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# Clinical and health care use characteristics of patients newly prescribed allopurinol, febuxostat and colchicine for gout

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## Abstract

**Background—**Gout is a common inflammatory arthritis with the increasing prevalence in the developed countries. It is well-known that many patients with gout have significant comorbidities and high health care utilization.

**Methods—**Using US insurance claims data (2009–2011), a population-based cohort study was conducted to describe clinical characteristics and health care utilization patterns in patients with gout newly prescribed allopurinol, febuxostat or colchicine.

**Results—**There were 25,051 allopurinol, 4,288 febuxostat and 6,238 colchicine initiators. Mean age was 53 years and 83%–87% were male. More than half of patients had hypertension and hyperlipidemia, 20% had diabetes and 10% cardiovascular disease. The mean uric acid level (mg/dl) was similar at baseline ranging from 8.1 to 8.5 across the groups. Compared to allopurinol or colchicine initiators, febuxostat initiators had more comorbidities and greater health care uses including outpatient, inpatient or emergency room visits, both at baseline and during the follow-up. Use of gout related drugs, such as opioids, steroids and non-steroidal anti-inflammatory drugs, was most common in febuxostat and least common in colchicine initiators. The median daily dose at both start and end of treatment was 300mg for allopurinol, 40mg for febuxostat, and 1.2mg for colchicine. The dosage of allopurinol and febuxostat was rarely increased during the follow-up.

**Conclusion—**Patients who started allopurinol, febuxostat or colchicine for gout generally had hyperuricemia and multiple comorbidities. Febuxostat initiators had more comorbidities and greater use of health care resources and gout-related drugs than other groups. Overall, the dosages of allopurinol or febuxostat remained unchanged over time.

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Franklin and Liu have nothing to disclose for financial support or conflict of interest

### Keywords

gout; allopurinol; febuxostat; colchicine

## INTRODUCTION

Gout is one of the most common inflammatory arthritis with the increasing prevalence in the U.S. as well as Europe. [1–3] A recent study reports that 8.3 million (4%) Americans have gout and 43.3 million (21%) have hyperuricemia, a main risk factor for gout, in the U.S. [3] It is well-known that gout and hyperuricemia is closely associated with cardiovascular disease (CVD), metabolic syndrome, and chronic kidney disease (CKD). [1, 4, 5] This increase in the prevalence of gout in the developed countries is thought to be related to the increasing prevalence of comorbidities such as obesity, hypertension and CKD. [3, 6, 7]

Any patients with gouty arthritis who have more than two attacks per year, high serum uric acid level usually defined 6.8 mg/dl or greater, presence of tophi or radiologic changes in bones, chronic kidney disease, or a history of urolithiasis should be considered for a urate-lowering treatment. [8] A xanthine oxidase inhibitor, either allopurinol or febuxostat, is recommended as the first line urate-lowering agent. Febuxostat is an effective, newer non-purine xanthine oxidase inhibitor and generally considered in patients who cannot tolerate allopurinol or have inadequate response to allopurinol. [9] To date, the data on the use and effectiveness of febuxostat is mostly based on clinical trials. For patients with impaired renal excretion of uric acid, uricosuric agents such as probenecid can be considered. [8] Because many patients with gout have significant comorbid conditions that may hinder or complicate a proper treatment, [10] some patients are suboptimally treated with steroids or colchicine on a *prn* basis without urate-lowering therapy. Although colchicine has no effect on serum uric acid levels, it is effective in reducing the frequency of recurrent episodes of acute gout attacks and therefore used for long-term prophylaxis in some patients with chronic recurrent gout. [11, 12]

The main objectives of this study were 1) to describe clinical characteristics and health care utilizations of patients with gout before and after initiating allopurinol, febuxostat, or colchicine and 2) to evaluate the patterns of these gout treatments and other gout-related drug use over time in a large U.S. population-based cohort. In addition, we estimated the rate of acute gout attacks after initiating allopurinol, febuxostat, or colchicine,

## METHODS

### Data Source

We conducted a cohort study using the commercial health insurance claims data from the 'Innovus InVision Data Mart' for the period January 1, 2009 to December 31, 2011. This database contains longitudinal claims information including medical diagnoses, procedures, hospitalizations, physician visits, and pharmacy dispensing on more than 14 million fully-insured subscribers with medical and pharmacy coverage at any particular time point across the United States. Personal identifiers were removed from the dataset before the analysis to

protect subject confidentiality. Patient informed consent was therefore not required. The study protocol was approved by the Institutional Review Board of Brigham and Women's Hospital.

## Study Cohort

Subjects aged 18 years and older who had at least one visit coded with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD 9-CM) code, 274.0X, 274.8X and 274.9 for gout were identified. Patients who had at least one dispensing for allopurinol, febuxostat or colchicine were eligible for the study cohort. Probenecid users were initially considered to be eligible but were subsequently excluded due to the small number of probenecid initiators (less than 700). At least 180 days of continuous health plan eligibility before receiving the first prescription of a study drug as well as at least 30 day of continuous use of a study drug were required. Colchicine starters with any use of allopurinol or febuxostat in the 180-day baseline period were excluded. However, for allopurinol or febuxostat starters, use of colchicine in the 180-day baseline period was allowed. Patients with a diagnosis of cancer or lymphoproliferative diseases and a receipt of more than one study drugs at the same index date were also excluded.

For allopurinol and febuxostat initiators, addition of colchicine was allowed during the follow-up. However, colchicine initiators were censored when they were started on either allopurinol or febuxostat. Overall, patients were followed from the dispensing date of the first study drug defined as the index date to the first of any of the following censoring events: discontinuation of study drugs, loss of health plan eligibility, end of study database, or death.

## Acute Gout attacks

Acute gout attacks were identified by a modified claims-based algorithm [10] in this study. The algorithm includes two main criteria: 1) an outpatient visit coded for gout and a new dispensing of colchicine (only in allopurinol and febuxostat initiators), selective or non-selective NSAIDS, oral or injectable glucocorticoids and 2) an emergency room or inpatient visit coded for gout. A gap of 21 days between two attacks was required to be considered as two separate gout attacks.

## Covariates

Patients' baseline variables potentially related to gout or initiation of the study drugs 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, stroke, CVD, chronic kidney disease, heart failure, stroke, malignancy, alcoholism, hyperlipidemia, smoking, and obesity), history of arthrocentesis, use of gout-related medications (non-selective NSAIDs, selective cyclooxygenase -2 inhibitors, opioids, and corticosteroids), use of cardiovascular medications (beta-blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, and diuretics), and markers of health care utilization intensity (number of visits to any physicians or emergency rooms, acute care hospitalizations, and different prescription drugs).

To quantify patients' comorbidities, we also calculated a combined comorbidity score that combined conditions included in both the Charlson Index and the Elixhauser system based on ICD-9-CM. [13] The combined comorbidity score 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. A higher score indicates a greater number of comorbid conditions. In a subgroup of the study cohort, outpatient laboratory test results such as serum blood urea nitrogen (BUN), creatinine, and uric acid levels were also available for analysis.

### Statistical Analysis

Baseline characteristics were compared across the treatment groups. For all pair-wise comparisons, c-statistics were estimated to assess the ability of multivariable logistic regression models to predict the treatment choice based on patients' baseline characteristics with low values (near 0.5) indicating a model with poor discrimination and high values (near 1.0) indicating high discrimination. To examine the gout treatment patterns over time, duration of treatment with each study drug, initial daily doses and changes in the daily doses were assessed during the follow-up period. The duration of study drug use was calculated as the number of days from the index date to the last drug available date, which is the last dispensing date plus the number of days' supply. Use of gout-related drugs and health care utilization patterns, and changes in serum BUN, creatinine and uric acid levels were assessed during the follow-up period. The incidence rates (IR) of acute gout attacks per 1,000 person-years with 95% confidence intervals (CI) were calculated as the number of acute gout attacks divided by the total person-years, in each treatment group. The IR of acute gout attacks in each group was further calculated for first 30, 31–90, and 91–120 days of follow-up. Multivariable Poission regression models were used to estimate the incidence rate ratio (IRR) of acute gout attacks for all pair-wise comparisons. [14] To deal with the potential overdispersion in Possion models, the standard errors were adjusted with the scale option in SAS. The final models were adjusted for all variables including demographic factors, comorbidities, use of gout-related and cardiovascular medications, and health care use patterns at baseline. Among a subset of patients with lab test results available at baseline, the multivariable models were further adjusted for serum uric acid levels. All analyses were done using SAS 9.3 Statistical Software (SAS Institute Inc., Cary, NC).

## RESULTS

### Cohort Selection

Between 2009 and 2011, there were 163,956 patients had at least one diagnosis of gout. After applying the inclusion and exclusion criteria, we identified 36,431 adult patients who had at least one diagnosis of gout and received the first prescription for allopurinol, febuxostat or colchicine after the 180-day eligibility period free of any cancer. Of these, 25,832 initiated allopurinol, 4,361 febuxostat and 18,128 colchicine. Our final cohort included 25,051 allopurinol, 4,288 febuxostat, and 6,238 colchicine initiators who continued the drug for at least 30 days.

### Baseline Characteristics

Baseline characteristics of the study cohort were presented in Table 1. Mean (SD) age was 53 (12) years across the three groups and 83% to 87% were male. More than half of patients had hypertension and hyperlipidemia, 19% to 23% had diabetes and 9% to 12% CVD. Use of NSAIDS, opioids and systemic corticosteroids was also common. Febuxostat initiators had more comorbidities such as CVD, heart failure, chronic kidney disase, than allopurinol or colchicine initiators. Use of cardiovascular medications as well as health care utilization such as emergency room visits and outpatient visits for both primary and rheumatology care was greater in febuxostat initiators compared to the other groups. During the 180-day baseline period, 9% of febuxostat and colchicine initiators and 8% of allopurinol initiators had at least one acute hospitalization. The mean number of prescription drugs that patients took at baseline ranged from 5.4 to 7.5 across the groups. Prior to initiating the treatment for gout, 13% of febuxostat, 9% of allopurinol and 10% of colchicine initiators had at least one arthrocentesis done. The proportion of patients with acute gout attacks during the baseline 180-day period was 43% in allopurinol, 59% in febuxostat, and 31% in colchicine groups.

The proportion of patients who had at least one visit to a rheumatologist was 15% in febuxostat, 6% in allopurinol and 8% in colchicine initiators. The proportion of patients who underwent at least one arthrocentesis in 180-day baseline period was also the highest (13%) in febuxostat. Fifty two percent of febuxostat initiators were previously on allopurinol. At least one baseline uric acid measurement was available in 4,813 (19%) allopurinol, 1,156 (27%) febuxostat and 1,032 (17%) colchicine initiators. Of these patients, only 8% of allopurinol, 12% of febuxostat and 13% of colchicine initiators had normouricemia (equal to or less than 6 mg/dl). The mean (SD) uric acid level (in milligram per deciliter) was similar ranging from 8.1 (1.9) to 8.5 (1.7) across the groups. The mean BUN and creatinine levels were the highest in febuxostat initiators.

Multivariable logistic regression models to predict the treatment choice based on all patients' baseline characteristics (including all the variables presented in Table 1 except lab tests) produced the c-statistic of 0.61 between allopurinol and colchicine initiators, 0.70 between febuxostat and colchicine initiators, and 0.67 between febuxostat and allopurinol initiators. Adding both baseline serum creatinine and uric acid levels to the models improved all three c-statistics slightly: 0.63 between allopurinol and colchicine initiators, 0.71 between febuxostat and colchicine initiators, and 0.68 between febuxostat and allopurinol initiators. Appendix 1 presents a list of predictors of initiating one gout treatment compared to the other drugs in the fully adjusted models.

### Medication and Health Care Use Patterns

The mean duration of treatment or follow-up period was 0.5 years for allopurinol, 0.4 years for febuxostat initiators and 0.2 for colchicine initiators. The median daily dose at both start and end of treatment was 300mg for allopurinol, 40mg for febuxostat, and 1.2mg for colchicine. Among the allopurinol initiators, 46% were prescribed a starting daily dose less than 300mg, 52% received 300mg and 3% were started on a dose greater than 300mg. Only one percent of the allopurinol initiators on a dose less than or equal to 300mg per day received a higher dose during the follow-up. Among febuxostat initiators, 77% were

prescribed a starting dose less than or equal to 40mg per day. Of these low dose febuxostat initiators, 9% had a dosage change to greater than 40mg per day.

During the follow-up period, the use of gout-related drug such as NSAIDs, oral, intravenous or intra-articular steroids was most common in febuxostat initiators and least common in colchicine initiators (Table 2). Furthermore, febuxostat initiators had the greatest health care use such as number of physician visits, emergency room visits, and prescription drugs.

**Changes in Laboratory Data**: The mean BUN and creatinine levels did not change before and after the index date across all three groups. The reduction in uric acid levels was the largest in febuxostat initiators and minimal in colchicine initiators. Among the patients who had a baseline uric acid level greater than 6.8 mg/dl, 40% of allopurinol, 56% of febuxostat, and 11% of colchicine initiators had a uric acid level ≤ 6 mg/dl during the follow-up period.

Table 3 shows the mean (SD) serum BUN, creatinine or uric acid levels (in milligram per deciliter) during the followup and the mean level changes before and after the index date among the subjects who had at least one lab test measurement available at baseline and during the follow-up period.

### Acute Gout Attacks

The majority of patients, 77% of allopurinol, 67% of febuxostat, and 89% of colchicine initiators, had no gout attacks during the follow-up period. However, 6% of allopurinol, 11% of febuxostat, and 2% of colchicine initiators had 2 or more attacks. Overall, there were 8,305 acute gout attack episodes in allopurinol initiators, 2,277 in febuxostat initiators, and 793 in colchicine initiators. Acute gout attacks occurred most frequently in patients initiating febuxostat. The IR of acute gout attacks per 1,000 person-days was 2.0 (95% CI 2.0–2.1) in allopurinol initiators, 3.4 (95% CI 3.2–3.5) in febuxostat, and 1.8 (95% CI 1.7–1.9) in colchicine initiators. The IR was the highest in the first 30 days of treatment in all three groups. (Table 4) Compared to colchicine initiators, the multivariable IRR of acute gout attacks adjusted for demographic factors, comorbidities, medications, and health care use patterns was 1.1 (95% CI 1.0–1.2) in allopurinol initiators and 1.4 (95% CI 1.2–1.7) in febuxostat initiators (Table 4). The multivariable IRR of acute gout attacks in febuxostat initiators was 1.3 (95% CI 1.3–1.4) compared to allopurinol.

With further adjustment for the baseline serum uric acid levels among a subgroup of patients with at least one baseline uric acid level available, the multivariable IRR of acute gout attacks was 1.0 (95% CI 0.9–1.2) in allopurinol and 1.4 (95% CI 1.2–1.8) in febuxostat initiators compared to those starting colchicine. The multivariable IRR of acute gout attacks further adjusted for baseline serum uric acid levels was 1.4 (95% CI 1.3–1.5) in febuxostat compared to allopurinol initiators.

## DISCUSSION

This large population-based study showed that many patients who initiated allopurinol, febuxostat or colchicine for management of chronic gout had a high number of comorbidities including hypertension, diabetes and CVD and took 5 to 8 other prescription drugs at baseline. Probenecid was seldom prescribed in patients with gout. The majority of

patients had hyperuricemia and the mean baseline serum uric acid levels were similarly elevated above 8 mg/dl in all three groups. The incidence of acute gout attacks were higher in febuxostat initiators compared to the other groups and peaked in the first 30 days of treatment. Unlike the recent guidelines, [8] many patients with gout and hyperuricemia were not receiving a urate-lowering therapy and the majority of patients receiving a urate-lowering therapy with allopurinol or febuxostat did not reach the target uric acid level of 6 mg/dl during the follow-up. Allopurinol initiators were generally started on a daily dose of 300 mg or higher and the dosage remained mostly unchanged over time.

Several important findings that might have implications in clinical practice or future research should be noted. First, we conducted a cohort study that included new users of three drugs mainly used for chronic gout management. To divide patients into two different categories of chronic gout treatment, urate-lowering vs. no urate-lowering therapy, colchicine initiators were required to be free of any of the drugs 180 days prior to the index date and to remain on colchicine for at least a month. [15] Patient characteristics at baseline were generally similar in both allopurinol and colchicine initiators; our multivariable logistic regression model showed a poor discrimination (c-statistics < 0.7) between the two groups. As noted in a recent study which showed a substantial emergency room utilization for acte gout care, [16] patients in our study also had a high utilization of not only emergency room but also inpatient and outpatient visits. Our results of a large number of comorbid conditions and a high health care utilization in patients with gout are generally consistent with prior studies. [10, 17, 18] Our study also showed that febuxostat initiators had more comorbid conditions, greater use of medications and health care resources compared to the other groups. These findings are not surprising as febuxostat is usually used as the 2$^{nd}$ line treatment. Chronic kidney disease was twice more common in febuxostat initiators compared to the other groups. Although no dose adjustment is required for febuxostat in patients with mild-to-moderate renal impairment, it is important to note that data on safety of febuxostat is limited in patients with severe renal impairment (i.e. creatinine clearance less than 30 milliliter per minute). [19]

Second, the 2012 American College of Rheumatology guidelines for gout management recommends the starting dose of allopurinol no greater than 100mg and gradual upward titration every 2 to 5 weeks. [8] However, most frequently prescribed initial daily dose in this study cohort was 300mg for allopurinol, 40mg for febuxostat and 1.2mg for colchicine. In fact, only one-third of allopurinol initiators were started on the daily dose equal to 100mg or less and the dosage of allopurinol was rarely titrated up (1%) during the follow-up.

Third, among patients who had at least one measurement of serum uric acid both at baseline and during the follow-up, the mean uric acid level decreased by more than 2 mg/dl in both allopurinol and febuxostat groups during the mean follow-up of 5 months. The mean uric acid level during the follow-up was 6.4 mg/dl in allopurinol, 5.9 mg/dl in febuxostat and 8.1 mg/dl in colchicine initiators. As noted in previous studies, [19–21] the mean uric acid level in allopurinol group was higher than the currently recommended target of 6 mg/dl and it could be due to suboptimal dose titration of allopurinol. [8] Among the patients who had a baseline uric acid level greater than 6.8 mg/dl, a greater proportion of febuxostat initiators

reached the target uric acid level of 6 mg/dl (56% vs. 40% in allopurinol) during the follow-up period.

Although the majority of patients across the three groups did not develop gout attacks during the followup, overall there were still a high number of acute attacks. The proportion of patients having 2 or more attacks was greater in the febuxostat group. Febuxostat initiators, thus, had the highest incidence of acute gout attacks; the IR peaked at 5.4 per 1,000 person-days during the first month of treatment. This result is consistent with a previous randomized clinical trial of febuxostat that showed more gout flares in those receiving febuxostat compared to placebo or allopurinol in the first 8 weeks of treatment. [19] However, it could be also explained by a potential confounding by indication inherent to any non-randomized studies. [22] In other words, patients starting febuxostat tend to have more severe gout and/or worse kidney function which could potentially lead to more frequent gout attacks compared to those starting allopurinol or colchicine. To minimize such bias in estimating IRRs, we used multivariable Poisson regression models simultaneoulsy adjusted for more than 20 potential confounders with and without the baseline serum uric acid levels.

This study has several limitations. First, since we mainly relied on the diagnosis codes to select patients with gout and identify their comorbidities, a potential for misclassification bias should be noted. However, all the patients in our study cohort received at least one drug mainly used for gout in addition to a diagnosis code. Second, patients' exposure status was primarily determined with pharmacy dispensing records and individuals' daily drug intake and use of over-the-counter pain medications were not verified. Third, we did not have serum uric acid levels in all patients. Since ordering a laboratory test is not a random process in clinical practice, patients in whom we had a uric acid level measured might have more severe gout manifestations or other comorbidities. Fourth, in this study, as acute gout attacks were defined as a gout diagnosis and a new prescription of colchicine, NSAIDs or steroids, mild attacks that did not require an encounter with a physician could have been missed. It is also possible that some patients in either allopurinol or febuxostat groups received colchicine, NSAIDs, or steroids for prophylaxis against gout flare-up, rather than for acute attacks. Lastly, the relatively short follow-up time in the study cohort might be related to that we had a total of 3-year data period but we required patients to have at least 180 days of baseline period prior to the index date. As our data was from a commercial insurance plan, patients would be censored when they switch a health plan.

In conclusion, patients who started allopurinol, febuxostat or colchicine for gout were mostly hyperuricemic and had multiple comorbidities and high gout-related drug and health care uses. These characteristics were most notable in febuxostat initiators. There were many patients not receiving a urate-lowering therapy, and even the majority of patients receiving a urate-lowering therapy were suboptimally treated. This study highlights the need to improve and optimize the pharmacologic management of patients with chronic gout.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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### Significance and Innovation

- In this large population-based cohort study, patients with gout who started allopurinol, febuxostat or colchicine had multiple comorbidities and use of cardiovascular drugs, diuretics, and pain medications.
- The median daily dose was 300mg for allopurinol and 40mg for febuxosat and the dosage was not changed in most patients during the follow-up.

## Table 1

Baseline characteristics of the study cohort in 180 days prior to the index date

| | Allopurinol (N=25,051) | Febuxostat (N=4,288) | Colchicine (N=6,238) |
|---|---|---|---|
| | Percentage or mean ± SD | | |
| ***Demographic*** | | | |
| Age | 53.0 ± 11.7 | 53.4 ± 11.7 | 53.4 ± 11.7 |
| Male | 86.8 | 86.1 | 83.5 |
| ***Comorbidities*** | | | |
| Comorbidity score | 0.1 ± 1.4 | 0.4 ± 1.7 | 0.2 ± 1.4 |
| Hypertension | 53.7 | 61.9 | 52.5 |
| Chronic kidney disease | 8.9 | 18.6 | 9.2 |
| Renal stones | 2.9 | 2.9 | 1.9 |
| Heart failure | 3.9 | 6.0 | 4.1 |
| Cardiovascular disease | 9.2 | 11.3 | 10.7 |
| Diabetes | 19.1 | 22.5 | 20.1 |
| Hyperlipidemia | 53.2 | 58.8 | 50.4 |
| Stroke | 2.9 | 3.1 | 3.7 |
| Obesity | 8.0 | 8.9 | 7.7 |
| COPD | 7.1 | 9.0 | 7.8 |
| ***Medications*** | | | |
| Diuretics | 18.6 | 22.6 | 18.0 |
| Beta blockers | 18.5 | 20.1 | 17.7 |
| ACEI | 24.8 | 25.4 | 23.1 |
| ARB | 14.0 | 18.5 | 14.0 |
| NSAIDs | 42.7 | 46.4 | 33.1 |
| Coxibs | 2.4 | 3.9 | 2.6 |
| Opioids | 31.8 | 38.0 | 29.7 |
| Oral steroids | 23.6 | 35.9 | 20.7 |
| Intravenous steroids | 13.4 | 20.3 | 13.2 |
| Intra-articular steroids | 15.4 | 22.7 | 14.6 |
| ***Health care use*** | | | |
| No. of prescription drugs | 5.6 ± 4.6 | 7.5 ± 5.4 | 5.4 ± 4.8 |
| Hospitalization | 7.7 | 8.7 | 9.3 |
| No. of ER visits | 0.2 ± 0.6 | 0.2 ± 0.6 | 0.3 ± 0.8 |
| No. of office visits | 3.5 ± 3.4 | 4.8 ± 4.2 | 3.6 ± 3.6 |
| No. of PCP visits | 2.6 ± 3.4 | 3.2 ± 3.7 | 2.4 ± 3.6 |
| No. of rheumatology visits | 0.1 ± 0.6 | 0.4 ± 1.0 | 0.2 ± 0.7 |

| | Allopurinol (N=25,051) | Febuxostat (N=4,288) | Colchicine (N=6,238) |
|---|---|---|---|
| ***Lab tests*** | | | |
| Arthrocentesis done | 8.8 | 13.3 | 9.8 |
| BUN ordered | 39.2 | 51.3 | 35.6 |
| Creatinine ordered | 40.0 | 52.4 | 36.5 |
| Uric acid ordered | 48.1 | 62.0 | 28.4 |

COPD: chronic obstructive pulmonary disease, ACEI: angiotensin converting enzyme inhibitor, ARB: angiotensin II receptor blockers, NSAIDs: non-steroidal anti-inflammatory drugs, Coxibs: Cyclooxygenase-2 inhibitors, ER: emergency room, PCP: primary care provider, BUN: blood urea nitrogen

**Table 2**

Use of gout-related drugs and health care resources during the follow-up period

| | Allopurinol (N=25,051) | Febuxostat (N=4,288) | Colchicine (N=6,238) |
|---|---|---|---|
| | Percentage or mean ± SD | | |
| Follow-up period, years | 0.4 ± 0.5 | 0.4 ± 0.5 | 0.2 ± 0.2 |
| ***Gout-related drugs*** | | | |
| NSAIDs | 28.0 | 27.2 | 13.3 |
| Coxibs | 1.9 | 3.1 | 1.4 |
| Opioids | 23.5 | 27.5 | 15.5 |
| Oral steroids | 16.6 | 23.7 | 8.6 |
| Intravenous steroids | 9.2 | 12.5 | 5.3 |
| Intra-articular steroids | 10.6 | 14.1 | 5.8 |
| ***Health care use*** | | | |
| No. of prescription drugs | 5.4 ± 5.3 | 6.4 ± 6.1 | 3.4 ± 3.8 |
| Hospitalization | 5.4 | 5.9 | 3.5 |
| No. of ER visits | 0.1 ± 0.5 | 0.2 ± 0.6 | 0.1 ±0.4 |
| No. of office visits | 3.1 ± 5.3 | 3.8 ± 6.5 | 1.5 ± 2.6 |
| No. of PCP visits | 2.1 ± 4.2 | 2.2 ± 4.4 | 1.0 ± 2.6 |
| No. of rheumatology visits | 0.2 ± 0.8 | 0.4 ± 1.6 | 0.1 ± 0.6 |

NSAIDs: non-steroidal anti-inflammatory drugs, ER: emergency room, PCP: primary care provider

## Table 3

Changes in lab test measurements (milligram per deciliter) before and after the index date

| | Allopurinol | Febuxostat | Colchicine |
|---|---|---|---|
| ***At baseline*** | | | |
| BUN | 18.4 ± 8.8 | 21.3 ± 12.7 | 18.7 ± 10.0 |
| Creatinine | 1.2 ± 1.0 | 1.4 ± 0.9 | 1.3 ± 1.3 |
| Uric acid | 8.5 ± 1.7 | 8.4 ± 1.9 | 8.1 ± 1.9 |
| ***During the follow-up*** | | | |
| BUN | 20.6 ±11.5 | 23.1 ± 14.3 | 21.6 ± 12.4 |
| Creatinine | 1.3 ± 0.8 | 1.4 ± 0.8 | 1.3 ± 0.7 |
| Uric acid | 6.4 ± 1.5 | 5.9 ± 1.9 | 8.1 ± 2.2 |
| ***Changes*** | | | |
| BUN | −0.1 ± 7.0 | −0.8 ± 8.2 | −0.3 ± 6.6 |
| Creatinine | −0.03 ± 0.7 | −0.08 ± 0.9 | −0.05 ± 0.6 |
| Uric acid | −2.3 ± 1.9 | −2.6 ± 2.3 | −0.3 ± 1.9 |

Mean ± standard deviation

## Table 4

Incidence rates (IR) per 1,000 person-days of acute gout attacks during the follow-up period

| | | Allopurinol (N=25,051) | Febuxostat (N=4,288) | Colchicine (N=6,238) |
|---|---|---|---|---|
| **Total** | No. of events | 8,305 | 2,277 | 793 |
| | IR (95% CI) | 2.0 (2.0–2.1) | 3.4 (3.2–3.5) | 1.8 (1.7–1.9) |
| | IRR (95% CI) * | 1.1 (1.1–1.2) | 1.5 (1.4–1.7) | Reference |
| **First 30 days** | No. of events | 2,389 | 675 | 398 |
| | IR (95% CI) | 3.3 (3.1–3.4) | 5.4 (5.0–5.8) | 2.3 (2.1–2.6) |
| | IRR (95% CI) * | 1.4 (1.3–1.5) | 1.9 (1.7–2.0) | Reference |
| **31–90 days** | No. of events | 2,749 | 725 | 271 |
| | IR (95% CI) | 2.5 (2.4–2.6) | 4.0 (3.7–4.3) | 1.5 (1.4–1.7) |
| | IRR (95% CI) * | 1.6 (1.5–1.8) | 2.2 (2.0–2.4) | Reference |
| **91–120 days** | No. of events | 678 | 183 | 32 |
| | IR (95% CI) | 2.0 (1.9–2.2) | 3.4 (2.9–3.9) | 1.3 (0.9–1.8) |
| | IRR (95% CI) * | 1.5 (1.2–1.8) | 2.0 (1.6–2.5) | Reference |

CI: confidence interval

* Adjusted for all demographic factors, comorbidities, medications, and health care utilization factors listed in Table 1

## Appendix 1

Multivariable odds ratios and 95% confidence intervals for initiating a gout treatment

| | Initiating allopurinol vs. colchicine | Initiating febuxostat vs. colchicine | Initiating febuxostat vs. allopurinol |
|---|---|---|---|
| **C-statistics** | **0.61** | **0.70** | **0.67** |
| ***Demographic*** | | | |
| Age* | 0.99 (0.99, 1.00) | **0.99 (0.98, 0.997)** | **0.99 (0.99, 0.996)** |
| Female | **0.72 (0.57, 0.90)** | **0.49 (0.36, 0.68)** | **0.81 (0.73, 0.89)** |
| ***Comorbidities*** | | | |
| Comorbidity score* | 0.91 (0.81, 1.02) | 0.90 (0.77, 1.04) | 0.96 (0.92, 1.01) |
| Hypertension | 1.06 (0.84, 1.33) | **1.36 (1.01, 1.84)** | **1.11 (1.01, 1.22)** |
| Chronic kidney disease | 1.02 (0.70, 1.50) | **2.26 (1.41, 3.61)** | **2.18 (1.88, 2.52)** |
| Renal stones | 1.19 (0.73, 1.94) | 0.58 (0.30, 1.11) | 0.82 (0.67, 1.00) |
| Heart failure | 0.97 (0.55, 1.70) | 1.34 (0.70, 2.70) | 1.12 (0.91, 1.37) |
| Cardiovascular disease | 1.09 (0.79, 1.49) | 1.09 (0.73, 1.63) | 0.94 (0.83, 1.06) |
| Diabetes | 0.95 (0.77, 1.16) | **0.65 (0.49, 0.86)** | **0.79 (0.72, 0.87)** |
| Hyperlipidemia | **1.17 (1.00, 1.43)** | **1.27 (1.01, 1.60)** | 1.03 (0.96, 1.12) |
| Stroke | 0.72 (0.46, 1.14) | 0.94 (0.52, 1.69) | 0.83 (0.68, 1.02) |
| Obesity | 0.95 (0.71, 1.26) | 1.00 (0.69, 1.45) | 0.94 (0.83, 1.06) |
| COPD | 1.20 (0.85, 1.70) | 1.17 (0.75, 1.82) | 0.98 (0.86, 1.19) |
| ***Medications*** | | | |
| Diuretics | **0.79 (0.62, 0.998)** | **0.49 (0.35, 0.67)** | **0.81 (0.73, 0.90)** |
| Beta blockers | 1.07 (0.85, 1.34) | 0.92 (0.69, 1.23) | **0.82 (0.75, 0.90)** |
| ACEI | **1.40 (1.13, 1.74)** | 0.98 (0.75, 1.28) | **0.80 (0.74, 0.87)** |
| ARB | 1.21 (0.95, 1.55) | 1.00 (0.74, 1.35) | 0.97 (0.88, 1.07) |
| ***Health care use*** | | | |
| No. of prescription drugs* | **1.04 (1.01, 1.07)** | **1.16 (1.12, 1.21)** | **1.10 (1.09, 1.11)** |
| Hospitalization | 1.08 (0.73, 1.58) | 0.69 (0.41, 1.14) | **0.69 (0.60, 0.81)** |
| No. of ER visits* | 0.93 (0.80, 1.09) | **0.81 (0.66, 0.99)** | **0.84 (0.79, 0.90)** |
| No. of office visits* | 0.99 (0.95, 1.02) | 0.99 (0.94, 1.03) | **1.02 (1.01, 1.03)** |
| No. of PCP visits* | 1.01 (0.97, 1.05) | 1.05 (0.97, 1.10) | 1.01 (0.997, 1.02) |
| No. of rheumatology visits* | **0.86 (0.78, 0.96)** | **1.26 (1.10, 1.43)** | **1.32 (1.27, 1.38)** |

*Modeled as a continuous variable.

The models were also adjusted for region of residence.