

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

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36 **KEY MESSAGES**

37 • Xanthine oxidase inhibitor users showed similar risks of all-cause mortality and  
38 MACE compared to non-users.

39 • Febuxostat users showed similar MACE and all-cause mortality outcomes  
40 compared to allopurinol users.

41 • Concurrent colchicine use reduced the risk of all-cause mortality and heart  
42 failure-related hospitalizations.

43

44 **ABSTRACT**

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

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

53 **Results:** Of the 13997 eligible participants, 3607 (25.8%) were XOI users and 10390  
54 (74.2%) were XOI non-users. After propensity score matching, compared to non-users  
55 (n = 3607), XOI users (n = 3607) showed similar incidence of MACE (hazard ratio  
56 [HR]: 0.997, 95% confidence interval [CI], 0.879-1.131; P>0.05) and all-cause  
57 mortality (HR=0.972, 95% CI 0.886-1.065, P=0.539). Febuxostat (n=276) users  
58 showed a similar risk of MACE compared to allopurinol users (n=828; HR: 0.672, 95%  
59 CI, 0.416-1.085; P=0.104) with a tendency towards a lower risk of heart failure (HF)-  
60 related hospitalizations (HR=0.529, 95% CI 0.272-1.029; P=0.061). Concurrent  
61 colchicine use reduced the risk for all-cause mortality amongst XOI users (HR=0.671,  
62 95% 0.586-0.768; P<0.001).

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

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

67

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

70

71

72 **Introduction**

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

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

92 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

115 60% of the cohort had  $\geq$  two cardiovascular risk factors [20]. Both trials address the  
116 comparative safety between allopurinol and febuxostat, whether the use of XOI agent  
117 has benefits compared to placebo remain unanswered [21]. Therefore, current studies  
118 assessing the effect of anti-hyperuricemia treatments, including XOI, on cardiovascular  
119 diseases are inconclusive until the results from the ongoing RCTs prove otherwise [22,  
120 23].

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

125

## 126 **Methods**

### 127 *Study design and data sources*

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



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

142

#### 143 *Study population and cohort definition*

144 Over a search period of five years (1<sup>st</sup> January 2013 to 31<sup>st</sup> December 2017), we  
145 recruited in-patients who had a diagnosis of gout or were prescribed xanthine oxidase  
146 inhibitors admitted to nine hospitals and out-patients from 47 clinics offering  
147 community-based primary care healthcare services. A case of gout was defined as  
148 having principal diagnosis with any of the following International Classification of  
149 Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) codes: 274.0 (gouty  
150 arthropathy), 274.10 (gouty nephropathy, unspecified), 274.81 (gouty tophi of ear),  
151 274.89 (gout with other specified manifestations) and 274.9 (gout, unspecified).

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

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

160

### 161 *Outcomes and follow-up*

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

177

178 *Covariates*

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

189

190 *Subgroup analyses*

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

199

200 *Statistical analysis*

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

218

219 **Results**

220 *Study population*

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

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

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

241 users and non-users. For the matched febuxostat and allopurinol users, probenecid use  
242 was relatively imbalanced (SMD=0.197) after matching due to that limited records  
243 were found from the allopurinol users. The median (IQR) follow-up time was 1.97 (0.75,  
244 3.57) years for the XOI users and 1.85 (0.71, 3.36) years for the XOI non-users after  
245 matching. For the secondary analysis cohorts, it was 1.50 (0.60, 2.58) years for the  
246 febuxostat users and 1.96 (0.79, 3.48) years for the allopurinol users after matching.

247

#### 248 *Primary analyses*

249 Comparing to XOI non-users, XOI users had similar a risk of meeting the primary  
250 outcome (Hazard Ratio=0.997, 95% CI 0.879-1.131; P=0.962) (**Figure 2A**). Separate  
251 analyses were conducted for the individual component of the primary outcome (**Table**  
252 **2**). No significant difference was observed between XOI users and XOI non-users for  
253 non-fatal MI (HR=1.111, 95% CI 0.849-1.453; P=0.444), congestive heart failure  
254 (HR=1.028, 95% CI 0.870-1.215; P=0.743), cardiovascular death (HR=0.680, 95% CI  
255 0.216-2.145; P=0.511) or stroke events (HR=0.821, 95% CI 0.640-1.054; P=0.121). For  
256 the secondary outcome, XOI users did not have a significant difference in all-cause  
257 mortality when compared to non-users (HR=0.972, 95% CI 0.886-1.065; P=0.539)  
258 (**Figure 2B**).

259

#### 260 *Secondary analyses*

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

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

269

#### 270 *Subgroup analyses*

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

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

283 XOI users and 1881 were XOI non-users and no difference were found in risk of  
284 primary or secondary outcome. Among those 3132 patients with prescriptions  $\leq 3$  days ,  
285 1406 were XOI users and 1726 were XOI non-users. The XOI users had a higher risk  
286 for heart failure-related hospitalizations (HR=1.353, 95% CI 1.045-1.750; P=0.022),  
287 but no difference in the primary or secondary outcome, or individual components of the  
288 primary outcome (**Supplementary Table 4**).

289 Analysis on the effect of concurrent use of colchicine within the matched XOI  
290 cohort (n=3706) was conducted. We compared 2628 colchicine users with 979  
291 colchicine non-users. The colchicine users had a significantly lower risk for all-cause  
292 mortality (HR=0.671, 95% 0.586-0.768; P<0.001) and a similar risk for the primary  
293 outcome including each individual cardiovascular endpoint. 2201 XOI users with  
294 prescription of colchicine  $> 3$  days were compared to 1406 XOI users with prescriptions  
295  $\leq 3$  days. Consistently, colchicine users with longer duration ( $> 3$  days vs.  $\leq 3$  days)  
296 showed a lower risk for all-cause mortality (HR=0.600, 95% CI 0.527-0.683; P<0.001).  
297 The risk for the primary outcome was lower amongst these colchicine users (HR=0.813,  
298 95% CI 0.680-0.972; P=0.023), which was mainly driven by a lower risk for heart  
299 failure-related hospitalizations (HR0.746, 95% CI 0.590-0.942; P=0.014)  
300 (**Supplementary Table 5**).

301

302 **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].

324 Moreover, our study found that febuxostat users did not have a significantly  
325 different risk of MACE or all-cause mortality compared to allopurinol users. These  
326 findings are in keeping with those of previous studies. In the large scale, randomized,  
327 double-blinded, non-inferiority CARES clinical trial [37], febuxostat demonstrated  
328 noninferiority to allopurinol with respect to rates of adverse cardiovascular events while  
329 all-cause mortality and cardiovascular mortality were higher with febuxostat. There are  
330 potential reasons as to why this was the case. There was a significant drop-out rate  
331 (45%) of both groups and premature discontinuation could bias towards the null for  
332 safety outcomes [38]. Furthermore, *post hoc* ascertainment led to the addition of more  
333 deaths to the allopurinol than to the febuxostat group, which would render the original  
334 hazard ratio non-significant (HR=1.09, 95% CI 0.94-1.28)[38]. Lastly, the CARES trial  
335 was restricted to use of XOIs in secondary prevention while we examined outcomes in  
336 primary prevention. Due to these reasons, the results from CARES trial have generated  
337 heated debates regarding their application to the wider patient populations with gout  
338 [21]. Thus, in this regard, population-based cohort studies have offered a  
339 complementary approach to answer clinical questions. Thus, a large scale population-  
340 based cohort study conducted using US Medicare claims data comparing febuxostat  
341 and allopurinol uses in gout patients has shown the no difference in composite  
342 cardiovascular events, heart failure and all-cause mortality [13].

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

346 observational study investigating XOI use in gout patients with stage 3 or 4 chronic  
347 kidney disease, those taking febuxostat were less likely to experience major  
348 cardiovascular events defined as coronary artery disease, cerebrovascular disease, and  
349 peripheral vascular disease and heart failure [5]. In a Korean nationwide cohort study,  
350 the composite cardiovascular endpoint of hospitalisation for myocardial infarction,  
351 stroke/transient ischaemic attack, or coronary revascularisation tended to be higher with  
352 allopurinol than with febuxostat [39]. An recently published observational study,  
353 febuxostat demonstrated a better cardioprotective effect than allopurinol in patients  
354 with heart failure [40]. Another randomized, double-blind, parallel between-group,  
355 comparative trial conducted in China also showed that the urate-lowering efficacy of  
356 daily febuxostat 80 mg was greater than that of febuxostat 40 mg and allopurinol 300  
357 mg, which exhibited comparable urate lowering efficacy [37]. The underlying  
358 mechanistic explanation to the difference in cardio-protective effects between  
359 febuxostat and allopurinol has been reported in various studies. Febuxostat selectively  
360 inhibits both oxidized and reduced forms of xanthine oxidase and has minimal effects  
361 on other enzymes of purine and pyrimidine metabolism [7]. It has been demonstrated  
362 that febuxostat has superior antioxidant and anti-inflammatory effects than allopurinol  
363 [41, 42]. Clinically, febuxostat has demonstrated a stronger urate-lowering effect than  
364 allopurinol [43]. Since serum uric acid is an independent risk factor for cardiovascular  
365 diseases [3], a greater degree of uric acid lowering by febuxostat leads to lower  
366 cardiovascular risks in patients than allopurinol.

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

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

380

#### 381 *Strengths and limitations of this study*

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

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

398

### 399        **Conclusion**

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

403

### 404        **Conflicts of interest**

405        There are no competing interests to declare.

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407

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410

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413

414 **References**

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547

548 **Figure Legends**

549 **Figure 1.** Selection process of the study cohort.

550 **Figure 2.** Kaplan-Meier curves comparing XOJ users and non-users for (A) primary  
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554

**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
<b>Demographics</b>								
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
<b>Comorbidity</b>								
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
<b>Cardiovascular medications</b>								
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
<b>Other gout medications</b>								
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
<b>Primary outcome</b>						
Composite out- come	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
<b>Secondary out- come</b>						
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
<b>Primary outcome</b>						
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
<b>Secondary outcome</b>						
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.