CLINICAL RESEARCH STUDY

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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 (XOIs), including allopurinol and febuxostat, modifies cardiovascular risks.

METHODS: We used US insurance claims data to conduct a cohort study among gout patients, comparing XOI initiators with non-users with hyperuricemia defined as serum uric acid level ≥6.8 mg/dL. We calculated incidence rates of a composite nonfatal 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 a mean age of 51 years and 88% male. The incidence rate per 1000 person-years for composite CVD was 24.1 (95% confidence interval [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 hazard ratio for composite CVD was 1.16 (95% CI, 0.99-1.34) in XOI initiators vs those with untreated hyperuricemia. In subgroup analyses, the PS-matched hazard ratio for composite CVD adjusted for serum uric acid levels was 1.10 (95% CI, 0.74-1.64) among XOI initiators.

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

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KEYWORDS: Allopurinol; Cardiovascular disease; Febuxostat; Gout; Heart failure; Myocardial infarction; Stroke; Xanthine oxidase inhibitor

Gout is one of the most common inflammatory arthritides, affecting 6% of men and 2% of women in the United States.[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

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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 and cardiovascular and all-cause mortality.[14-16] 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]

CLINICAL SIGNIFICANCE

- Two percent of patients with gout developed incident CVD events over the mean 1.3-year of follow-up.
- Xanthine oxidase inhibitor treatment was not associated with an increased or decreased risk of composite CVD compared with those with untreated hyperuricemia.
- The overall adherence to XOI treatment was inadequate.

Although a randomized, controlled trial comparing an XOI with 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 with 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 US 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 United States. Claims data from the United HealthCare were linked to laboratory test results provided by 2 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 because the dataset was deidentified 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 an 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 an XOI but had serum uric acid levels of 6.8 mg/dL or higher ("untreated group"). The index date was the first XOI dispensing date for the XOI group and the earliest laboratory 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 before the index date. Patients with a diagnosis of malignancy or end-stage renal disease or receipt of dialysis in the 180 days before the index date were excluded.

Outcome Definition

For the primary outcome, we defined a composite cardiovascular endpoint as the first occurrence of nonfatal myocardial infarction, coronary revascularization, nonfatal stroke, or heart failure after the index date, according to inpatient diagnosis codes and/or procedure codes (**Supplementary 1**, available online). We decided a priori to include heart failure as a component of the primary outcome, on the basis of conflicting results from the literature.[12,17,18] In addition, we 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 (nonselective nonsteroidal anti-inflammatory drugs [NSAIDs], selective cyclooxygenase-2 inhibitors, opioids, colchicine, and corticosteroids), use of cardiovascular drugs (anticoagulants, antiplatelets, β-blockers, calcium channel blockers,

angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, digoxin, lipid-lowering drugs, and diuretics), 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 the 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, and 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 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 an XOI drug vs 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 (CIs) 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 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 because 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, Cary, N.C.).

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 nonusers after creating the PS-matched cohorts. They both had a mean age of 51 years (Table 1), and 88% were male. Nearly all XOI initiators (96%) 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 was 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 nonusers. 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 rate for both the primary and secondary endpoints was similar between the 2 groups (Table 2). In the primary as-treated analysis, XOI initiation was not associated with the risk of composite cardiovascular events (hazard raio [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 4018 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 (**Supplementary 2**, available online). 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 cohorts (n = 11,313 pairs) also showed similar risk of composite cardiovascular disease in XOI initiators compared with the untreated group (HR 1.20; 95% CI, 0.97-1.50).

DISCUSSION

In this large cohort of gout patients using data from a US nationwide commercial insurance, cardiovascular endpoints occurred frequently, with incidence rates per 1000 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. 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 nonrandomized epidemiologic studies; even though we used rigorous

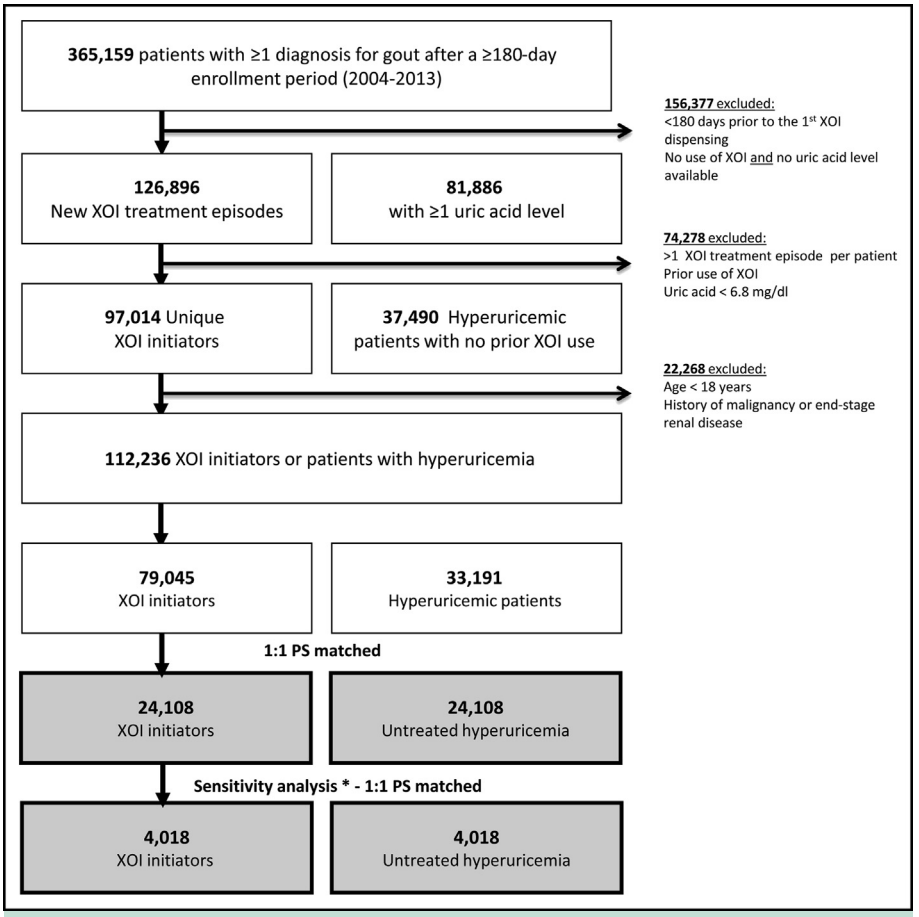

Figure 1 Study cohort selection. The final cohort included 24,108 propensity score (PS)-matched pairs of gout patients who started a xanthine oxidase inhibitor and those with untreated hyperuricemia for the primary analysis. *Sensitivity analysis was conducted in 4018 PS-matched pairs of gout patients with serum uric acid levels at baseline.

Table 1 Baseline Characteristics of 1:1 Propensity Score-matched Cohorts in the 180 Days Before the Index Date

Characteristic	Xanthine Oxidase Inhibitor (n = 24,108)	Untreated Hyperuricemia (n = 24,108)
Follow-up, y	1.4 ± 1.6	1.3 ± 1.5
Demographic		
Age, y	51.2 ± 11.0	51.1 ± 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*	0.00 ± 1.2	−0.02 ± 1.1
Medications		
Antiplatelet 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
β-Blockers	17.2	17.2
Calcium channel blockers	17.0	16.9
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†	7.9 ± 2.0	8.5 ± 1.3
Median (IQR)	8.0 (6.5-9.2)	8.3 (7.5-9.2)

Values are percentages or mean ± SD, unless otherwise noted.

ACE = angiotensin-converting enzyme; BUN = blood urea nitrogen; COXIB = cyclooxygenase 1 inhibitor; ESR = erythrocyte sedimentation rate; IQR = interquartile range; NSAID = nonsteroidal anti-inflammatory drug; PS = propensity score.

*The range of comorbidity score is −2 to 26.

†Calculated among patients with a baseline serum uric acid level available.

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 with 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 United Kingdom–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.[16] Because 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 with other cardiovascular endpoints. In other words, XOI initiators might be more likely to have underlying cardiac dysfunctions that were not captured in the claims data compared with 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 US commercially insured population and found that 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.

Table 2 Primary As-treated Analysis for Risks of Cardiovascular Disease in Initiators of Xanthine Oxidase Inhibitor Versus Those with Untreated Hyperuricemia

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

The logistic model for propensity score includes age, sex, comorbidities, medications, health care utilization, and laboratory tests ordered.
CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio; IR = incidence rate.
*Per 1000 person-years.
†Untreated hyperuricemia was the reference group in the Cox models; HRs were estimated by stratified Cox regression models by the propensity score-matched pair.

There are limitations to our study. First, because 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 1 prescription for XOI or had at least 1 high serum uric acid level measured. Second, patients' exposure status was determined primarily 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 2 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 that 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,

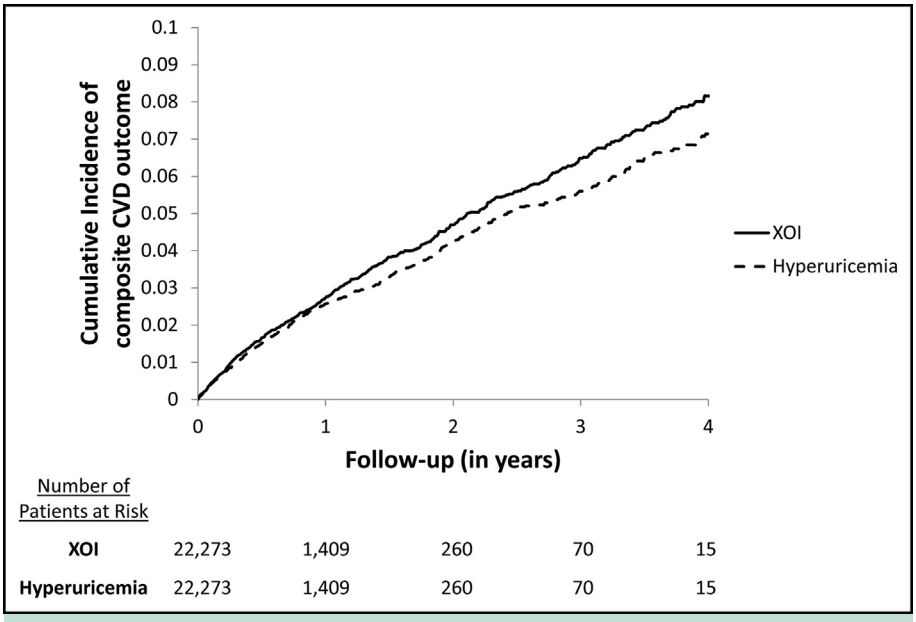

Figure 2 Kaplan-Meier curves for cumulative incidence of cardiovascular disease: primary as-treated analysis. CVD = cardiovascular disease; XOI = xanthine oxidase inhibitor. The groups are matched on the propensity score.

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. Treatment with XOIs was not associated with an increased or decreased risk of composite cardiovascular disease compared with those with untreated hyperuricemia, but the adherence to XOI treatment was inadequate, with the PDC of 57.4% for 1 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.

References

1. Zhu Y, Pandya B, Choi H. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. *Arthritis Rheum*. 2011;63:3136-3141.
2. Choi HK, Mount DB, Reginato AM. Pathogenesis of gout. *Ann Intern Med*. 2005;143:499-516.
3. Annemans L, Spaepen E, Gaskin M, et al. Gout in the UK and Germany: prevalence, comorbidities and management in general practice 2000-2005. *Ann Rheum Dis*. 2008;67:960-966.
4. Kim SC, Schmidt BM, Franklin JM, et al. Clinical and health care use characteristics of patients newly prescribed allopurinol, febuxostat and colchicine for gout. *Arthritis Care Res (Hoboken)*. 2013;65:2008-2014.
5. Singh JA, Strand V. Gout is associated with more comorbidities, poorer health-related quality of life and higher healthcare utilisation in US veterans. *Ann Rheum Dis*. 2008;67:1310-1316.
6. Zhu Y, Pandya B, Choi H. Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007-2008. *Am J Med*. 2012;125:679-687.
7. Grayson PC, Kim SY, LaValley M, Choi HK. Hyperuricemia and incident hypertension: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken)*. 2011;63:102-110.
8. Kim SY, Guevara JP, Kim KM, et al. Hyperuricemia and risk of stroke: a systematic review and meta-analysis. *Arthritis Rheum*. 2009;61:885-892.
9. Kim SY, Guevara JP, Kim KM, et al. Hyperuricemia and coronary heart disease: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken)*. 2010;62:170-180.
10. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res (Hoboken)*. 2012;64:1431-1446.
11. Kelkar A, Kuo A, Frishman WH. Allopurinol as a cardiovascular drug. *Cardiol Rev*. 2011;19:265-271.
12. Gotsman I, Keren A, Lotan C, Zwas DR. Changes in uric acid levels and allopurinol use in chronic heart failure: association with improved survival. *J Card Fail*. 2012;18:694-701.
13. Grimaldi-Bensouda L, Alpérovitch A, Aubrun E, et al. Impact of allopurinol on risk of myocardial infarction. *Ann Rheum Dis*, in press.
14. Feig DI, Soletsky B, Johnson RJ. Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension: a randomized trial. *JAMA*. 2008;300:924-932.
15. Terawaki H, Nakayama M, Miyazawa E, et al. Effect of allopurinol on cardiovascular incidence among hypertensive nephropathy patients: the Gonryo study. *Clin Exp Nephrol*. 2012;17:554.
16. Wei L, Mackenzie IS, Chen Y, Struthers AD, MacDonald TM. Impact of allopurinol use on urate concentration and cardiovascular outcome. *Br J Clin Pharmacol*. 2011;71:600-607.
17. Givertz MM, Mann DL, Lee KL, et al. Xanthine oxidase inhibition for hyperuricemic heart failure patients: design and rationale of the EXACT-HF study. *Circ Heart Fail*. 2013;6:862-868.
18. Thanassoulis G, Brophy J, Richard H, Pilote L. Gout, allopurinol use, and heart failure outcomes. *Arch Intern Med*. 2010;170:1358-1364.
19. Edwards NL. Febuxostat: a new treatment for hyperuricaemia in gout. *Rheumatology (Oxford)*. 2009;48(suppl 2):ii15-ii19.
20. Schumacher HRJ, Becker MA, Wortmann RL, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. *Arthritis Rheum*. 2008;59:1540-1548.
21. Andrade SE, Harrold LR, Tjia J, et al. A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data. *Pharmacoepidemiol Drug Saf*. 2012;21(suppl 1):100-128.
22. Saczynski JS, Andrade SE, Harrold LR, et al. A systematic review of validated methods for identifying heart failure using administrative data. *Pharmacoepidemiol Drug Saf*. 2012;21(suppl 1):129-140.
23. Kiyota Y, Schneeweiss S, Glynn RJ, et al. Accuracy of Medicare claims-based diagnosis of acute myocardial infarction: estimating positive predictive value on the basis of review of hospital records. *Am Heart J*. 2004;148:99-104.
24. Choma NN, Griffin MR, Huang RL, et al. An algorithm to identify incident myocardial infarction using Medicaid data. *Pharmacoepidemiol Drug Saf*. 2009;18:1064-1071.
25. Gagne JJ, Glynn RJ, Avorn J, Levin R, Schneeweiss S. A combined comorbidity score predicted mortality in elderly patients better than existing scores. *J Clin Epidemiol*. 2011;64:749-759.
26. Rubin D. Estimating causal effects from large data sets using propensity scores. *Ann Intern Med*. 1997;127:757-763.
27. Austin PC. The performance of different propensity score methods for estimating marginal odds ratios. *Stat Med*. 2007;26:3078-3094.
28. Austin PC. Some methods of propensity-score matching had superior performance to others: results of an empirical investigation and Monte Carlo simulations. *Biom J*. 2009;51:171-184.
29. Rassen JA, Glynn RJ, Brookhart MA, Schneeweiss S. Covariate selection in high-dimensional propensity score analyses of treatment effects in small samples. *Am J Epidemiol*. 2011;173:1404-1413.
30. Schneeweiss S, Rassen JA, Glynn RJ, et al. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. *Epidemiology*. 2009;20:512-522.
31. Kleinbaum D, Klein M. Evaluating the proportional hazards Assumption. In: Gail M, Krickberg K, Samet J, Tsiatis A, Wong W, eds. *Survival Analysis: A Self-Learning Text*. 3rd ed. New York: Springer; 2012.
32. Schneeweiss S, Rassen JA, Glynn RJ, et al. Supplementing claims data with outpatient laboratory test results to improve confounding adjustment in effectiveness studies of lipid-lowering treatments. *BMC Med Res Methodol*. 2012;12:180.
33. Halpern R, Mody RR, Fuldeore MJ, Patel PA, Mikuls TR. Impact of noncompliance with urate-lowering drug on serum urate and gout-related healthcare costs: administrative claims analysis. *Curr Med Res Opin*. 2009;25:1711-1719.
34. Harrold LR, Mazor KM, Negron A, et al. Primary care providers' knowledge, beliefs and treatment practices for gout: results of a physician questionnaire. *Rheumatology (Oxford)*. 2013;52:1623-1629.
35. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol*. 2003;158:915-920.
36. Kanbay M, Huddam B, Azak A, et al. A randomized study of allopurinol on endothelial function and estimated glomular filtration rate in asymptomatic hyperuricemic subjects with normal renal function. *Clin J Am Soc Nephrol*. 2011;6:1887-1894.
37. Melendez-Ramirez G, Perez-Mendez O, Lopez-Osorio C, Kuri-Alfaro J, Espinola-Zavaleta N. Effect of the treatment with

allopurinol on the endothelial function in patients with hyperuricemia. *Endocr Res*. 2012;37:1-6.
38. Doehner W, Schoene N, Rauchhaus M, et al. Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: results from 2 placebo-controlled studies. *Circulation*. 2002;105:2619-2624.
39. Engberding N, Spiekermann S, Schaefer A, et al. Allopurinol attenuates left ventricular remodeling and dysfunction after experimental myocardial infarction: a new action for an old drug? *Circulation*. 2004;110:2175-2179.

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SUPPLEMENTARY DATA

Supplementary tables accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.amjmed.2015.01.013.

Supplementary Table 1 Diagnosis and Procedure Codes for Cardiovascular Disease

Disease	ICD-9 Code	Procedure Code
Myocardial infraction	410.x except 410.x2	
Coronary revascularization	00.66, 36.03, 36.09, 36.06, 36.07, 36.1x, 36.2x	92982, 92995, 92997, 92982-92984, 92980, 92981, 33510- 33536, 33545, 33572
Stroke	430.x, 431.x 434.x, 435.x, 436.x	
Heart failure	428.x	

ICD-9 = International Classification of Diseases, 9th Revision.

Supplementary Table 2 Baseline Characteristics of 1:1 Propensity Score-matched Subgroup with Serum Uric Acid Levels Available in the 180 Days Before the Index Date

Variable	Xanthine Oxidase Inhibitor (n = 4,045)	Untreated Hyperuricemia (n = 4,045)
Demographic		
Age	51.0 ± 10.7	51.1 ± 10.5
Male	87.4	89.0
Comorbidities		
Hypertension	57.1	54.0
Diabetes mellitus	20.4	16.4
Coronary heart disease	8.7	8.4
Stroke	2.1	2.1
Heart failure	2.3	3.1
Peripheral vascular disease	1.4	1.4
Lung disease	6.5	6.5
Chronic kidney disease	7.1	6.6
Liver disease	2.9	2.3
Nephrolithiasis	3.2	2.8
Hyperlipidemia	55.0	51.2
Obesity	6.8	7.6
Smoking	3.6	3.6
Alcoholism	0.7	0.5
Comorbidity score*	0.0 ± 1.2	−0.04 ± 1.2
Medications		
Antiplatelet drug	2.7	3.1
Anticoagulants	3.1	2.9
Statins	24.5	25.7
Other lipid-lowering drugs	10.7	9.9
Steroids, oral	19.7	21.8
NSAIDs	49.5	53.1
Colchicine	26.8	23.5
COXIBs	4.0	3.8
Opioids	30.0	30.3
ACE inhibitors	21.6	24.6
Angiotensin receptor blockers	14.4	14.0
β-Blockers	15.2	18.0
Calcium channel blockers	17.2	16.8
Diuretics	15.3	17.3
Proton pump inhibitors	10.5	10.6
Health care use		
Outpatient physician visits	3.8 ± 3.0	3.6 ± 3.1
Emergency room visits	0.1 ± 0.4	0.2 ± 0.5
Acute hospitalization	5.7	6.3
No. of prescription drugs	5.9 ± 3.8	5.7 ± 4.1
Laboratory test		
BUN ordered	61.5	63.1
Creatinine ordered	61.8	63.6
C-reactive protein ordered	12.3	11.1
ESR ordered	23.3	22.5
Uric acid ordered	100	100
Uric acid level available	100	100
Uric acid, mg/dL (median, IQR)	8.0 ± 2.0 (8.2, 6.6-9.3)	8.5 ± 1.3 (8.3, 7.5-9.2)

Values percentages or mean ± SD, unless otherwise noted.

ACE = angiotensin-converting enzyme; BUN = blood urea nitrogen; COXIB = cyclooxygenase 1 inhibitor; ESR = erythrocyte sedimentation rate; IQR = interquartile range; NSAID = nonsteroidal anti-inflammatory drug; PS = propensity score; SD = standard deviation.

*The range of comorbidity score is −2 to 26.