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,