Cost Comparison of Urate-Lowering Therapies in Patients with Gout and Moderate-to-Severe Chronic Kidney Disease

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ABSTRACT

BACKGROUND: Patients with chronic kidney disease (CKD) are at increased risk for developing gout and having refractory disease. Gout flare prevention relies heavily on urate-lowering therapies such as allopurinol and febuxostat, but clinical decision making in patients with moderate-to-severe CKD is complicated by significant comorbidity and the scarcity of real-world cost-effectiveness studies.

OBJECTIVE: To compare total and disease-specific health care expenditures by line of therapy in allopurinol and febuxostat initiators after diagnosis with gout and moderate-to-severe CKD.

METHODS: A retrospective observational cohort study was conducted to compare mean monthly health care cost (in 2012 U.S. dollars) among gout patients with CKD (stage 3 or 4) who initiated allopurinol or febuxostat. The primary outcome was total mean monthly health care expenditures, and the secondary outcome was disease-specific (gout, diabetes, renal, and cardiovascular disease [CVD]) expenditures. Gout patients (ICD-9-CM 274.xx) aged ≥ 18 years with concurrent CKD (stage 3 or 4) were selected from the MarketScan databases (January 2009-June 2012) upon allopurinol or febuxostat initiation. Patients were followed until disenrollment, discontinuation of the qualifying study agent, or use of the alternate study agent. Patients initiating allopurinol were subsequently propensity score-matched (1:1) to patients initiating febuxostat. Five generalized linear models (GLMs) were developed, each controlling for propensity score, to identify the incremental costs (vs. allopurinol) associated with febuxostat initiation in first-line (without prior allopurinol exposure) and second-line (with prior allopurinol exposure) settings.

RESULTS: Propensity score matching yielded 2 cohorts, each with 1,486 patients (64.6% male, mean [SD] age 67.4 [12.8] years). Post-match, 74.6% of patients had stage 3 CKD; 82.9% had CVD; and 42.1% had diabetes. The post-match sample was well balanced on numerous comorbidities and medication exposures with the following exception: 50.0% of febuxostat initiators were treated in the second-line setting; that is, they had baseline exposure to allopurinol, whereas only 4.2% of allopurinol initiators had baseline exposure to febuxostat. Unadjusted mean monthly cost was $1,490 allopurinol and $1,525 febuxostat ($P = 0.809$). GLM results suggest that first-line febuxostat users incurred significantly ($P = 0.009$) lower cost than allopurinol users ($1,299 vs. $1,487), whereas second-line febuxostat initiators incurred significantly ($P = 0.001$) higher cost ($1,751 vs. $1,487). Febuxostat initiators in both settings had significantly ($P < 0.001$) higher gout-specific cost, due to higher febuxostat acquisition cost. Increased gout-specific cost in the first-line febuxostat cohort was offset by significantly ($P < 0.001$) lower CVD ($288 vs. $459) and renal-related cost ($86 vs. $216). There were no significant differences in either renal or CVD costs (adjusted) between allopurinol initiators treated almost exclusively in the first-line setting and second-line febuxostat patients.

CONCLUSIONS: Gout patients with concurrent CKD, initiating treatment with febuxostat in a first-line setting, incurred significantly less total cost than patients initiating allopurinol during the first exposure to each agent. Conversely, patients treated with second-line febuxostat following allopurinol incurred significantly higher total cost than patients initiating allopurinol. There was no significant difference in total cost between the agents across line of therapy. Although study findings suggest the potential for CVD and renal-related savings to offset febuxostat's higher acquisition cost in gout patients with moderate-to-severe CKD, this is the first such retrospective evaluation. Future research is warranted to both demonstrate the durability of study findings and to better elucidate the mechanism by which associated cost offsets occur.

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What is already known about this subject

- Urate-lowering therapies (ULTs) such as allopurinol and febuxostat are the mainstay of treatment for gout flare prevention, and clinical trial results suggest that febuxostat is as effective as allopurinol in lowering serum uric acid levels.
- For patients with moderate-to-severe chronic kidney disease (CKD), management of gout is complicated by significant comorbidity and potential hypersensitivity reactions to allopurinol, resulting in suboptimal dosing of allopurinol for some CKD patients.
- Previous economic comparisons of allopurinol and febuxostat have compared overall patient populations in real-world settings, but no study has done so in a renally impaired population.

What this study adds

- This study is the first to employ real-world data to compare economic outcomes among gout patients with preexisting stage 3 or 4 CKD initiating allopurinol or febuxostat.
- This analysis, which employed propensity score matching to analyze a large administrative database, demonstrated that in the first-line setting, gout patients with concurrent CKD treated with febuxostat incurred significantly less total cost than patients treated with allopurinol, despite the higher drug acquisition cost of febuxostat.
- These findings suggest that quantifying the cost burden associated with ULT may be more complex than a simple comparison of drug acquisition cost alone.

Gout, a metabolic disorder that causes acute, intermittent, and painful flares of arthritis in the joints of the foot, knee, hand, and wrist, occurs in some patients when there is a sudden onset of inflammation as a result of excess serum uric acid (sUA) in the blood (hyperuricemia) with deposition of crystals in tissue. It affects more than 3% of the U.S. adult population.[1] Gout prevalence is rising, in part due to an ever-increasing prevalence of comorbidities that promote hyperuricemia (e.g., hypertension, obesity, metabolic syndrome, type 2 diabetes mellitus, and chronic kidney disease [CKD]) and in part due to the extensive use of thiazide and loop diuretics for cardiovascular disease (CVD).[2-4]

The disease is more common in older adults, with an incidence of 8% in individuals aged 70-79 years compared with only 1.7% in those aged less than 50 years.[5] Data from the Rochester Epidemiology Project suggest that the incidence of gout without diuretic exposure doubled in the United States between the 1970s and the 1990s.[1] Studies have also described increased incidence of gout among populations with chronic renal failure[1] and increased prevalence with successive stages of CKD.[6] Among those with self-reported gout, 71% reported having CKD stage ≥2.[7] CKD has also been shown to be an independent risk factor for more refractory gout.[8]

Numerous studies have demonstrated the substantial economic burden associated with gout,[9-16] with the annual direct burden of illness for new cases of acute gout among men in the United States estimated to be $27.4 million.[10] Gout has also been shown to have a substantial impact on a patient's health-related quality of life (HRQOL).[2,17-19] Gout symptoms can cause significant discomfort, disruption, and disability with the patient's HRQOL in the areas of sexual function, sleep, social life, emotional health, hobbies, and footwear.[20] Both the physical and mental health consequences worsen as the frequency and severity of flares increase.[21]

Gout flare prevention relies heavily on urate-lowering therapies (ULTs) such as allopurinol and febuxostat,[22] and a primary goal of treatment is to achieve a sUA level target of <6 mg/dl.[2] However, management of gout in renally impaired patients is multifaceted, as clinical decision making is complicated by significant additional comorbidity. Hypersensitivity reactions to allopurinol are more likely to occur in patients with renal impairment, for whom a reduced dose of allopurinol is recommended, although there is no precise dosing consensus.[4,23] The failure of patients to reach target sUA and thus reduce gout flare risk has been associated with the appropriateness of allopurinol dosing, a low frequency of sUA measurements, and poor allopurinol compliance.[24]

Clinical trial results suggest that febuxostat 80 mg per day is more effective than allopurinol 300 mg per day in lowering sUA levels.[25-27] However, some researchers have suggested that, given its comparatively high acquisition cost, use of this medication should be limited to patients with renal impairment, those intolerant to allopurinol, and those who do not achieve sUA targets on the maximum recommended dosage of allopurinol.[28,29] However, few studies have compared the cost burden associated with specific gout therapies in real-world settings, and no study, to our knowledge, has done so in a renally impaired population.

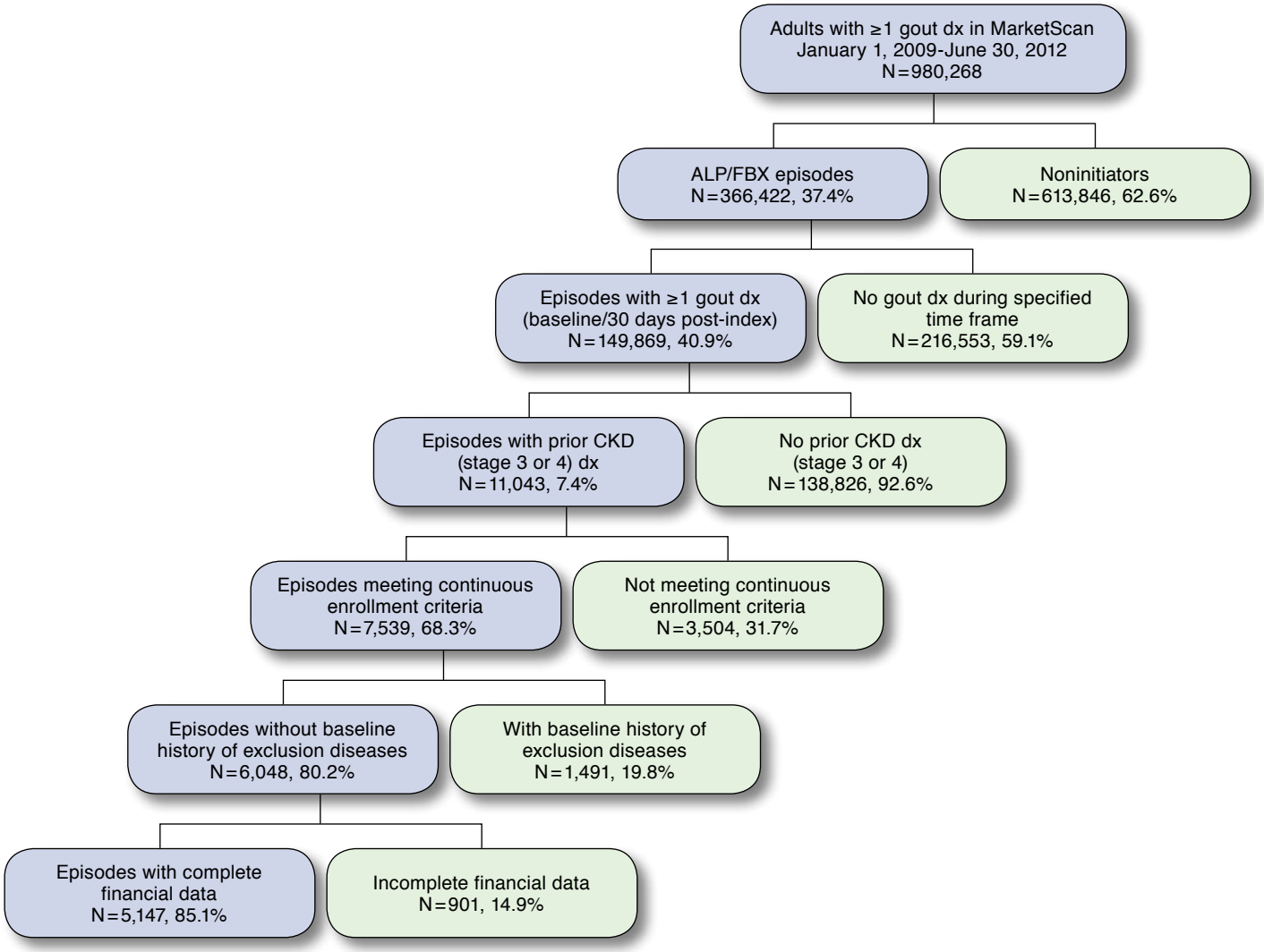
The primary objective of this study was to estimate total and disease-specific cost among gout patients with preexisting stage 3 or 4 CKD who initiated allopurinol or febuxostat. The study hypothesis was that the higher acquisition cost of febuxostat would be offset by decreases in renal and CVD-specific costs due either to febuxostat's greater clinical effectiveness in lowering uric acid levels or to the underdosing of allopurinol in renally impaired patients. This hypothesis presumes a causal relationship between hyperuricemia and CVD outcomes, for which there is a growing body of evidence.[30-36]

Methods

The data source for this research was the MarketScan Commercial Claims and Medicare Supplemental/Coordination of Benefits databases. Patients were included in the analysis if they were aged ≥18 years and had at least 31 days of continuous therapy (i.e., more than two 30-day prescriptions) with either allopurinol or febuxostat between January 1, 2009, and June 30, 2012. Patients were also required to have a diagnosis (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM]) for gout (274.xx) on a nondiagnostic claim either before or within 30 days of initiating either agent. In addition, patients were required to have a diagnosis of stage 3 or 4 CKD (ICD-9-CM 585.3 or 585.4) on at least 1 nondiagnostic claim either before or within 30 days of ULT initiation. Furthermore, patients were required to have at least 12 months of continuous eligibility before ULT initiation, at least 31 days after initiation, and complete data availability for the duration of their study eligibility. Patients with end-stage renal disease or evidence of transplant, dialysis, non-skin-based malignancy, or HIV/AIDS in the 12 months preceding the index date; that is, baseline, were excluded from the study. Patients were allowed to contribute only the initial episode of treatment with each agent to the study. Patients were followed, within each episode, until disenrollment from MarketScan, discontinuation of the qualifying ULT (defined as a gap in therapy greater than 30 days), or use of the alternate study agent. The databases complied with all aspects of the Health Insurance Portability and Accountability Act of 1996, and the study data were de-identified and therefore exempt from institutional review board approval.

Propensity score matching[37-40] was employed to minimize the impact of selection bias. Patients treated with febuxostat were matched to patients treated with allopurinol with similar predicted probabilities using the nearest neighbor method, without replacement, and a caliper equal to one tenth of the standard error of the estimated propensity score. Explanatory

FIGURE 1 Application of Study Eligibility Criteria



ALP = allopurinol; CKD = chronic kidney disease; dx = diagnosis; FBX = febuxostat.

variables in the propensity model included basic demographics (age group, sex, U.S. census region, benefit design, index year); cardiovascular conditions and other comorbidities (baseline history of dysrhythmia/conduction disorder, heart failure, chronic liver disease, stroke, chronic obstructive pulmonary disease, rheumatoid arthritis, diabetes, dyslipidemia, or cellulitis); baseline medication exposure (antibiotics, opiates, angiotensin-converting enzyme [ACE] inhibitors, angiotensin II receptor blockers [ARBs]); and CKD stage nearest index as a measure of renal disease severity. Measures of gout severity in the model included baseline evidence of tophi, number of baseline gout flares, using an algorithm published by Kim et al. (2013) to define gout flares,[41] and medications used to treat gout flares (colchicine, glucocorticoids, nonsteroidal anti-inflammatory drugs [NSAIDs], or probenecid). As a measure of resource intensivity, the model included baseline cost per patient per month. Post-match balance across study covariates was considered acceptable if the standardized difference between the 2 cohorts was < 10%,[42] and traditional tests of significance (e.g., chi-square, t-test) were > 0.05.

The primary study outcome was direct medical expenditure (health plan-insured paid amounts, coordination of benefits, patient copayment, deductible, and coinsurance amounts) as measured during each treatment episode. Secondary study outcomes included disease-specific cost per month. Gout-specific expenditure was defined as claims with a diagnosis of gout

TABLE 1 Baseline Demographic, Clinical, and Gout Characteristics Pre- and Post-Propensity Matching

	Pre-match						Post-match					
	Allopurinol (n = 3,534)		Febuxostat (n = 1,613)		*P* Value	Std Diff	Allopurinol (n = 1,486)		Febuxostat (n = 1,486)		*P* Value	Std Diff
Demographics												
Mean [SD] age, years	68.5	[12.8]	67.4	[12.7]	<0.001	8.2	67.3	[12.9]	67.5	[12.6]	0.665	-1.6
Male (n, %)	2,195	62.1	1,055	65.4	0.037	-6.9	962	64.7	958	64.5	0.878	0.6
Comorbidities (n, %)												
CVD, any	2,951	83.5	1,337	82.9	0.929	1.6	1,231	82.8	1,233	83.0	0.922	-0.4
Cerebrovascular	329	9.3	119	7.4	0.022	7.0	109	7.3	111	7.5	0.889	-0.5
Dysrhythmias	835	23.6	383	23.7	0.963	-0.3	344	23.1	351	23.6	0.762	-1.1
Heart failure	817	23.1	333	20.6	0.067	6.0	313	21.1	308	20.7	0.822	0.8
Hypertension	2,517	71.2	1,111	68.9	0.890	5.1	1,044	70.3	1,032	69.4	0.632	1.8
IHD/atherosclerosis	1,035	29.3	462	28.6	0.336	1.4	400	26.9	437	29.4	0.131	-5.5
Peripheral vascular	314	8.9	138	8.6	0.845	1.2	114	7.7	129	8.7	0.315	-3.7
Chronic liver	24	0.7	23	1.4	0.013	-7.3	15	1.0	17	1.1	0.722	-1.3
COPD	446	12.6	166	10.3	0.011	7.3	155	10.4	158	10.6	0.858	-0.7
CKD stage 3[a]	2,646	74.9	1,203	74.6	0.810	0.7	1,112	74.8	1,106	74.4	0.800	0.9
CKD stage 4[a]	709	20.1	342	21.2	0.719	-2.8	317	21.3	318	21.4	0.964	-0.2
Diabetes mellitus	1,483	42.0	673	41.7	0.735	0.5	627	42.2	624	42.0	0.911	0.4
Dyslipidemia	1,124	31.8	448	27.8	0.124	8.8	412	27.7	417	28.1	0.838	-0.8
Renal failure	763	21.6	356	22.1	0.741	-1.2	324	21.8	323	21.7	0.965	0.2
Gout measures (n, %)												
Presence of tophi	75	2.1	92	5.7	<0.001	-18.5	61	4.1	52	3.5	0.388	3.2
Patients ≥ 1 gout attack	1,774	50.2	975	60.4	<0.001	-20.7	879	59.2	873	58.7	0.823	0.8
Mean [SD] attacks	0.6	[0.8]	0.9	[1.0]	<0.001	-31.5	0.8	[0.9]	0.8	[0.9]	0.510	-2.4
First-line ULT	3,409	96.5	799	49.5	<0.001	124.5	1,424	95.8	743	50.0	<0.001	120.4
Second-line ULT	125	3.5	814	50.5	<0.001	-124.5	62	4.2	743	50.0	<0.001	-120.4
Colchicine	1,359	38.5	852	52.8	<0.001	-29.1	760	51.1	762	51.3	0.942	-0.3
Glucocorticoids	2,037	57.6	1,109	68.8	<0.001	-23.2	994	66.9	996	67.0	0.938	-0.3
NSAIDs	1,209	34.2	563	34.9	0.601	-1.5	501	33.7	510	34.3	0.728	-1.3
Probenecid	52	1.5	41	2.5	0.009	-7.6	33	2.2	30	2.0	0.702	1.4
Other medications (n, %)												
Antihyperlipidemics	2,428	68.7	1,098	68.1	0.513	1.4	1,025	69.0	1,013	68.2	0.635	1.7
ACE inhibitors	1,563	44.2	638	39.6	0.002	9.5	589	39.6	595	40.0	0.822	-0.8
ARBs	1,245	35.2	669	41.5	<0.001	-12.9	589	39.6	609	41.0	0.455	-2.7
Antibiotics	2,285	64.7	1,098	68.1	0.047	-7.2	1,001	67.4	1,007	67.8	0.814	-0.9
Antidiabetic agents	1,381	39.1	655	40.6	0.542	-3.1	605	40.7	610	41.0	0.852	-0.7
Antihyperlipidemics	2,428	68.7	1,098	68.1	0.513	1.4	1,025	69.0	1,013	68.2	0.635	1.7
Opiate analgesics	2,122	60.0	1,028	63.7	0.044	-7.6	954	64.2	935	62.9	0.469	2.7
Mean [SD] CCI	3.9	[1.9]	3.8	[1.9]	0.401	2.6	3.8	[1.8]	3.8	[1.9]	0.929	-0.3
Mean [SD] cost ($)	1,666	[2,300]	1,785	[2,408]	0.261	-5.1	1,749	[2,724]	1,751	[2,309]	0.982	-0.1

[a]*CKD stage based on the stage reported nearest the study index date.*

ACE inhibitor = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CCI = Charlson Comorbidity Index; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; IHD = ischemic heart disease; NSAID = nonsteroidal anti-inflammatory drug; SD = standard deviation; Std Diff = standard difference; ULT = urate-lowering therapy.

or any of the following gout-specific medications or services: allopurinol, colchicine, febuxostat, probenecid, glucocorticoids, prescription NSAIDs, sulfinpyrazone, intra-articular aspiration and/or injection, microscopic examination of specimen from musculoskeletal system/joint fluid, or uric acid measurement. Non-gout-specific expenditure was categorized into 4 mutually exclusive disease groups: renal, diabetes, cardiovascular, and other non-gout. The 4 non-gout disease groups were defined using a combination of ICD-9-CM diagnosis codes, specific medications, and/or medication classes (see the Appendix, available in online article). The "other non-gout" group was defined as the presence of any code that was not included in the definition of gout, renal, diabetes, or cardiovascular. The cost applied to each disease category was assigned proportionally based on the total number of diagnoses on the claim and the number of diagnoses associated with each disease group.

TABLE 2 Cost Per Patient Per Month in the Post-match Sample, Unadjusted[a]

	Allopurinol (n = 1,486)		Febuxostat (n = 1,486)		
	Mean, $	SD, $	Mean, $	SD, $	*P* Value
Total cost	1,490	3,945	1,525	3,867	0.809
Gout-specific cost	87	389	243	265	<0.001
Non-gout-specific cost	1,403	3,861	1,282	3,820	0.389
Renal	214	1,293	171	1,693	0.435
Cardiovascular	459	1,856	384	1,900	0.272
Diabetes	182	974	165	652	0.581
Other	548	930	562	880	0.668

[a]*Cost is reported in 2012 U.S. dollars.*
SD = standard deviation.

A sensitivity analysis was conducted, which assigned cost solely based on the primary diagnosis.

Multivariate analyses were employed because the propensity model could not adjust for the line of ULT treatment for the 2 cohorts. Five generalized linear models (GLMs) were developed, controlling for propensity score, to identify the incremental costs (total, gout, cardiovascular, diabetes, renal-related costs) associated with initiating febuxostat (vs. allopurinol) in first- and second-line settings. Total, diabetes, cardiovascular, and renal-related costs were modeled with gamma distributions and log link; gout-specific cost was modeled with a gaussian distribution and identity link. Distributional assumptions were determined by the Park test. Goodness-of-fit was assessed using scaled deviance and scaled Pearson metrics. Two part models were employed if the proportion of patients with non-zero cost exceeded 5%.

Results

Population Selection

Among the 980,268 adults with a gout diagnosis in the MarketScan databases between January 1, 2009, and June 30, 2012, 37% (n = 366,422) had a prescription for allopurinol or febuxostat. After applying the remaining study criteria, a total of 5,147 episodes in 4,941 patients were entered into the propensity model. The most common reasons for exclusion were no history of stage 3 or 4 CKD before allopurinol/febuxostat initiation, failure to meet continuous enrollment criteria, and prior use of allopurinol or febuxostat (Figure 1).

There were notable differences in the pre-match sample at baseline. Febuxostat patients were younger and more likely to be male, to reside in the southern United States, to have commercial insurance, and to have a history of chronic liver disease and prior exposure to ARBs, antibiotics, or opiate analgesics/agonists. Moreover, febuxostat patients were more likely to have tophi documented on a medical claim, to have had more frequent gout flares, and to have had prior exposure to allopurinol; that is, to have been treated with febuxostat in a second-line setting. Accordingly, febuxostat patients were also more likely to have received colchicine, glucocorticoids, or probenecid before initiation.

After propensity matching, the final post-match sample contained 1,486 episodes in each cohort. A total of 206 patients had an episode in both cohorts (6.9%). The post-match sample was well balanced on all covariates except prior exposure to the alternate agent (Table 1). Fifty percent of febuxostat initiators had no prior exposure to allopurinol; that is, they were receiving first-line treatment as opposed to 95.8% of allopurinol patients. Mean (standard deviation [SD]) duration of follow-up was 8.6 (7.3) months in the febuxostat cohort and 8.7 (7.6) months in the allopurinol cohort. Eighty-three percent of the post-match sample had a history of CVD (hypertension [69.9%], ischemic heart disease [28.2%], dysrhythmia or other conduction disorder [23.4%], or heart failure [20.9%]). Forty-two percent had diabetes and, by definition, 100% had renal disease.

Mean (SD) dose per day of allopurinol during follow-up was 183.4 (94.1) mg, with 25% of patients receiving a dosage of at least 260 mg. Mean (SD) dose per day of febuxostat during follow-up was 50.1 (17.8) mg, with 25% of patients receiving a dosage of at least 62 mg. Patients in the allopurinol cohort were significantly more likely to receive colchicine during follow-up ($P = 0.005$) but were less likely to receive glucocorticoids ($P = 0.025$) than patients in the febuxostat cohort. During the follow-up period, 5.2% of allopurinol patients and 5.0% of febuxostat patients progressed to end-stage renal disease.

Economic Outcomes

Unadjusted Analyses. There were no significant differences in mean monthly per patient expenditure, unadjusted ($1,490 allopurinol, $1,525 febuxostat; Table 2). Gout-specific cost per month represented 10.9% of total cost. Cardiovascular, renal, diabetes, and other non-gout-specific costs represented, respectively, 31.4%, 14.3%, 12.9%, and 41.3% of non-gout cost.

Overall, febuxostat patients were significantly less likely to have had an emergency room visit ($P = 0.013$), and they had fewer hospitalizations ($P = 0.017$). However, when hospitalized, febuxostat patients had significantly longer lengths of stay

TABLE 3 Gout-Specific Cost and Utilization in the Post-match Sample, Unadjusted[a]

	Allopurinol (n = 1,486)		Febuxostat (n = 1,486)		*P* Value
Gout-specific utilization					
Hospitalization, any (n, %)	62	4.2	58	3.9	0.709
Repeat hospitalization (n, %)	5	0.3	6	0.4	0.763
Mean [SD] hospitalizations per month	0.01	[0.05]	0.01	[0.05]	0.813
Mean [SD] length of stay, hospitalizations	4.23	[3.17]	5.39	[5.14]	<0.001
Office visit, any (n, %)	904	60.8	929	62.5	0.346
Mean [SD] office visits per month	0.26	[0.43]	0.25	[0.38]	0.846
ER visit, any (n, %)	69	4.6	74	5.0	0.668
Mean [SD] ER visits per month	0.03	[0.26]	0.04	[0.24]	0.877
Mean [SD] gout-specific cost per month, $					
Hospitalization, any	20	[269]	24	[198]	0.688
Repeat hospitalization	113	[626]	131	[449]	0.372
Office visit, any	11	[29]	12	[23]	0.786
Repeat office visits	19	[35]	19	[26]	0.936
ER visit, any	2	[22]	3	[22]	0.833
Repeat ER visits	53	[90]	53	[83]	0.959
Prescription drug	33	[72]	195	[132]	<0.001
Allopurinol	5	[3]	NA	NA	NA
Febuxostat	NA	NA	168	[105]	NA
Other gout-specific prescription drugs	28	[71]	27	[63]	0.912
Total costs	87	[389]	243	[265]	<0.001

[a]*Gout-specific cost is reported in 2012 U.S. dollars and is defined to include 100% of gout-specific procedures and/or medications and the relevant proportion as per the protocol of any other service with a gout diagnosis.*

ER = emergency room; NA = not applicable; SD = standard deviation.

(*P* = 0.001). Unadjusted inpatient cost per month was lower (*P* = 0.465) in the febuxostat cohort ($397 vs. $489), but these gains were offset by significantly higher outpatient pharmacy cost in the febuxostat cohort (*P* < 0.001).

Mean (SD) expenditure per month for gout-specific services was $243 ($265) and $87 ($389) in the febuxostat and allopurinol cohorts, respectively (*P* < 0.001). Eighty percent of gout-specific cost in the febuxostat cohort was driven by gout-specific outpatient pharmacy cost ($195 vs. $33 in the allopurinol cohort, *P* < 0.001), namely the cost of the comparator agents (Table 3).

Mean (SD) expenditure per month for all non-gout-specific services, unadjusted, was $1,282 ($3,820) in the febuxostat cohort and $1,403 ($3,861) in the allopurinol cohort (*P* = 0.389). Table 4 provides utilization detail for each of the measured non-gout conditions. Patients in the febuxostat cohort had marginally (*P* = 0.065) fewer renal hospitalizations per month and significantly fewer repeat hospitalizations (*P* = 0.036), but significantly longer lengths of stay (*P* = 0.001). Febuxostat patients were also significantly (*P* = 0.002) less likely to have had renal-related emergency room visits and had significantly (*P* = 0.048) lower renal outpatient cost. Similarly, patients in the febuxostat cohort had significantly fewer cardiovascular hospitalizations per month (*P* = 0.022) and repeat hospitalizations (*P* = 0.017), but longer lengths of stay (*P* < 0.001). The cost of cardiovascular-related office visits (*P* = 0.003) as well as overall outpatient cardiovascular cost (*P* = 0.038) was significantly lower, unadjusted, in the febuxostat cohort.

Multivariate Analyses. Multivariate analysis was required because the post-match cohorts were not balanced in terms of line of ULT. GLM results (Table 5) suggest that febuxostat users treated in the second-line setting (n = 743) incurred significantly (*P* = 0.001) more total cost per patient per month than allopurinol users (n = 1,486) treated primarily in the first-line setting. Conversely, febuxostat users treated in the first-line setting (n = 743) incurred significantly (*P* = 0.009) less total cost than allopurinol users treated almost exclusively (95.8%) in the same setting.

Multivariate models also found that febuxostat users in both settings had significantly (*P* < 0.001) higher gout-specific cost, due almost entirely to higher febuxostat acquisition cost. Increased gout-specific expenditure in the first-line febuxostat cohort was offset by significantly lower cardiovascular and renal-related costs (*P* < 0.001) and marginally lower diabetes-related cost (*P* = 0.060). There were no significant differences in renal, cardiovascular, or diabetes-related costs between the allopurinol cohort and febuxostat patients treated in the second-line setting. Sensitivity analyses employing alternate distributional assumptions (Wald) in those models with ambiguous Park test coefficients were very similar to those produced in the

TABLE 4 Non-Gout-Related Utilization in the Post-match Sample, Unadjusted

	Allopurinol (n = 1,486)		Febuxostat (n = 1,486)		*P* Value
Renal-specific					
Hospitalization, any (n, %)	244	16.4	208	14.0	0.066
Repeat hospitalization (n, %)	42	2.8	25	1.7	0.036
Mean [SD] hospitalizations per month	0.03	[0.12]	0.03	[0.09]	0.065
Mean [SD] length of stay, days	5.12	[4.86]	5.71	[4.92]	0.001
Office visit, any (n, %)	1,065	71.7	1,065	71.7	1.000
Mean [SD] office visits per month	0.31	[0.39]	0.29	[0.36]	0.233
ER visit, any (n, %)	95	6.4	57	3.8	0.002
Mean [SD] ER visits per month	0.04	[0.45]	0.02	[0.16]	0.116
Cardiovascular-specific					
Hospitalization, any (n, %)	298	20.1	274	18.4	0.264
Repeat hospitalization (n, %)	75	5.0	49	3.3	0.017
Mean [SD] hospitalizations per month	0.04	[0.13]	0.03	[0.10]	0.022
Mean [SD] length of stay, days	4.92	[4.70]	5.72	[5.82]	<0.001
Office visit, any (n, %)	1,109	74.6	1,096	73.8	0.586
Mean [SD] office visits per month	0.47	[0.61]	0.44	[0.57]	0.124
ER visit, any (n, %)	264	17.8	231	15.5	0.104
Mean [SD] ER visits per month	0.18	[0.85]	0.14	[0.78]	0.134
Prescription drug use (n, %)	1,410	94.9	1,391	93.6	0.135
Diabetes-specific					
Hospitalization, any (n, %)	99	6.7	89	6.0	0.451
Repeat hospitalization (n, %)	24	1.6	10	0.7	0.016
Mean [SD] hospitalizations per month	0.02	[0.09]	0.01	[0.06]	0.069
Mean [SD] length of stay, days	4.21	[3.57]	6.03	[7.63]	<0.001
Office visit, any (n, %)	517	34.8	528	35.5	0.673
Mean [SD] office visits per month	0.19	[0.40]	0.18	[0.39]	0.808
ER visit, any (n, %)	90	6.1	78	5.2	0.341
Mean [SD] ER visits per month	0.10	[1.35]	0.05	[0.37]	0.206
Prescription drug use (n, %)	560	37.7	554	37.3	0.820
Other non-gout-specific					
Hospitalization, any (n, %)	23	1.5	19	1.3	0.534
Repeat hospitalization (n, %)	2	0.1	2	0.1	1.000
Mean [SD] hospitalizations per month	0.00	[0.02]	0.00	[0.02]	0.956
Mean [SD] length of stay, days	4.76	[4.24]	4.18	[3.50]	<0.001
Office visit, any (n, %)	1,108	74.6	1,133	76.2	0.287
Mean [SD] office visits per month	0.53	[0.70]	0.55	[0.64]	0.427
ER visit, any (n, %)	392	26.4	346	23.3	0.051
Mean [SD] ER visits per month	0.37	[1.43]	0.28	[1.08]	0.040
Prescription drug use (n, %)	1,442	97.0	1,427	96.0	0.133

ER = emergency room; SD = standard deviation.

gamma, log link models. Scaled deviance ranged from 1.0 to 1.3. Sensitivity analysis, which allocated cost based only on the primary diagnosis, shifted cost from disease-specific categories to "other" but did not otherwise alter study findings.

Discussion

To our knowledge, the current study is the first to compare economic outcomes among renally compromised gout patients in the year following initiation on the 2 most common ULTs, allopurinol and febuxostat. This study demonstrated that in the first-line setting, gout patients with concurrent CKD treated with febuxostat incurred significantly less total cost than patients treated with allopurinol, despite the higher drug acquisition cost of febuxostat. Higher gout-specific expenditure was offset by lower cardiovascular ($P < 0.001$), renal ($P < 0.001$), and diabetes-related ($P = 0.060$) costs. In addition, patients treated with second-line febuxostat following allopurinol incurred significantly higher total cost than first-line allopurinol users ($P = 0.001$). This difference may be due to the presence of more aggressive disease from delayed effective

TABLE 5 Cost Per Patient Per Month in the Post-match Sample, Adjusted

	Allopurinol[a] (n = 1,486)		Febuxostat			
			First-Line Setting (n = 743)		Second-Line Setting (n = 743)	
	Mean, $	95% CI, $	Mean, $	95% CI, $	Mean, $	95% CI, $
Total cost[b]	1,487	1,477-1,498	1,299	1,287-1,311[c]	1,751	1,733-1,769[d]
Gout-specific cost	87	86-87	243	243-244[e]	242	241-243[e]
Non-gout-specific cost						
Renal	216	212-219	86	84-88[e]	245	241-252
Cardiovascular	459	455-463	288	284-291[e]	476	470-482
Diabetes	179	178-180	151	150-152[f]	183	182-184

[a]*Allopurinol is the referent.*
[b]*Total cost is reported in 2012 U.S. dollars.*
[c]*P = 0.0091.*
[d]*P = 0.0013.*
[e]*P < 0.0001.*
[f]*P = 0.0622.*
CI = confidence interval.

ULT, given that these patients had previously failed treatment with allopurinol. Patients with concurrent gout and CKD represent a clinically complex and resource-intensive population requiring management of both gout- and non-gout-related conditions. Accordingly, the cost impact of the decision to treat with allopurinol or febuxostat is likely more complex than a comparison of ULT drug acquisition cost alone.

Total, all-cause, and gout-specific cost in patients with gout has been reported in several studies. In the current study, total cost per month ($1,507) and gout-specific cost ($165) per month were slightly higher than results from studies conducted in a broad cross-section of patients,[11,21,43] but more closely aligned with studies conducted in more highly comorbid populations. Wu et al. (2008) reported total annual cost among gout patients ≥ 65 years at $14,734 ($1,228 per month) and gout-specific cost at $876 ($73 per month).[14] In a separate study, Wu et al. (2012) reported total cost among patients with 6 or more flares per year at $25,778 ($2,148 per month) and gout-specific cost at $12,620 per year ($1,052 per month).[15]

Kim et al. described clinical characteristics and health care utilizations of gout patients in a large U.S. population-based cohort initiating allopurinol, febuxostat, or colchicine.[41] This study found that febuxostat initiators were highly comorbid, had twice the rate of CKD, and had greater use of medications and health care resources than those initiating allopurinol or colchicine. Febuxostat initiators also had the highest incidence of acute gout flares, which the authors acknowledge may be due to the tendency to treat more severe gout with febuxostat.

In the United Kingdom, a cost-effectiveness study by Beard et al. (2014)[28] concluded that second-line treatment with febuxostat 80 mg/120 mg is cost-effective following allopurinol 300 mg, even when accounting for mild-to-moderate renal impairment and titration of allopurinol. The Beard study differed from the current study with respect to the cost outcome (gout-related costs vs. total direct medical expenditure), study design (Markov health-state model vs. retrospective observational cohort study), and study population (all gout patients and a subgroup of patients with mild-to-moderate renal impairment vs. gout patients with CKD stage 3 or 4). Despite these differences, the current study came to the same conclusion as Beard et al.; first-line treatment with allopurinol results in lower gout-related costs. However, the Beard study did not examine cost impact beyond gout-related costs, whereas the current study demonstrated that the higher gout-related costs with first-line febuxostat were offset by significantly lower cardiovascular and renal-related costs in a real-world setting.

Gandhi et al. (2015)[44] recently published a Markov model of clinical trial data, comparing direct health care costs for febuxostat and allopurinol from a U.S. payer's perspective. Over a 5-year period, the expected treatment success for febuxostat was 72%, with an expected success rate of 42% for allopurinol. The authors found an incremental cost-effectiveness ratio of $6,322 (in 2014 U.S. dollars) per treatment success for febuxostat, leading the authors to conclude that febuxostat was cost-effective from a U.S. payer's perspective. The Gandhi study differed from the present study with respect to study design (Markov health-state model vs. retrospective observational cohort study) and study population (all gout patients and a subgroup of patients with mild-to-moderate renal impairment vs. gout patients with CKD stage 3 or 4). Jutkowitz et al. (2014) also used Markov modeling to assess the lifetime cost impact of 5 urate-lowering treatment strategies in a cross-section of gout patients.[45] The authors concluded that allopurinol as a single therapy option is cost saving compared with no treatment, and that dose escalation of allopurinol-febuxostat sequential

therapy is also cost-effective. Like the Gandhi study, this study used the literature to construct a theoretical model in a broad cross-section of patients. Neither of these models focused on the subset of patients with moderate-to-severe CKD.

The results of the current study have important implications for the management of gout in a renally challenged population. Despite considerable evidence that gout is a disease with suboptimal management and low adherence to treatment,[46] there remains a lack of consensus on the optimal management of gout patients with renal disease. In 2012, the American College of Rheumatology (ACR) released guidelines that included recommendations that CKD patients (stage 2-4) be considered candidates for ULT, with either allopurinol or febuxostat as the first-line agent.[2] Although the ACR guidelines specify that allopurinol hypersensitivity syndrome can be minimized by dose titration in patients with renal impairment,[2] these guidelines do not contain specific recommendations on use of ULTs in renally impaired patients.[46] In contrast, other guidelines recommend only allopurinol as the first-line ULT, citing economic models in the United Kingdom that show the cost-effectiveness of febuxostat in the general population only in second-line settings.[46] Choice of first-line ULT may also be influenced by the potential risk of cardiovascular events with use of febuxostat. According to guidance from the National Institute for Health and Care Excellence (NICE),[47] febuxostat is not recommended for people with ischemic heart disease or congestive heart failure. The U.S. Food and Drug Administration (FDA) label[48] includes a warning to monitor for signs of myocardial infarction and stroke.

A growing number of clinicians have concluded that hyperuricemia is an independent cardiovascular risk factor.[30,31,33,34,36,49,50] Systematic reviews have demonstrated significant relationships between gout or elevated sUA and incident coronary artery disease, CVD-related mortality,[51-54] stroke incidence, and mortality.[55] In addition, studies have suggested sUA as a strong independent prognostic factor in patients with heart failure[56,57] and determined that a high-normal sUA level is associated with worse ejection fraction in heart failure patients, impaired stroke volume and cardiac output, cognitive function, and arterial stiffness in overall healthy adult-elderly subjects.[58] Another recent meta-analysis demonstrated a linear association between sUA level and mortality: elevated sUA increased the risk of all-cause mortality (relative risk [RR] = 1.24, 95% confidence interval [CI] = 1.09-1.42) and cardiovascular mortality (RR = 1.37, 95% CI = 1.19-1.57).[59] In studies of urate-lowering medications, control of sUA was associated with a reduction in cardiovascular risk, but it is not known if this is due to direct effects of lowered sUA or to other benefits from these medications such as reduced oxidative stress and other pleiotropic effects on the endothelium.[39]

This possibility underlines the importance of appropriate gout management, especially in patients with comorbid conditions. Although the present study did not analyze the impact of gout treatment on comorbid conditions clinically, the findings did show a beneficial impact of first-line febuxostat on the cost of cardiovascular and renal comorbid conditions. Although this finding seems to contradict the small numerically higher rate of cardiovascular thromboembolic events observed in patients treated with febuxostat in clinical trials (as noted in the FDA and NICE product guidance), it is important to note that this increased rate was not statistically significant and there is no evidence to date of a causal relationship between febuxostat and cardiovascular events.[60] In the current study, it is not clear why cardiovascular and renal-related costs were lower with febuxostat. Although we presume cost reductions reflect the favorable impact of lower sUA on cardiovascular events, unmeasured confounding may exist. Further studies are warranted to examine the relationship between cardiovascular events and use of febuxostat.

Limitations

Although the current study was based on a sufficient sample of patients with gout and CKD, it is not a random sample and the sources of the data are worth reviewing. The MarketScan databases represent patients with either commercial or Medicare supplemental insurance. As such, study findings may not be generalizable to other populations such as the uninsured or patients with other coverage, such as Medicaid.

These data are collected to facilitate reimbursement and as such do not contain all relevant socioeconomic and clinical data. Medical records were not available to supplement or validate CKD stage, comorbidity may have been underreported, measures of alcohol and tobacco use were absent, and sUA results were unavailable. Medication exposure may have been under- or overstated because prescription medications were presumed to be taken based on their pharmacy fill dates with coverage windows based on days supply. Moreover, sample size limitations prevented propensity matching the first-line and second-line treatment groups separately, primarily because of the limited use of allopurinol in a second-line setting. Postmatch multivariate modeling was used to address the residual imbalance.

Finally, it is also conceivable that clinicians are cautious in using febuxostat in patients with existing CVD and therefore self-select patients with comparatively mild or stable disease. Similarly, it is conceivable that clinicians are also cautious in using allopurinol in patients with renal disease so that they self-select patients they perceive as having more stable disease. Although the current study used multiple methods to address such selection bias, some degree of unmeasured confounding may remain.

Conclusions

Gout patients with concurrent CKD who initiated treatment with febuxostat in a first-line setting incurred significantly less total cost than patients initiating allopurinol during the first exposure to each agent. Conversely, patients treated with second-line febuxostat following allopurinol incurred significantly higher total cost than patients initiating allopurinol. There was no significant difference in total cost between the agents across line of therapy.

Although study findings suggest the potential for cardiovascular- and renal-related savings to offset febuxostat's higher acquisition in gout patients with moderate-to-severe CKD, this is the first such retrospective evaluation. Future research is warranted to both demonstrate the durability of study findings and to better elucidate the mechanism by which associated cost offsets occur.

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APPENDIX ICD-9-CM Diagnosis Code Definitions of Disease States

Disease State	ICD-9-CM Code	Description	Pharmacy/Procedures
Gout	274.xx	Gout	Allopurinol, febuxostat Colchicine, probenecid, glucocorticoids Prescription NSAIDs, sulfinpyrazone Intra-articular aspiration and/or injection (CPT codes 20600, 20605, 20610) Examination musculoskeletal system/joint fluid (ICD-9-CM procedure code 91.5 or CPT code 89060) Uric acid estimation, blood and other (CPT 84550, 84560)
Cardiovascular	390-398 401-405 410-414 415-417 420-429 430-438 440-449 451.xx 452.xx 453.xx 457.xx 458.xx 459.xx	Acute rheumatic fever & chronic rheumatic heart disease Hypertensive disease Ischemic heart disease Diseases of pulmonary circulation Other forms of heart disease Cerebrovascular disease Diseases of arteries, arterioles, capillaries Phlebitis and thrombophlebitis Portal vein thrombosis Other venous embolism, thrombosis Noninfectious dislymphatic channels Hypotension Other disorders of circulatory system	Antiarrhythmic agents Anticoagulants Hemorrheologic agents Sclerosing agents Thrombolytics Angiotensin-converting enzyme inhibitors Angiotensin II receptor blockers Antiplatelets Beta-blockers Calcium channel blockers Digitalis preparations Diuretics Vasodilators
Diabetes	250.xx 357.2 362.0x 366.41	Diabetes mellitus Polyneuropathy in diabetes Diabetic retinopathy Diabetic cataract	All oral or injectable antidiabetic agents
Renal	580-589 590.xx 591.xx 592.xx 593.xx	Nephritis, nephrotic syndrome, nephrosis Infections of kidney Hydronephrosis Calculus of kidney and ureter Other disorders of kidney and ureter	N/A

CPT = Current Procedural Terminology; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; NSAID = nonsteroidal anti-inflammatory drug.