infarction and cerebrovascular accident [2-5]. Therefore, understanding the cardiovascular effects of uric acid lowering drugs is important for treatment options that can reduce cardiovascular morbidity and mortality.

Xanthine oxidase inhibitors, which inhibit the conversion of purines to uric acid, are commonly prescribed for gout patients [6, 7]. They are indicated in the treatment of gout to achieve urate target levels and to cure signs and symptoms of inflammatory response to deposition of urate crystals within the joints [8]. Their use is associated with reduced production of superoxide species and intracellular oxidative stress, leading to potentially improved endothelial and cardiac function [9, 10]. Recognition of this molecular mechanism prompted researchers to conduct observational studies [11-15] and clinical trials [16] to examine potential cardioprotective effects of xanthine oxidase inhibitors.

However, studies reporting on the association between exposure to gout

93 medications and cardiovascular risk have demonstrated conflicting results. In a Danish
94 population study involving more than 65,000 hyperuricemic patients revealed 11%
95 reduced risk for adverse cardiovascular events in allopurinol users compared to
96 propensity score matched non-users [14]. No association was observed in a general gout
97 patient cohort from the United States insurance claim database [15]. A randomized
98 controlled trial conducted in the United States found that allopurinol did not improve
99 clinical status, exercise capacity, quality of life, or left ventricular ejection fraction after
100 24 weeks of treatment in hyperuricemic patients with heart failure [17]. Another study
101 even reported an elevated cardiovascular risk with allopurinol users using a cohort from
102 a Taiwan-based insurance database [18].

103 Moreover, to date, the majority of studies have been limited to allopurinol [6, 14,
104 19] until the launch of the Cardiovascular Safety of Febuxostat and Allopurinol in
105 Patients With Gout and Cardiovascular Morbidities (CARES) trial [16]. The finding of
106 higher all-cause mortality including cardiovascular mortality in patients prescribed with
107 febuxostat led to an issue of public safety alert by the U.S. Food and Drug
108 Administration (FDA). However, the results were limited by the substantial loss-of-
109 follow-up rate (45.0% overall, 45.0% in the febuxostat group and 44.9% in the
110 allopurinol group). In Europe, The European Union Risk Management Plan for
111 febuxostat has called for a pharmacovigilance plan with a large cardiovascular safety
112 investigation of febuxostat, Febuxostat versus Allopurinol Streamlined trial (FAST).
113 This ongoing investigation is in response to reports of cardiovascular events during its
114 Phase III randomised controlled trials and long-term clinical extension studies, where

60% of the cohort had ≥ two cardiovascular risk factors [20]. Both trials address the comparative safety between allopurinol and febuxostat, whether the use of XOI agent has benefits compared to placebo remain unanswered [21]. Therefore, current studies assessing the effect of anti-hyperuricemia treatments, including XOI, on cardiovascular diseases are inconclusive until the results from the ongoing RCTs prove otherwise [22, 23].

Given the above controversies, this study was conducted to compare adverse cardiovascular events and all-cause mortality between XOI users and non-users, and between allopurinol and febuxostat users, who did not have a history of major adverse cardiovascular events in a real-world setting in Hong Kong.

Methods

Study design and data sources

We conducted a retrospective cohort study using a territory-wide population representative sample derived from the Clinical Data Analysis and Reporting System, an electronic health record system managed by the Hong Kong Hospital Authority. This is a computerized regional electronic health database linking all the patients' health records under primary, secondary, and tertiary care provided by 121 government-subsidized out-patient clinics, and 43 acute and sub-acute hospitals. These serve more than 90% of the local population and were used for producing high quality research by pharmacoepidemiologic studies from local research teams [24-28].

Clinical data from the database include patient-specific personal information, diagnosis, procedure, prescription, laboratory test results, admission and discharge information. Patient information are coded using reference numbers and hospital numbers to protect patient confidentiality. Ethics approval was obtained from The Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee.

Study population and cohort definition

Over a search period of five years (1st January 2013 to 31st December 2017), we recruited in-patients who had a diagnosis of gout or were prescribed xanthine oxidase inhibitors admitted to nine hospitals and out-patients from 47 clinics offering community-based primary care healthcare services. A case of gout was defined as having principal diagnosis with any of the following International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) codes: 274.0 (gouty arthropathy), 274.10 (gouty nephropathy, unspecified), 274.81 (gouty tophi of ear), 274.89 (gout with other specified manifestations) and 274.9 (gout, unspecified).

Patients who were ever-treated by at least one XOI were defined as the XOI user cohort. Patients with no exposure to XOI were defined as the comparator cohort. Among the XOI user cohort, febuxostat users (febuxostat 40 mg/80 mg/120 mg daily) and allopurinol users (allopurinol 100 mg/200 mg/300 mg daily) were identified on the intention-to-treat basis and were defined as the febuxostat user cohort and the

allopurinol cohort, respectively. Patients under 18 years old or had a history of MACE or heart failure before the first gout diagnosis were excluded from the study cohorts. Patients initiated any XOI before the first gout diagnosis record were further excluded.

Outcomes and follow-up

The primary analytic outcome was taken to be a composite of hospitalisation due to heart failure and the 3-point major adverse cardiovascular event (MACE) defined by FDA, including nonfatal infarction, nonfatal stroke and cardiovascular death. The secondary outcome was all-cause mortality. Analyses for both outcomes were made by comparing XOI user cohort versus XOI non-user cohort as primary analyses, and febuxostat user cohort versus allopurinol user cohort as secondary analyses. The primary cause of death was recorded as ICD-10 CM code in the Clinical Data Analysis and Reporting System. The index date for the XOI non-user cohort was defined as the date of diagnosis of gout. The index date for the XOI user cohort, including the allopurinol and febuxostat user subgroups, was defined as the initiation of XOIs, whether allopurinol or febuxostat. In order to address the issue of potential immortal time bias, the patient-years of XOI users between the diagnosis of gout and the start of XOI treatment were included in the XOI non-user cohort for any analyses. All patients were followed from the index data either the occurrence of the primary outcome, death or the last day of search, whichever occurs first.

Covariates

In order to control potential confounders, the following baseline characteristics were obtained at the index admission: age, sex, comorbidities (peripheral vascular diseases, rheumatic diseases, liver diseases, diabetes mellitus and renal diseases), Deyo's Charlson Comorbidity Index, concurrent long-term cardiovascular medications (beta blockers, diuretics, lipid-lowering drugs, anticoagulants, anti-platelets, calcium channel blockers, antidiabetic drugs, nitrates, angiotensin converting enzyme inhibitors and angiotensin II receptor blockers) and other gout medications (non-steroid anti-inflammatory drugs, probenecid and colchicine). Deyo's Charlson comorbidity score was calculated based on ICD-9 CM using 17 major medical conditions, such as dementia, malignancy, diabetes, renal and hepatic diseases.

Subgroup analyses

We conducted two subgroup analyses based on colchicine use. The first subgroup analyses were stratified by colchicine use. In the second subgroup analyses, we defined the stratification as whether individual patients have received a colchicine prescription with the duration longer than 3 days. All subgroups were split from the main matched cohort without further matching [29, 30]. Hazard ratios for both primary and secondary outcomes were calculated for two subgroup analyses. Following the subgroup analyses, we conducted further analyses to investigate the effect of concurrent colchicine on the primary and secondary outcomes within the XOI user cohort.

Statistical analysis

To minimize bias by confounding, propensity score matching was applied to adjust all baseline covariates. The propensity scores were generated by multivariate logistic regression using all variables listed in **Table 1.** In primary analyses, XOI users were matched with XOI non-users at a fixed 1:1 ratio. In secondary analyses, febuxostat users were matched with allopurinol users a fixed 1:3 ratio. Both matchings were performed by the nearest-neighbour matching method. Baseline characteristics between the matched cohorts were compared using both P-value and standardized mean difference. Pearson's Chi-square test or Fisher's exact test were used to compare between groups for categorical variables as appropriate. Considering normality, Student's t-test or Mann-Whitney U test were applied for continuous variables. Time-to-event analysis was conducted using Cox proportional hazards regression. Crude hazard ratios (HR) were presented in 95% confidence intervals for each outcome. Time-dependent co-variates were evaluated to ensure our models did not violate the assumption of proportional hazards. Propensity score matching was conducted with R statistical software version 3.5.2 and all other statistical analyses were conducted using Statistical Package for Social Sciences. (IBM SPSS version 25.0, Armonk, NY). Two-sided P-values of less than 0.05 were considered statistically significant.

Results

Study population

Of the 20114 patients identified, 15696 (78.0%) subjects did not have a history of MACE or heart failure before a diagnosis of gout was made. Based on drug dispensing records, 5306 XOI users were identified. To identify the patients who are XOI-naïve, those receiving XOI treatment before the first gout diagnosis were excluded (n = 1699). Thus, the remaining XOI users (n=3607) were propensity score (PS)-matched in a 1:1 ratio to XOI non-users. Moreover, 276 intention-to-treat febuxostat users and 3331 intention-to-treat allopurinol users were identified from 3607 eligible XOI users. Febuxostat users were then matched 1:3 with allopurinol users. The selection of study population is summarized in **Figure 1**.

The baseline characteristics of the unmatched cohorts are detailed in **Supplementary Table 1**. Compared to XOI non-users, XOI users tended to have more male sex, younger age, more pretreatment renal conditions, diabetes mellitus, higher Charlson's Comorbidity Index Score and more concurrent uses anti-diabetic medications, angiotensin converting enzyme inhibitors/angiotensin II receptor blockers, beta-blockers, calcium channel blockers, anticoagulants/antiplatelet agents and less NSAIDs. Furthermore, among XOI users, febuxostat users tended to have higher Charlson's Comorbidity Index Score, more concurrent uses of antidiabetic medications, diuretics, colchicine and probenecid than allopurinol users.

The baseline characteristics of the study population after 1:1 and 1:3 PS-matching are shown in **Table 1**. All the baseline covariates were well-matched between the XOI

users and non-users. For the matched febuxostat and allopurinol users, probenecid use was relatively imbalanced (SMD=0.197) after matching due to that limited records were found from the allopurinol users. The median (IQR) follow-up time was 1.97 (0.75, 3.57) years for the XOI users and 1.85 (0.71, 3.36) years for the XOI non-users after matching. For the secondary analysis cohorts, it was 1.50 (0.60, 2.58) years for the febuxostat users and 1.96 (0.79, 3.48) years for the allopurinol users after matching.

Primary analyses

Comparing to XOI non-users, XOI users had similar a risk of meeting the primary outcome (Hazard Ratio=0.997, 95% CI 0.879-1.131; P=0.962) (**Figure 2A**). Separate analyses were conducted for the individual component of the primary outcome (**Table 2**). No significant difference was observed between XOI users and XOI non-users for non-fatal MI (HR=1.111, 95% CI 0.849-1.453; P=0.444), congestive heart failure (HR=1.028, 95% CI 0.870-1.215; P=0.743), cardiovascular death (HR=0.680, 95% CI 0.216-2.145; P=0.511) or stroke events (HR=0.821, 95% CI 0.640-1.054; P=0.121). For the secondary outcome, XOI users did not have a significant difference in all-cause mortality when compared to non-users (HR=0.972, 95% CI 0.886-1.065; P=0.539) (**Figure 2B**).

Secondary analyses

Allopurinol users showed similar rates of the primary outcome, individual MACE

outcomes, and all-cause mortality when compared to XOI non-users (**Supplementary Table 2**). Febuxostat use was associated with a similar risk of MACE and heart failure (HR=0.672, 95% CI 0.416-1.085; P=0.104) (**Figure 3A**). Analyses for individual components of the primary outcome revealed no significant association but the risk for congestive heart failure tended to be lower (HR=0.529, 95% CI 0.272-1.029; P=0.061) (**Table 3**). Febuxostat users showed a similar all-cause mortality compared to allopurinol users (HR=0.985, 95% CI 0.725-1.338; P=0.921) (**Figure 3B**).

Subgroup analyses

The first subgroup analysis on colchicine use was conducted. Among 5277 colchicine users, there were 2628 XOI users and 2649 XOI non-users. No significant difference in the primary or secondary outcome was observed. Among the 1937 colchicine non-users, 979 patients were from the matched XOI user cohort and 958 were from the matched XOI non-user cohort. Whilst there was no difference in the risk for primary outcome between either group, XOI users showed a higher incidence of heart failure-related hospitalizations (HR=1.434, 95% CI 1.015-2.026; P=0.041) but a lower risk in all-cause mortality (HR=0.849, 95% CI 0.728-0.990; P=0.036) (**Supplementary Table 3**).

The second subgroup analysis was conducted for duration of colchicine prescription. Of these, 4082 patients with prescriptions >3 days and 3132 patients with prescriptions less than this duration. Among the 4082 patients with prescriptions >3 days, 2201 were

XOI users and 1881 were XOI non-users and no difference were found in risk of primary or secondary outcome. Among those 3132 patients with prescriptions <=3 days , 1406 were XOI users and 1726 were XOI non-users. The XOI users had a higher risk for heart failure-related hospitalizations (HR=1.353, 95% CI 1.045-1.750; P=0.022), but no difference in the primary or secondary outcome, or individual components of the primary outcome (**Supplementary Table 4**).

Analysis on the effect of concurrent use of colchicine within the matched XOI cohort (n=3706) was conducted. We compared 2628 colchicine users with 979 colchicine non-users. The colchicine users had a significantly lower risk for all-cause mortality (HR=0.671, 95% 0.586-0.768; P<0.001) and a similar risk for the primary outcome including each individual cardiovascular endpoint. 2201 XOI users with prescription of colchicine >3 days were compared to 1406 XOI users with prescriptions <=3 days. Consistently, colchicine users with longer duration (> 3 days vs. <= 3 days) showed a lower risk for all-cause mortality (HR=0.600, 95% CI 0.527-0.683; P<0.001). The risk for the primary outcome was lower amongst these colchicine users (HR=0.813, 95% CI 0.680-0.972; P=0.023), which was mainly driven by a lower risk for heart failure-related hospitalizations (HR0.746, 95% CI 0.590-0.942; P=0.014) (**Supplementary Table 5**).

Discussion

303 The main findings of this retrospective study of gout patients using electronic
304 health records are that i) no benefit of XOI use on risk of major cardiovascular events
305 or all-cause mortality; ii) febuxostat treatment was associated with a similar risk of
306 cardiovascular events and all-cause mortality compared to allopurinol treatment; iii)
307 concurrent colchicine use reduced the risk for all-cause mortality amongst XOI users;
308 and iv) colchicine use longer than 3 days significantly reduce heart failure-related
309 hospitalizations.

310 The null association between XOI treatment and cardiovascular events and all-
311 cause mortality has been reported in previous cohort studies, and confirmed by
312 systematic reviews and meta-analyses of randomized controlled trials [4, 31, 32]. A
313 cohort study conducted using the U.S. insurance claims-based data reported that XOI
314 users did not have a different cardiovascular risk compared to patients with untreated
315 hyperuricemia [33], a finding that is supported by our results. The crude incidence rates
316 of individual cardiovascular endpoints in this study were also similar to the results
317 reported in other studies [13]. A meta-analysis of 91 randomized controlled trials
318 comparing the use of XOI with placebo has also shown similar results for MACE
319 (OR=0.71, 95% CI 0.46-1.09) and death (OR=0.89, 95% CI 0.59-1.33) comparing to
320 our study [4]. Moreover, The EXACT-HF study failed to demonstrate benefits of
321 allopurinol in patients with symptomatic HF [17]. Therefore, this study adds value to
322 the existing literature that xanthine oxidase inhibition does not produce significant
323 cardiovascular benefits [34-36].

Moreover, our study found that febuxostat users did not have a significantly different risk of MACE or all-cause mortality compared to allopurinol users. These findings are in keeping with those of previous studies. In the large scale, randomized, double-blinded, non-inferiority CARES clinical trial [37], febuxostat demonstrated noninferiority to allopurinol with respect to rates of adverse cardiovascular events while all-cause mortality and cardiovascular mortality were higher with febuxostat. There are potential reasons as to why this was the case. There was a significant drop-out rate (45%) of both groups and premature discontinuation could bias towards the null for safety outcomes [38]. Furthermore, *post hoc* ascertainment led to the addition of more deaths to the allopurinol than to the febuxostat group, which would render the original hazard ratio non-significant (HR=1.09, 95% CI 0.94-1.28)[38]. Lastly, the CARES trial was restricted to use of XOIs in secondary prevention while we examined outcomes in primary prevention. Due to these reasons, the results from CARES trial have generated heated debates regarding their application to the wider patient populations with gout [21]. Thus, in this regard, population-based cohort studies have offered a complementary approach to answer clinical questions. Thus, a large scale population-based cohort study conducted using US Medicare claims data comparing febuxostat and allopurinol uses in gout patients has shown the no difference in composite cardiovascular events, heart failure and all-cause mortality [13].

Notably, our febuxostat user cohort has numerically lower incidence for cardiovascular outcomes (HR=0.67) and congestive heart failure (HR=0.53) than allopurinol users. Similar results were reported in previously conducted studies. In one

observational study investigating XOI use in gout patients with stage 3 or 4 chronic kidney disease, those taking febuxostat were less likely to experience major cardiovascular events defined as coronary artery disease, cerebrovascular disease, and peripheral vascular disease and heart failure [5]. In a Korean nationwide cohort study, the composite cardiovascular endpoint of hospitalisation for myocardial infarction, stroke/transient ischaemic attack, or coronary revascularisation tended to be higher with allopurinol than with febuxostat [39]. An recently published observational study, febuxostat demonstrated a better cardioprotective effect than allopurinol in patients with heart failure [40]. Another randomized, double-blind, parallel between-group, comparative trial conducted in China also showed that the urate-lowering efficacy of daily febuxostat 80 mg was greater than that of febuxostat 40 mg and allopurinol 300 mg, which exhibited comparable urate lowering efficacy [37]. The underlying mechanistic explanation to the difference in cardio-protective effects between febuxostat and allopurinol has been reported in various studies. Febuxostat selectively inhibits both oxidized and reduced forms of xanthine oxidase and has minimal effects on other enzymes of purine and pyrimidine metabolism [7]. It has been demonstrated that febuxostat has superior antioxidant and anti-inflammatory effects than allopurinol [41, 42]. Clinically, febuxostat has demonstrated a stronger urate-lowering effect than allopurinol [43]. Since serum uric acid is an independent risk factor for cardiovascular diseases [3], a greater degree of uric acid lowering by febuxostat leads to lower cardiovascular risks in patients than allopurinol.

The results from the subgroup analyses suggested that the concurrent use of

colchicine with XOI could reduce the risk for all-cause mortality. Long-term use of colchicine could ameliorate the effect of XOI on new-onset heart failure. This could be due to the possible anti-inflammatory effect of colchicine. Our study found that colchicine use reduced heart failure-related hospitalizations. In one prospective randomised study investigating the effect of colchicine in stable chronic heart failure, colchicine effectively reduced the level of inflammatory biomarkers but without improvement in cardiac function of patients [44]. A meta-analysis found that colchicine alone did not exert any benefit on the prevention of heart failure [45]. One cohort study found that colchicine reduced the risks for cardiovascular events and all-cause mortality in gout patient [46]. While there is much uncertainty on the cardiovascular effect of colchicine, further studies are required to investigate colchicine alone and also its effect with concurrent XOI usage.

Strengths and limitations of this study

This study was strengthened by extracting all eligible cases over the study period based on pre-defined billing codes followed by propensity score matching to generate a population representative sample to minimize confounding bias. In order to minimize the bias imposed by the presence of otherwise high-risk individuals, patients with the history of MACE before the index date of diagnosis with gout were excluded hence all study subjects were in primary prevention. Third, our study population was homogenous Chinese, our study was free from confounding by ethnicity.

There are some limitations to our study. First, we were not able to collect patients' lifestyle and socioeconomic information such as diet, physical activities, smoking and alcohol drinking histories, body mass index, use of over-the-counter medicines and adherence to prescribed medications, which are potential confounders. Second, insufficient laboratory results were recorded, especially the serum urate level after drug treatments, which restricted us from conducting a more comprehensive analysis. Third, Severity of gout could not be assessed from the database, which is particularly concerning as we compared XOI users to non-users. Last, the small number of febuxostat users in the secondary analyses rendered insufficient statistical power.

Conclusion

In gout patients, XOI users showed similar risk of MACE and all-cause mortality compared to non-users. Compared to allopurinol users, febuxostat users showed similar MACE and all-cause mortality risks but lower HF-related hospitalizations.

Conflicts of interest

There are no competing interests to declare.

Disclosure

No disclosures.

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Figure Legends

Table 1. Baseline characteristics after 1:1 matching of XOI users to non-users, and 1:3 matching of febuxostat to allopurinol users.

	After 1:1 matching				After 1:3 matching			
	XOI users n= 3607	XOI non-users n= 3607	P-value	SMD	Febuxostat users n=276	Allopurinol users n=828	P-value	SMD
Demographics								
Male	2563 (71.1)	2546 (70.6)	0.679	0.010	186 (67.4)	549 (66.3)	0.797	0.023
Age	71.46 (14.59)	72.12 (15.36)	0.061	0.044	70.41 (14.35)	70.01 (14.90)	0.703	0.027
Comorbidity								
PVD	50 (1.4)	56 (1.6)	0.625	0.014	4 (1.4)	16 (1.9)	0.794	0.037
Rheumatic disease	30 (0.8)	35 (1.0)	0.618	0.015	5 (1.8)	11 (1.3)	0.771	0.039
Liver disease	24 (0.7)	19 (0.5)	0.541	0.018	3 (1.1)	12 (1.4)	0.881	0.032
DM	681 (18.9)	663 (18.4)	0.607	0.013	59 (21.4)	185 (22.3)	0.802	0.023
Renal disease	527 (14.6)	519 (14.4)	0.815	0.006	46 (16.7)	139 (16.8)	1.000	0.003
Charlson's score	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.535	0.013	0.00 [0.00, 2.00]	0.00 [0.00. 2.00]	0.632	0.030
Cardiovascular medications								
Lipid-lowering drugs	1501 (41.6)	1505 (41.7)	0.943	0.002	123 (44.6)	374 (45.2)	0.917	0.012
ACE inhibitors/ARBs	1514 (42.0)	1521 (41.4)	0.633	0.012	131 (47.5)	402 (48.6)	0.808	0.022
Antidiabetic drugs	798 (22.1)	779 (21.6)	0.608	0.013	82 (29.7)	256 (30.9)	0.763	0.026
Diuretics	1099 (30.5)	1074 (29.8)	0.538	0.015	108 (39.1)	328 (39.6)	0.943	0.010
Beta-blockers	1412 (39.1)	1482 (41.1)	0.097	0.040	117 (42.4)	373 (45.0)	0.484	0.054
Nitrates	320 (8.9)	314 (8.7)	0.835	0.006	17 (6.2)	50 (6.0)	1.000	0.005
CCBs	2081 (57.7)	2103 (58.3)	0.616	0.012	160 (58.0)	471 (56.9)	0.806	0.022
Anticoagulants/ Antiplatelet agents	1368 (37.9)	1382 (38.3)	0.753	0.008	99 (35.9)	285 (34.4)	0.715	0.030
Other gout medications								
Colchicine	2628 (72.9)	2649 (73.4)	0.595	0.013	237 (85.9)	716 (86.5)	0.879	0.017
Probenecid	9 (0.2)	9 (0.2)	1.000	<0.001	7 (2.5)	2 (0.2)	0.001	0.197
NSAIDs	2063 (57.2)	2036 (56.4)	0.537	0.015	159 (57.6)	485 (58.6)	0.833	0.020

All data was presented in number (percentage) or median [interquartile range] as appropriate. XOI, xanthine oxidase inhibitors; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers; DM, diabetes mellitus; IQR, interquartile range; PVD, peripheral vascular disease; NSAID, non-steroid anti-inflammatory drugs.

Table 2. Adjusted hazard ratios for the composite primary and secondary outcomes comparing XOI users to non-users.

Outcome	XOI users (n=3607) Event (n)	XOI users Crude IR (per 1000 patient-years)	XOI non-users (n=3067) Event (n)	XOI non-users Crude IR (per 1000 patient-years)	HR (95% CI)	P-value
Primary outcome						
Composite outcome	497	62.77	487	66.13	0.997 (0.879-1.131)	0.962
Nonfatal MI	115	14.50	99	13.15	1.111 (0.849-1.453)	0.444
Stroke	117	14.75	139	18.64	0.821 (0.640-1.054)	0.121
Cardiovascular death	5	0.63	7	0.93	0.680 (0.216-2.145)	0.511
Hospitalization due to CHF	287	36.18	274	36.39	1.028 (0.870-1.215)	0.743
Secondary outcome						
All-cause mortality	922	106.90	913	111.35	0.972 (0.886-1.065)	0.539

XOI, xanthine oxidase inhibitors; MI, myocardial infarction; CHF, congestive heart failure; CI, confidence interval; HR, hazard ratio; IR, incidence rate.

Table 3. Adjusted hazard ratios for the primary and secondary outcomes comparing febuxostat users to allopurinol users.

Outcome	Febuxostat users (n=276) Event (n)	Febuxostat users Crude IR (per 1000 patient-years)	Allopurinol users (n=828) Event (n)	Allopurinol users Crude IR (per 1000 patient-years)	HR (95% CI)	P-value
Primary outcome						
Composite outcome	21	43.41	107	59.53	0.672 (0.416-1.085)	0.104
Nonfatal MI	4	8.27	19	10.57	0.789 (0.267-2.329)	0.667
Stroke	6	12.40	25	13.91	0.891 (0.363-2.185)	0.800
Cardiovascular death	0	0	0	0	-	-
Hospitalization due to CHF	11	22.74	67	37.28	0.529 (0.272-1.029)	0.061
Secondary outcome						
All-cause mortality	52	104.27	204	105.49	0.985 (0.725-1.338)	0.921

XOI, xanthine oxidase inhibitors; MI, myocardial infarction; CHF, congestive heart failure; CI, confidence interval; HR, hazard ratio; IR, incidence rate.