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Effects of xanthine oxidase inhibitors on cardiovascular disease in patients with gout: a cohort study

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Abstract

Background—Hyperuricemia and gout are associated with an increased risk of cardiovascular disease (CVD). It is unknown whether treating hyperuricemia with xanthine oxidase inhibitors (XOI) including allopurinol and febuxostat modifies cardiovascular risks.

Methods—We used U.S. insurance claims data to conduct a cohort study among gout patients, comparing XOI initiators to non-users with hyperuricemia defined as serum uric acid level ≥ 6.8 mg/dl. We calculated incidence rates (IR) of a composite fatal and non-fatal cardiovascular outcome that included myocardial infarction, coronary revascularization, stroke, and heart failure. Propensity score (PS)-matched Cox proportional hazards regression compared the risk of composite cardiovascular endpoint in XOI initiators vs. those with untreated hyperuricemia, controlling for baseline confounders. In a subgroup of patients with uric acid levels available, PS-matched Cox regression further adjusted for baseline uric acid levels.

Results—There were 24,108 PS-matched pairs with mean age of 51 years and 88% male. The IR per 1,000 person-years for composite CVD was 24.1 (95% CI 22.6–26.0) in XOI initiators and 21.4 (95% CI 19.8–23.2) in the untreated hyperuricemia group. The PS-matched HR for composite CVD was 1.16 (95% CI 0.99–1.34) in XOI initiators versus those with untreated hyperuricemia. In subgroup analyses, the PS-matched HR for composite CVD adjusted for serum uric acid levels was 1.10 (95% CI 0.74–1.64) among XOI initiators.

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Authors' contributions

SCK had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. She is the guarantor for the study. All authors conceived and designed the study, analysed and interpreted the data, and critically revised the manuscript for important intellectual content. SCK drafted the paper.

Disclosures

Liu has nothing to disclose.

Conclusions—Among patients with gout, initiation of XOI was not associated with an increased or decreased cardiovascular risk compared to those with untreated hyperuricemia. Subgroup analyses adjusting for baseline uric acid levels also showed no association between XOI and cardiovascular risk.

Keywords

xanthine oxidase inhibitor; allopurinol; febuxostat; gout; cardiovascular disease; myocardial infarction; stroke; heart failure

INTRODUCTION

Gout is one of the most common inflammatory arthritides, affecting 6% of men and 2% of women, in the U.S.[1] Arthritis attacks, the main clinical manifestation of gout, are triggered by the crystallization of uric acid within the joints.[2] Patients with gout and hyperuricemia often have comorbid conditions such as hypertension, chronic kidney disease, and cardiovascular disease.[3–6] Although it has been debated whether hyperuricemia is a cause or consequence of these comorbidities, a number of prospective epidemiologic studies show significantly increased risks of myocardial infarction, stroke and hypertension after accounting for traditional cardiovascular risk factors in hyperuricemic patients.[7–9] Cardiovascular mortality is estimated to increase by 12% for each increase of 1 mg/dl in uric acid level.[9]

The 2012 American College of Rheumatology guidelines recommend a urate-lowering therapy in any patient with an established diagnosis of gout who has frequent gout attacks, tophaceous gout, chronic kidney disease stage 2 or worse, or a history of urolithiasis.[10] A xanthine oxidase inhibitor (XOI), either allopurinol or febuxostat, is recommended as first-line urate-lowering therapy with a serum uric acid level <6.0 mg/dl as the treatment target. [10]

Given the association between hyperuricemia and cardiovascular disease, a potential role for XOIs to reduce cardiovascular risk has been suggested.[11–13] Few prior studies reported a beneficial effect of allopurinol on hypertension, cardiovascular and all-cause mortality. [14,15] [16] A recent French case-control study reported a possible, but not statistically significant, protective effect of allopurinol on the risk of myocardial infarction among patients without a history of coronary artery disease or stroke.[13] However, studies of the potential role of XOIs in patients with heart failure showed inconsistent findings.[12,17,18] Furthermore, completed phase 3 and long-term extension studies raised a question that febuxostat might be associated with increased cardiovascular risk.[19,20]

While an RCT comparing an XOI to placebo would be ideal, many patients with hyperuricemia do not receive treatment. Thus, well designed observational studies with adequate balance of potential confounders should be able to contribute important information regarding the potential cardiovascular benefits of an XOI. The objective of this study was to compare the cardiovascular risk in gout patients initiating a XOI drug to the risk in similar gout patients with untreated hyperuricemia.

METHODS

Data Source

We conducted a cohort study using claims data from United HealthCare, a commercial U.S. health plan, for the period January 1, 2004 to December 31, 2013. This database contains longitudinal claims information including medical diagnoses, procedures, hospitalizations, physician visits, and pharmacy dispensings on more than 13 million fully-insured subscribers with medical and pharmacy coverage at any particular time point across the U.S. Claims data from the United HealthCare were linked to lab test results provided by two large national laboratory providers; Thus, results for outpatient laboratory tests, including serum uric acid levels were available in a subset of beneficiaries. Patient informed consent was not required as the dataset was de-identified to protect subject confidentiality. The study protocol was approved by the Institutional Review Board of the Brigham and Women's Hospital.

Study Cohort

Adult patients aged 18 years or older who had at least 1 visit coded with the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD 9-CM) code, 274.0, 274.8 or 274.9, for gout were eligible for the study. Individuals who initiated a XOI, either allopurinol or febuxostat, were identified ('XOI group'). Among patients with serum uric acid levels available, we selected those individuals who did not initiate a XOI but had serum uric acid levels of 6.8 mg/dl or higher ('untreated group'). The index date was the 1st XOI dispensing date for the XOI group and the earliest lab test date showing hyperuricemia for the untreated group. Patients were required to have at least 180 days of continuous health plan enrollment without record of XOI dispensings prior to the index date. Patients with a diagnosis of malignancy or end-stage renal disease or receipt of dialysis in the 180 days prior to the index date were excluded.

Outcome Definition

For the primary outcome, we defined a composite cardiovascular endpoint as the first occurrence of fatal and non-fatal myocardial infarction, coronary revascularization, fatal and non-fatal stroke, or heart failure after the index date, based on inpatient diagnosis codes and/or procedure codes (Appendix 1). We *a priori* decided to include heart failure as a component of the primary outcome based on conflicting results from the literature. [12,17,18] We also assessed each component of the composite cardiovascular endpoint separately. In prior studies, the positive predictive values of these claims-based algorithms for cardiovascular events were at least 80%. [21–24] Hospital admission or procedure dates were used as the date of outcome occurrence.

Covariates

Patients' baseline variables potentially related to initiation of the XOI and development of cardiovascular disease were examined using data from the 180 days before the index date. These variables included demographic factors (age, sex and region of residence), comorbidities (hypertension, diabetes, coronary heart disease, stroke, heart failure, chronic

kidney disease, liver disease, peripheral vascular disease, nephrolithiasis, alcoholism, hyperlipidemia, smoking, and obesity), use of gout-related medications (non-selective non-steroidal anti-inflammatory drugs (NSAID), selective cyclooxygenase-2 inhibitors, opioids, colchicine, and corticosteroids), use of cardiovascular drugs (anticoagulants, anti-platelets, beta-blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, digoxin, lipid-lowering drugs, and diuretics), and markers of health care utilization intensity (number of visits to any physicians or emergency rooms, acute care hospitalizations, number of different prescription drugs), and number of outpatient laboratory test orders such as acute phase reactants, renal function test, and uric acid. To quantify patients' comorbidities further, we also calculated a comorbidity score that combined conditions included in both the Charlson Index and the Elixhauser system based on ICD-9-CM.[25] This comorbidity score, ranging from -2 to 26, is a summative score, based on 20 major medical conditions such as metastatic cancer, congestive heart failure, dementia, renal failure, weight loss, hemiplegia, pulmonary and liver disease.[25] Serum uric acid levels at baseline were examined in the subgroup of patients with uric acid results available.

Statistical Analysis

We compared the baseline characteristics between the XOI and untreated groups. To control for potential confounders, we used a propensity score (PS) matching.[26] Multivariable logistic regression models that included all baseline demographic factors, comorbidities, use of gout-related and other cardiovascular drugs, health care utilization factors, ordered laboratory tests for serum uric acid, and the index year estimated the PS, defined as the predicted probability of a patient starting a XOI drug versus not.[26] We then used nearest neighbor matching within a "caliper" of 0.025 on the PS at a fixed ratio of 1:1.[27,28]

For the *primary as-treated* analysis, the follow-up time was calculated from a day after the index date to the first of any of the following events: XOI discontinuation for XOI initiators or XOI initiation for the untreated group, outcome occurrence, disenrollment, end of study database, or death. To measure patients' adherence with XOI treatment among XOI initiators, we calculated the proportion of days covered (PDC) as the total number of days supply provided by prescriptions for a given study drug up to 180 days from the index date divided by 180 days. The PDC up to 365 days was also calculated for the XOI group.

Incidence rates with 95% confidence intervals (CI) for the aforementioned cardiovascular endpoints were calculated in the PS matched groups. Kaplan-Meier curves were plotted for the cumulative incidence of composite cardiovascular disease in the PS-matched groups.

We conducted a sensitivity analysis further adjusted for baseline serum uric acid levels among the PS-matched pairs for whom baseline serum uric acid levels were available. To improve covariate adjustment, we also performed another sensitivity analysis using the high-dimensional propensity score (hd-PS) matching.[29,30] The hd-PS was estimated by an automated algorithm that empirically selects 500 claims-based covariates in addition to the aforementioned covariates included in the multivariable logistic model for the PS.[30] The hd-PS is thought to minimize residual confounding as it may capture confounders that are unknown to the investigators.[30]

The proportional hazards assumption was assessed by testing the significance of the interaction term between exposure and follow-up time and was not violated in any models. [31] All analyses were done using SAS 9.3 Statistical Software (SAS Institute Inc., Cary, NC).

RESULTS

Cohort Selection

Figure 1 shows the study cohort selection process. After applying the inclusion and exclusion criteria, the cohort included 79,045 XOI initiators and 33,191 patients with untreated hyperuricemia. Matching on the PS with a 1:1 ratio selected a total of 24,108 pairs of XOI initiators and untreated hyperuricemia patients.

Patient Characteristics

All the baseline characteristics were well-balanced between the XOI users and non-users after creating the PS-matched cohorts. They both had a mean age of 51 years (Table 1), and 88% were male. Nearly all (96%) XOI initiators were treated with allopurinol. The most common recorded comorbidity at baseline was hypertension (56%) followed by hyperlipidemia (52%) and diabetes (19%). Use of NSAIDs, steroids, opioids, colchicine, and diuretics were common. Baseline uric acid levels were available in 16.7% of XOI initiators and 100% of the hyperuricemic group, by definition. The median uric acid level was 8.0 mg/dl in XOI users and 8.3 mg/dl in non-users. The mean (SD) follow-up was 1.4 (1.6) years for the XOI group and 1.3 (1.5) for the untreated group.

Risk of Cardiovascular Disease

The incidence rates for both the primary and secondary endpoints were similar between the two groups (Table 2). In the primary as-treated analysis, XOI initiation was not associated with the risk of composite cardiovascular events (HR 1.16, 95% CI 0.99–1.34), myocardial infarction (HR 0.99, 95% CI 0.71–1.38), coronary revascularization (HR 1.00, 95% CI 0.78–1.28), stroke (HR 1.01, 95% CI 0.73–1.41) and heart failure (HR 1.18, 95% CI 0.96–1.45). The Kaplan-Meier curves comparing the cumulative incidence of composite cardiovascular disease between the PS-matched groups suggest comparable risk between groups throughout follow-up (Figure 2). In the XOI group, the mean (SD) PDC was 66.3% (31.2%) up to 180 days and 57.4% (33.4%) up to 365 days.

Sensitivity Analyses

There were 4,018 PS-matched pairs of XOI initiators and patients with untreated hyperuricemia who had baseline serum uric acid levels available. All the baseline characteristics were well-balanced between these pairs with serum uric acid levels available and similar to the main groups (Appendix 2). The HR (1.10, 95% CI 0.74–1.64) for composite cardiovascular disease adjusted for baseline uric acid levels changed little and remained not significantly increased in XOI initiators. The primary as-treated analysis in the hd-PS matched groups (n=11,313 pairs) also showed similar risk of composite cardiovascular disease in XOI initiators compared to the untreated group (HR 1.20, 95% CI 0.97–1.50).

DISCUSSION

In this large cohort of gout patients using data from a U.S. nationwide commercial insurance, cardiovascular endpoints occurred frequently, with incidence rates per 1,000 person-years of 24.2 in XOI initiators and 21.4 in the untreated group. Unlike most insurance claims databases, we had outpatient laboratory test results including serum uric acid levels linked to the claims database in a subset of the population to further improve control for confounding by indication.[32] In the primary as-treated analysis of the PS-matched cohorts, initiating XOI treatment was not associated with an increased or decreased risk of composite or individual cardiovascular outcomes. The sensitivity analysis further adjusted for baseline serum uric acid levels also showed no significant cardiovascular risk associated with XOI.

Our findings do not support a beneficial role for XOI in preventing cardiovascular disease in gout patients. There are several possible explanations for this finding. First, in contrast to our hypothesis, hyperuricemia may not be causally related to cardiovascular disease. Although large prospective studies showed an independent association between hyperuricemia and cardiovascular disease,[7–9] epidemiologic studies may suffer from biases. Second, even if hyperuricemia has a causal association with cardiovascular disease, its risk may not be reduced by lowering uric acid levels with XOI, particularly over a relatively short period of time. Low adherence to XOI treatment in our cohort, albeit consistent with the published studies, also may explain the null association.[4,33,34] Furthermore, the null association between XOI and cardiovascular disease may be due to residual confounding inherent in non-randomized epidemiologic studies; even though we used rigorous pharmacoepidemiologic methods - the new user design and PS and hd-PS matching methods,[26,30,35] residual confounding cannot be ruled-out.

In the primary analysis, the HR for heart failure associated with XOI was 1.18 (95% CI 0.96–1.45) compared to untreated hyperuricemia. Previous studies suggested potential beneficial effects of allopurinol on endothelial function.[36–38] There was an animal study that showed a marked attenuation of left ventricular remodeling and dysfunction after experimental myocardial infarction.[39] However, not all studies consistently showed a beneficial effect of XOI on heart failure. A prior U.K.-based study of patients with heart failure reported an increased risk of all-cause mortality and cardiovascular mortality as well as cardiovascular hospitalization associated with use of allopurinol.[40] Since hyperuricemia may be associated with heart failure or its treatment with diuretics, the degree of residual confounding by indication may be greater for the heart failure endpoint compared to other cardiovascular endpoints. In other words, XOI initiators might be more likely to have underlying cardiac dysfunction that were not captured in the claims data compared to those with untreated hyperuricemia. Currently, there is an ongoing multicenter randomized clinical trial that examines the effect of allopurinol on cardiovascular risks among patients with symptomatic heart failure.[17]

Our study has several implications for clinical practice and future research. We examined a large cohort of gout patients in a population that is representative of the U.S. commercially-insured population and found more than 2% of patients developed cardiovascular disease in

approximately 1.3 years. Although the association between gout and cardiovascular disease is known, our results highlight substantial morbidity of cardiovascular disease and emphasize the need for further work on the primary and/or secondary prevention of cardiovascular disease among patients with gout. This study also confirms that adherence to XOI therapy in gout patients is poor and recommends more work on determining the cause of low adherence and improving the chronic management of gout in clinical practice.

There are limitations to our study. First, since we mainly relied on the diagnosis codes to select patients with gout and identify their comorbidities, the presence of misclassification bias is possible. However, all the patients in our study cohort received at least one prescription for XOI or had at least one high serum uric acid level measured. Second, patients' exposure status was primarily determined with pharmacy dispensing records and individuals' use of over-the-counter pain medications was not recorded. Third, we did not have data on serum uric acid levels in XOI initiators who had a blood test done in laboratory providers other than the two we have the claims data linked to. However, we included physicians' orders for serum uric acid in the PS model to minimize potential differences between the groups.[32] Furthermore, we selected patients with baseline serum uric acid levels and performed a sensitivity analysis adjusting for serum uric acid levels which showed similar findings. Fourth, even though we simultaneously adjusted for more than 45 variables using the PS matching methods and performed sensitivity analyses using the hd-PS matching method, this study may be subject to residual confounding by severity of gout, physical activity, obesity, smoking, family history of cardiovascular disease, and use of over-the-counter drugs such as aspirin or NSAIDs. Fifth, our results may not be generalizable to patients with different health care plans. Lastly, as the follow-up time was relatively short with poor adherence to XOI therapy, this study was unable to determine the long-term effect of XOI on cardiovascular risks.

CONCLUSIONS

Over the mean 1.3-year of follow-up, approximately 2% of patients with gout developed incident cardiovascular events. XOI treatment was not associated with an increased or decreased risk of composite cardiovascular disease compared to those with untreated hyperuricemia, but the adherence to XOI treatment was inadequate with the PDC of 57.4% for one year. Future research should determine how to improve patients' adherence to XOI treatment and examine the long-term effectiveness of XOI treatment in the primary or secondary prevention of cardiovascular disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CI	confidence interval
hd-PS	high-dimensional propensity score
HR	hazards ratio
ICD-9 CM	International Classification of Diseases, 9th Revision, Clinical Modification
NSAID	non-steroidal antiinflammatory drug
PS	propensity score
XOI	xanthine oxidase inhibitor

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Figure 1. Study cohort selection

Our final cohort included 24,108 propensity score-matched pairs of gout patients who started a xanthine oxidase inhibitor and those with untreated hyperuricemia for the primary analysis.

* Sensitivity analysis was conducted in 4,018 propensity score-matched pairs of gout patients with serum uric acid levels at baseline.

	Number of Patients at Risk				
XOI	22,273	1,409	260	70	15
Hyperuricemia	22,273	1,409	260	70	15

Figure 2. Kaplan-Meier curves for cumulative incidence of cardiovascular disease: primary as-treated analysis

CVD: cardiovascular disease, XOI: xanthine oxidase inhibitor

The groups are matched on the propensity score.

Table 1

Baseline characteristics of 1:1 propensity score-matched cohorts in the 180 days before the index date

	Xanthine oxidase inhibitor	Untreated hyperuricemia
N	24,108	24,108
<i>Percentage or mean $\pm$ SD</i>		
Follow-up, year	1.4 $\pm$ 1.6	1.3 $\pm$ 1.5
Demographic		
Age	51.2 $\pm$ 11.0	51.1 $\pm$ 10.7
Male	87.7	88.4
Comorbidities		
Hypertension	55.9	55.1
Diabetes mellitus	18.6	17.0
Coronary heart disease	8.1	7.7
Stroke	2.3	2.0
Heart failure	2.8	2.6
Peripheral vascular disease	1.4	1.2
Lung disease	6.3	6.0
Chronic kidney disease	7.1	6.8
Liver disease	2.6	2.4
Nephrolithiasis	2.7	2.7
Hyperlipidemia	52.2	51.1
Obesity	8.7	8.4
Smoking	4.4	4.2
Alcoholism	0.8	0.7
Comorbidity score ^a	0.00 $\pm$ 1.2	-0.02 $\pm$ 1.1
Medications		
Anti-platelet drug	3.2	3.1
Anticoagulants	3.1	3.1
Statins	26.3	26.3
Other lipid-lowering drugs	9.7	9.7
Steroids, oral	23.0	23.5
NSAIDs	49.9	52.7
Colchicine	25.1	26.8
COXIBs	2.9	2.9
Opioids	30.0	29.9
ACE inhibitors	23.6	24.3
Angiotensin receptor blockers	14.1	13.8
Beta blockers	17.2	17.2
Calcium channel blockers	17.0	16.9

	Xanthine oxidase inhibitor	Untreated hyperuricemia
Diuretics	17.2	16.6
Proton pump inhibitors	10.4	10.1
Health care use		
Outpatient physician visits	3.7 ± 3.0	3.7 ± 3.1
Emergency room visits	0.2 ± 0.6	0.2 ± 0.5
Acute hospitalization	5.0	4.6
No. of prescription drugs	5.9 ± 3.7	5.8 ± 4.2
Laboratory test		
BUN ordered	61.3	61.7
Creatinine ordered	62.2	62.3
C-reactive protein ordered	11.3	11.1
ESR ordered	21.6	21.6
Uric acid ordered	98.8	99.0
Uric acid level available	16.7	100
Uric acid, mg/dl * (median, IQR)	7.9 ± 2.0 (8.0, 6.5–9.2)	8.5 ± 1.3 (8.3, 7.5–9.2)

PS: propensity score, SD: standard deviation, IQR: interquartile range, NSAID: non-steroidal anti-inflammatory drug, COXIB: cyclooxygenase 1 inhibitor, ACE: angiotensin-converting enzyme, ESR: erythrocyte sedimentation rate

^aThe range of comorbidity score is –2 to 26.

* Calculated among patients with a baseline serum uric acid level available

Primary as-treated analysis for risks of cardiovascular disease in initiators of xanthine oxidase inhibitor versus those with untreated hyperuricemia

Table 2

Endpoint	Xanthine oxidase inhibitors (N=24,108)			Untreated hyperuricemia (N=24,108)			
	Cases	Person-years	IR <i>a</i> (95% CI)	Cases	Person-years	IR <i>a</i> (95% CI)	Hazard ratio <i>b</i> (95% CI)
Composite CVD	788	32,505	24.24 (22.61–25.99)	628	29,305 (19.82–23.17)	21.43	1.16 (0.99–1.34)
Myocardial infarction	145	33,313	4.35 (3.70–5.12)	135	29,848 (3.82–5.35)	4.52	0.99 (0.71–1.38)
Coronary revascularization	306	33,020	9.27 (8.29–10.37)	256	29,637 (7.64–9.77)	8.64	1.00 (0.78–1.28)
Stroke	184	33,293	5.53 (4.79–6.39)	150	29,899 (4.28–5.89)	5.02	1.01 (0.73–1.41)
Heart failure	392	33,092	11.85 (10.73–13.08)	308	29,728 (9.27–11.58)	10.36	1.18 (0.96–1.45)
Composite CVD without heart failure	520	32,794	15.86 (14.55–17.28)	423	29,490 (19.82–23.17)	21.43	1.07 (0.89–1.30)

IR: incidence rate, HR: hazard ratio, CI: confidence interval, CVD: cardiovascular disease

^a Per 1,000 person-years

^b Untreated hyperuricemia was the reference group in the Cox models; HRs were estimated by stratified Cox regression models by the propensity score-matched pair.

The logistic model for propensity score includes age, sex, comorbidities, medications, health care utilization, and laboratory tests ordered.