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ORIGINAL RESEARCH

Characteristics, Comorbidities, and Potential Consequences of Uncontrolled Gout: An Insurance-Claims Database Study

Megan Francis-Sedlak · Brian LaMoreaux · Lissa Padnick-Silver · Robert J. Holt · Alfonso E. Bello

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ABSTRACT

Introduction: Gout is a common, progressive, systemic inflammatory arthritis caused by hyperuricemia. Current guidelines recommend that serum uric acid (sUA) levels be maintained below 6.0 mg/dl to minimize acute gout attacks, tophi development, and long-term joint and organ damage. This study examined the influence of uncontrolled gout on post-diagnosis comorbidities and medication use.

Methods: The Humana Research Database (2007–2016, commercial insurance and Medicare) was searched (PearlDiver tool) for patients who had a gout diagnosis code, claims data for at least 6 months before and after diagnosis, and at least 90 days of continuous urate-lowering therapy within 1 year of diagnosis. Patients with controlled (all sUA measurements < 6.0 mg/dl) and uncontrolled (all sUA measurements ≥ 8.0 mg/dl) gout were further examined and compared to better understand the influence of uncontrolled gout on post-diagnosis comorbidities, medication use, and reasons for seeking medical care.

Results: A total of 5473 and 1358 patients met inclusion and classification criteria for the controlled and uncontrolled groups, respectively. Identified comorbidities in both groups included hypertension, hyperlipidemia, diabetes, cardiovascular disease, and chronic kidney disease (CKD). However, the uncontrolled group was more likely to have diabetes, CKD, and cardiovascular disease (including heart failure and atrial fibrillation). Additionally, CKD tended to be more advanced in the uncontrolled gout population (Stage 4–5: 34.6 vs. 22.2%). Overall opioid use was higher in uncontrolled patients.

Conclusions: The current study identified differences between controlled and uncontrolled gout patients, including usage of medication, severity of CKD, and prevalence of CKD, diabetes, and heart disease.

Keywords: Gout comorbidities; Refractory gout; Uncontrolled gout

M. Francis-Sedlak (✉) · B. LaMoreaux · L. Padnick-Silver · R. J. Holt
Horizon Therapeutics plc, 150 South Saunders Road, Lake Forest, IL 60045, USA
e-mail: mfrancis-sedlak@horizontherapeutics.com

A. E. Bello
Illinois Bone and Joint Institute, 2401 Ravine Way, Glenview, IL 60025, USA

PLAIN LANGUAGE SUMMARY

Gout is a common, inflammatory arthritis caused by high uric acid levels in the blood. Serum uric acid (sUA) levels should remain below 6.0 mg/dl to reduce the number of gout flares, tophi development (urate build-ups on

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bones and in joints), and long-term joint and organ damage. This study examined insurance claims (2007–2016 Humana Research Database) to see if there were differences between patients with uncontrolled (sUA $\geq$ 8.0 mg/dl) and controlled (sUA $<$ 6 mg/dl) gout in comorbidities, medication use, and reasons for seeking medical care. Patients who had a gout diagnosis, information for at least 6 months before and after gout diagnosis, and at least 90 days of urate-lowering therapy within 1 year of gout diagnosis were included. A total of 5473 and 1358 patients made up the controlled and uncontrolled groups, respectively. Both groups commonly had high blood pressure, high amounts of blood lipids (includes cholesterol), diabetes, cardiovascular disease, and chronic kidney disease (CKD). However, patients with uncontrolled gout had a higher prevalence of diabetes, CKD, and cardiovascular disease (including heart failure and atrial fibrillation). Specifically, CKD was more advanced in patients with uncontrolled gout (34.6% of patients had advanced CKD [Stage 4–5] compared to 22.2% of patients with controlled gout). Overall opioid use was higher in uncontrolled gout patients. This study found major differences between controlled and uncontrolled gout patients that contribute to higher disease burden for uncontrolled patients.

Key Summary Points

Why carry out this study?

Gout is a common inflammatory arthritis that can develop when serum uric acid levels (sUA) remain elevated. Unfortunately, some patients do not respond to or cannot tolerate standard urate-lowering therapies and gout can become uncontrolled.

Elevated sUA levels have been associated with numerous comorbidities (e.g., hypertension, kidney disease, and cardiac disease) and increased rates of death.

This study examined insurance claims data of patients with a gout diagnosis to better understand post-diagnosis comorbidities, medication use, and reasons for seeking medical care when gout was controlled (sUA $<$ 6.0 mg/dl) and uncontrolled (sUA $\geq$ 8 mg/dl).

What was learned from the study?

Identified comorbidities in both controlled and uncontrolled gout patients included hypertension, hyperlipidemia, diabetes, cardiovascular disease, and chronic kidney disease (CKD).

Compared to controlled gout patients, uncontrolled patients had higher kidney disease prevalence and severity, as well as a higher prevalence of diabetes and heart disease. Further, gout therapies and stronger pain/anti-inflammatory medications—including opioids, indomethacin, and glucocorticoids—were used more frequently in the uncontrolled gout population.

These data reinforce and demonstrate that uncontrolled gout is an inadequately treated disease with significant unmet medical needs including a higher comorbidity burden.

DIGITAL FEATURES

This article is published with digital features, including a Summary Slide and Plain Language Summary, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13235069.

INTRODUCTION

Gout is a progressive, systemic inflammatory arthritis that is caused by hyperuricemia and is estimated to affect 3.9% of the population in

the United States (8.3 million people in 2008 [1], 9.2 million people in 2016 [2]) and between 0.9 and 2.5% of the population in Europe [3–5]. Uric acid has a serum solubility limit of 6.8 mg/dl and current guidelines recommend that gout patients maintain a serum uric acid (sUA) level of < 6 mg/dl [6]. Chronically elevated sUA levels can lead to monosodium urate crystal deposition in joints, soft tissues, cartilage, and organs [7, 8]. As a result, patients who do not meet target sUA levels have increased rates of gout flares and more persistent visible tophi. Therefore, patients with severe disease, as determined by the presence of visible tophi, chronic arthropathy, and/or frequent gout attacks, have a lower target sUA of < 5 mg/dl [9]. Unfortunately, some patients have refractory gout, defined as the persistence of active disease symptoms and hyperuricemia (sUA > 6 mg/dl) despite the use of urate-lowering therapies. It has been estimated that 2–6% of gout patients have hyperuricemia because of refractory disease or urate-lowering therapy contraindications or intolerability [10].

Gout results in chronic inflammation throughout the body, even when patients are in asymptomatic, flare-free periods. As a result, ongoing systemic and joint damage can occur [11, 12], particularly in patients with an sUA > 6 mg/dl [13]. Gout has been previously associated with renal disease [14, 15], cardiovascular complications [15, 16], and death [16, 17], and, more recently, a higher premature death rate [14, 18]. Gout-associated comorbidities generally include hypertension [19–21], type 2 diabetes [22, 23], hyperlipidemia [19], cardiovascular disease [24], coronary heart disease [24–26], heart failure [27, 28], atrial fibrillation [28, 29], and stroke [30].

Comorbidities of gout have been well studied in comparison to non-gouty populations. However, differences between controlled and uncontrolled gout patients are not well reported or understood. The current study examined and compared a relatively large population of controlled and uncontrolled gout patients that underwent at least 90 days of urate-lowering therapy. De-identified patient data were obtained from the Humana Research Database (2007–2016) and were specifically examined for comorbidities, medication usage, and reasons for seeking medical care.

METHODS

The PearlDiver software (PearlDiver, Inc., Colorado Springs, CO, USA) was used to identify gout patients in the Humana Research Database (2007–2016), which contains data of both private-pay and Medicare patients. This study used only summarized de-identified patient data that was obtained from an existing database and did not involve the collection, use, or transmittal of individually identifiable data. Therefore, institutional review board approval for this study was not needed.

Adult patients who were enrolled in Humana for at least 6 months before and after the first documentation of a gout ICD-9/10 diagnosis code (274.*, M10.*, M1A.*) were included. The Humana claims database was examined for patients who had controlled (sUA < 6.0 mg/dl [9]) or uncontrolled (sUA ≥ 8.0 mg/dl) gout based on sUA levels measured at least 90 days after beginning urate-lowering therapy. Uncontrolled gout was conservatively defined as an sUA of ≥ 8 mg/dl to make differences between groups more distinct and allow for better detection of both renal [31] and non-renal comorbidities. Patients excluded were those who (1) had fewer than two sUA measurements, (2) had inconsistent sUA measurements (i.e., not all sUA measurements < 6.0 mg/dl or ≥ 8 mg/dl), (3) had sUA levels between 6.0 and 8.0 mg/dl, or (4) had not received ≥ 90 days of urate-lowering therapy.

Comorbidities and medication use following gout diagnosis were examined and compared between groups to better understand the influence of chronically elevated sUA on gout and other conditions. Further, we identified the reasons why gout patients sought medical care. This included diagnosis codes entered during hospital inpatient, hospital outpatient, emergency room—hospital, inpatient psychiatric facility, and comprehensive outpatient rehabilitation facility visits. Smokers were identified using tobacco-specific ICD-9 (305.1, V15.82)

and ICD-10 (F17.2*, T65.2*, Z71.6, Z72.0, and Z87.891) diagnosis codes.

Data are presented as mean ± standard deviation when possible. Differences between groups were examined using Student's *t* tests for continuous variables. Fisher's exact tests or odds ratios (ORs) were used to compare categorical variables between groups (controlled gout group served as reference for OR calculations). Statistical significance was defined as $p < 0.05$.

RESULTS

Patient Population

Search of the Humana claims database identified 539,802 gout patients. A total of 33,488 of these patients had undergone at least 90 days of continuous urate-lowering therapy (probenecid, probenecid/colchicine combination therapy, allopurinol, and/or febuxostat), had at least two sUA measurements after 90 days of therapy, and had been enrolled in the database for at least 6 months before and after the initial gout diagnosis. A total of 5473 (80.1%) and 1358 (19.9%) patients met all study inclusion and classification criteria for the controlled and uncontrolled gout groups, respectively (Fig. 1). The 6831 included patients had an average age of 71.8 years and 4604 patients (67.4%) were male.

Controlled Gout Population

The controlled gout population is fully described in Table 1. Briefly, mean patient age was 72.5 years, 3666 patients (67.0%) were male, they were followed for 2.67 ± 1.93 years, and had a mean sUA level of 4.51 ± 0.87 mg/dl (range, 1.1–5.9 mg/dl). Controlled patients were predominantly white (72.7%) with commonly identified comorbidity codes of hypertension (84.5%), hyperlipidemia (55.4%), diabetes (49.9%), heart disease (45.7%), and chronic kidney disease (CKD; 32.4%, Tables 1 and 2). More specifically, the most common codes identified were unspecified essential hypertension (50.8%, ICD-9-D-401.9), essential (primary) hypertension (49.0%, ICD-10-D-I10), other and unspecified hyperlipidemia (40.5%, ICD-9-D-272.4), benign essential hypertension (39.5%, ICD-9-D-401.1), and diabetes mellitus

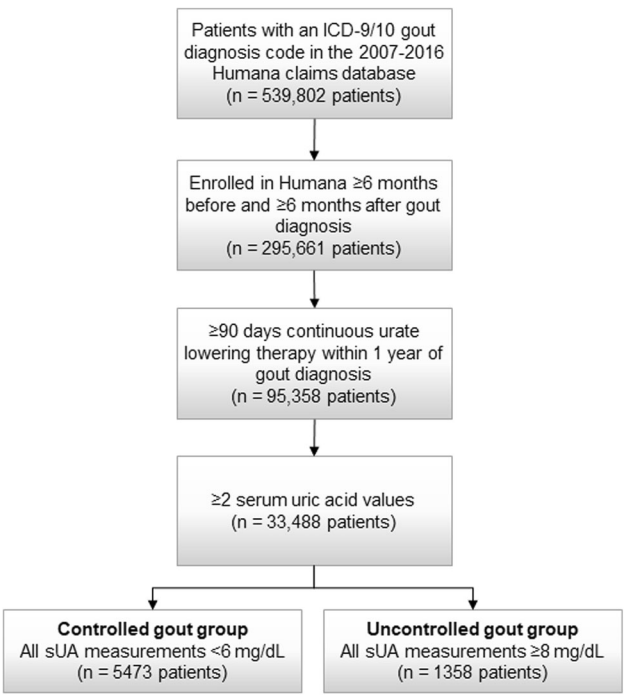

Fig. 1 Flowchart demonstrating gout subject selection from the Humana Research Database (2007–2016)

Table 1 Demographic and clinical characteristics of gout patients who underwent urate-lowering therapy for at least 90 days

	Controlled gout (n = 5473)	Uncontrolled gout (n = 1358)	p value[a]
Male	3666 (67.0%)	938 (69.1%)	0.146
Race			
White	3981 (72.7%)	815 (60.0%)	< 0.001
Black	864 (15.8%)	244 (18.0%)	0.053
Asian	57 (1.0%)	27 (2.0%)	0.008
Hispanic	53 (1.0%)	27 (2.0%)	0.003
Other/unknown	516 (9.4%)	231 (17.0%)	< 0.001
Age, years, mean	72.5	69.1	
Smokers	114 (2.1%)	27 (2.0%)	0.915
Mean time followed after gout diagnosis, years	2.67 ± 1.93	1.85 ± 1.62	< 0.001
Serum uric acid, mg/dl	4.51 ± 0.87	9.45 ± 1.35	< 0.001

Data presented as mean ± standard deviation or n (%) as applicable

[a] Comparison between controlled and uncontrolled groups performed using unpaired t tests for continuous variables and Fisher's exact tests for categorical variables

Table 2 Most common comorbidity types in patients with controlled and uncontrolled gout who underwent urate-lowering therapy for at least 90 days

Grouped ICD9/10 Comorbidity code type	Controlled gout (n = 5473)		Uncontrolled gout (n = 1358)		OR	95% CI	p value
	n	Percent	n	Percent			
Hypertension	4627	84.5%	1126	82.9%	0.89	0.757–1.041	0.141
Heart disease	2500	45.7%	761	56.0%	1.52	1.345–1.709	< 0.001
Heart failure[a]	1039	19.0%	520	38.3%	2.65	2.329–3.012	< 0.001
Atrial fibrillation	1098	20.1%	369	27.2%	1.49	1.297–1.704	< 0.001
Diabetes	2730	49.9%	738	54.3%	1.20	1.062–1.347	0.003
Diabetes with renal manifestations	842	15.4%	320	23.6%	1.70	1.466–1.961	< 0.001
Chronic kidney disease	1772	32.4%	671	49.4%	2.04	1.808–2.301	< 0.001
Hyperlipidemia	3030	55.4%	638	47.0%	0.71	0.634–0.805	< 0.001

OR odds ratio, *CI* confidence interval

[a] Heart failure includes all types of heart failure, including (but not limited to) acute, chronic, systolic, and diastolic heart failure

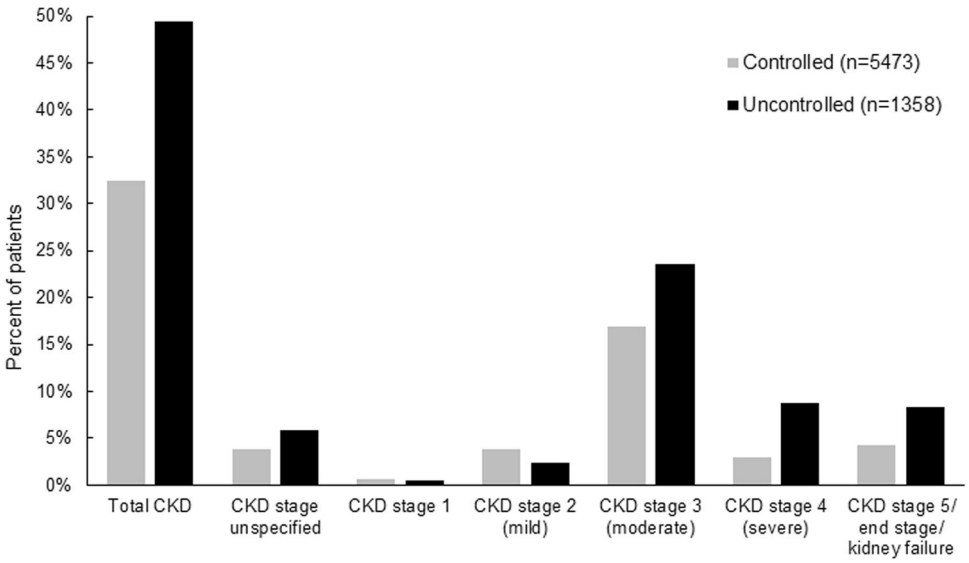

Fig. 2 Chronic kidney disease in gout patients who underwent at least 90 days of urate-lowering therapy. *CKD* chronic kidney disease. Last CKD code available was utilized to avoid counting patients in multiple stages

without mention of complication type II or unspecified type not stated as uncontrolled (39.4%, ICD-9-D-250.00). Of the 1772 controlled gout patients (32.4%) with CKD, 926 (52.3%) had stage 3 kidney disease (ICD-9-D-585.3 and/or ICD-10-D-N18.3, Fig. 2).

Concomitant medications most commonly used by the controlled gout group were indicated for lowering sUA (allopurinol, 95.0%), pain (any opioid, 55.5%; hydrocodone and acetaminophen, 41.1%; any NSAID, 41.2%), hypertension (lisinopril, 34.8%; amlodipine, 33.7%; furosemide, 29.6%), upper respiratory infection (azithromycin, 31.7%), urinary tract infection (ciprofloxacin, 28.0%), hyperlipidemia (simvastatin, 30.1%; atorvastatin, 28.5%), and stomach discomfort (omeprazole, 29.8%; Table 3). Gout and pain medications were individually examined and their use is summarized in Table 3. The most common diagnosis codes reported for seeking medical care during the study period included unspecified chest pain (20.7%, ICD-9-D-786.50), unspecified essential hypertension (14.9%, ICD-9-D-401.9), and shortness of breath (14.7%, ICD-9-D-786.05; Table 4).

Uncontrolled Gout Population

Mean patient age was 69.1 years and 938 patients (68.9%) were male. The uncontrolled gout group was followed for 1.85 ± 1.62 years and had a mean sUA of 9.45 ± 1.35 mg/dl (range, 8.0–18.5 mg/dl). Uncontrolled patients were predominantly white (60.0%) and the most commonly identified comorbidities were related to hypertension (82.9%), heart disease (56.0%), diabetes (54.3%), CKD (49.4%), and hyperlipidemia (47.0%). More specifically, the most commonly occurring diagnosis codes were unspecified hypertension (46.0%), diabetes mellitus without mention of complication type II or unspecified type not stated as uncontrolled (38.3%), essential (primary) hypertension (36.5%), benign essential hypertension (34.6%), and other and unspecified hyperlipidemia (32.5%).

Concomitant medications most commonly used by the uncontrolled sUA group were indicated for lowering sUA (allopurinol, 91.6%), pain (any opioid, 59.9%; hydrocodone and acetaminophen, 45.8%; any NSAID, 43.8%), hypertension (furosemide, 48.1%; lisinopril, 38.2%; amlodipine, 31.4%), acute gout attack

Table 3 Medication usage in controlled and uncontrolled gout patients who underwent urate-lowering therapy for at least 90 days

	Controlled gout		Uncontrolled gout		*p* value
	n (%)	Average dose (mg/day)	*n* (%)	Average dose (mg/day)	
n, patients	5473	–	1358	–	–
Gout medications					
Allopurinol	5198 (95.0%)	262.3	1244 (91.6%)	173.4	< 0.001
Colchicine	571 (10.4%)	0.9	465 (34.2%)	1.0	< 0.001
Febuxostat	207 (3.8%)	52.7	121 (8.9%)	49.6	< 0.001
Probenecid	68 (1.2%)	777.3	16 (1.2%)	796.5	< 0.999
Probenecid and colchicine	49 (0.9%)	–	20 (1.5%)	–	0.068
Pain and anti-inflammatory medications					
Prednisone	1499 (27.4%)	20.9	505 (37.2%)	22.5	< 0.001
Methylprednisolone	1174 (21.5%)	13.6	363 (26.7%)	14.0	< 0.001
All opioids[a]	3037 (55.5%)	–	814 (59.9%)	–	0.003
Hydrocodone/acetaminophen	2250 (41.1%)	–	622 (45.8%)	–	0.002
All NSAIDs[b]	2254 (41.2%)	–	595 (43.8%)	–	0.080
Meloxicam	898 (16.4%)	13.1	169 (12.4%)	13.7	< 0.001
Diclofenac sodium	574 (10.5%)	113.8	125 (9.2%)	106.0	0.177
Ibuprofen	527 (9.6%)	2061.2	97 (7.1%)	2139.2	0.004
Naproxen sodium	469 (8.6%)	933.3	117 (8.6%)	942.0	0.957
Indomethacin	289 (5.3%)	111.7	263 (19.4%)	112.3	< 0.001
Celecoxib	209 (3.8%)	257.5	33 (2.4%)	211.5	0.014
Diuretics					
Furosemide	1622 (29.6%)	48.6	653 (48.1%)	66.9	< 0.001
Carvedilol	817 (14.9%)	26.2	376 (27.7%)	29.7	< 0.001
Spironolactone	365 (6.7%)	36.0	209 (15.4%)	35.1	< 0.001
Metolazone	157 (2.9%)	3.7	208 (15.3%)	4.1	< 0.001
Hypertension					
Lisinopril	1903 (34.8%)	23.3	519 (38.2%)	23.8	0.019
Amlodipine besylate	1846 (33.7%)	7.2	426 (31.4%)	7.6	0.101
Isosorbide mononitrate	391 (7.1%)	46.9	146 (10.8%)	49.1	< 0.001
Hydralazine hydrochloride	357 (6.5%)	126.4	158 (11.6%)	130.4	< 0.001

Table 3 continued

	Controlled gout		Uncontrolled gout		*p* value
	n (%)	Average dose (mg/day)	*n* (%)	Average dose (mg/day)	
Hypercholesterolemia					
Simvastatin	1650 (30.1%)	32.4	362 (26.7%)	32.4	0.012
Atorvastatin calcium	1562 (28.5%)	33.5	370 (27.2%)	33.7	0.364
Antibiotics					
Azithromycin	1733 (31.7%)	321.5	405 (29.8%)	312.3	0.202
Ciprofloxacin	1532 (28.0%)	892.5	347 (25.6%)	865.2	0.072
Hyperglycemia					
Glipizide	508 (9.3%)	12.3	175 (12.9%)	10.5	< 0.001
Insulin glargine	386 (7.1%)	52.9	153 (11.3%)	66.0	< 0.001
Omeprazole (reflux)	1629 (29.8%)	29.0	332 (24.4%)	28.3	< 0.001
Potassium chloride (hypokalemia)	1235 (22.6%)	928.5	416 (30.6%)	1131.0	< 0.001
Albuterol (asthma, COPD)	997 (18.2%)	45.2	282 (20.8%)	48.1	0.033
Warfarin sodium (anticoagulant)	763 (13.9%)	4.4	251 (18.5%)	4.6	< 0.001

p-values represent prevalence comparisons between groups, performed using Fisher's exact tests

NSAIDs nonsteroidal anti-inflammatory agents, *COPD* chronic obstructive airway disease

[a] Includes hydrocodone, oxycodone, codeine, hydromorphone hydrochloride, morphine sulfate, fentanyl, and meperidine

[b] Includes listed NSAIDs and diflunisal, fenoprofen calcium, flurbiprofen, ketoprofen, meclofenamate sodium, nabumetone, piroxicam, sulindac, tolmetin sodium

(prednisone, 37.2%; colchicine, 34.2%), hypokalemia (potassium chloride, 30.6%), upper respiratory infection (azithromycin, 29.8%), and congestive heart failure (carvedilol, 27.7%, Table 3). Gout medications were individually examined and their use is summarized in Table 3. The most common diagnosis codes associated with medical visits included unspecified chest pain (24.2%, ICD-9-D-786.50), shortness of breath (23.6%, ICD-9-D-786.05), unspecified congestive heart failure (20.0%, ICD-9-D-428.0), unspecified acute kidney failure (19.9%, ICD-9-D-584.9), and limb pain (16.4%, ICD-9-D-729.5; Table 4).

Comparisons Between the Controlled and Uncontrolled Gout Populations

Patient Characteristics

The controlled and uncontrolled gout groups had comparable demographic parameters (Table 1) in terms of age and gender make-up. The controlled group was slightly older (72.5 vs. 69.1 years) and had a significantly larger proportion of white patients (72.7 vs. 60.0%, $p < 0.001$) than the uncontrolled group. With the exception of black patients, the proportion of minority groups was significantly higher in the uncontrolled gout population (all $p < 0.01$, Table 1). Additionally, the controlled population had a longer follow-up time (from original

Table 4 Most common diagnosis codes associated with medical care in patients with uncontrolled gout

	Controlled gout (n = 5473)	Uncontrolled gout (n = 1358)	OR[a]	95% CI	p value
Chest pain, unspecified (ICD-9-D-786.50)	1133 (20.7%)	328 (24.2%)	1.22	1.060–1.404	0.006
Shortness of breath (ICD-9-D-786.05)	805 (14.7%)	320 (23.6%)	1.79	1.545–2.069	< 0.001
Congestive heart failure, unspecified (ICD-9-D-4280)	400 (7.3%)	271 (20.0%)	3.16	2.674–3.739	< 0.001
Acute kidney failure, unspecified (ICD-9-D-5849)	425 (7.8%)	270 (19.9%)	2.95	2.497–3.480	< 0.001
Pain in limb (ICD-9-D-7295)	540 (9.9%)	223 (16.4%)	1.79	1.516–2.125	< 0.001
Atrial fibrillation (ICD-9-D-42731)	480 (8.8%)	192 (14.1%)	1.71	1.432–2.049	< 0.001
Other respiratory abnormalities (ICD-9-D-78609)	445 (8.1%)	172 (12.7%)	1.64	1.359–1.976	< 0.001
Essential hypertension, unspecified (ICD-9-D-4019)	816 (14.9%)	168 (12.4%)	0.81	0.674–0.963	0.019
Abdominal pain, unspecified site (ICD-9-78900)	558 (10.2%)	153 (11.3%)	1.12	0.925–1.352	0.247
Coronary atherosclerosis, native artery (ICD-9-D-41401)	577 (10.5%)	152 (11.2%)	1.07	0.885–1.293	0.519

OR odds ratio, *CI* confidence interval

[a] Controlled gout group served as reference

gout diagnosis) than the uncontrolled population (2.67 ± 1.93 vs. 1.85 ± 1.62 years, $p < 0.001$).

Numerous comorbidities were present in both study groups. Hypertension, coronary atherosclerosis, and other malaise and fatigue were equally prevalent in uncontrolled and controlled gout patients. Hyperlipidemia was more prevalent in the controlled group (47.0 vs. 55.4%, OR 0.714, $p < 0.001$). Patients in the uncontrolled gout group were more likely than the controlled gout group to have heart disease (56.0 vs. 45.7%, odds ratio [OR] = 1.52), diabetes (54.3 vs. 49.9%, OR 1.20; with renal manifestations [23.6 vs. 15.4%, OR 1.70]), chronic kidney disease (49.4 vs. 32.4%, OR 2.04), atrial fibrillation (27.2 vs. 20.1%, OR 1.49; all $p < 0.01$, Table 2). Furthermore, acute gouty arthropathy was more likely to develop in uncontrolled patients (10.3 vs. 2.9%; OR 3.87, $p < 0.001$).

Medical Care Needs

Patients with uncontrolled gout sought medical care (not necessarily for gout) more often than those with controlled gout (34.0 vs. 24.9 visits/patient). This difference largely stemmed from inpatient encounters (12.6 vs. 6.6 visits/patient).

The uncontrolled gout population tended to seek medical care for different reasons than the controlled population. Both patient groups had similar rates of medical care for coronary artery atherosclerosis (approximately 17-19%) and unspecified abdominal pain (approximately

10%-11%), but the uncontrolled gout group was more likely to seek medical care for diagnosis codes associated with unspecified chest pain (24.2 vs. 20.7%, OR 1.22), shortness of breath (23.6 vs. 14.7%, OR 1.79), limb pain (16.4 vs. 9.9%, OR 1.79), unspecified acute kidney failure (19.9 vs. 7.8%, OR 2.95), atrial fibrillation (14.1 vs. 8.8%, OR 1.71), other respiratory abnormalities (12.7 vs. 8.1%, OR 1.64), and congestive heart failure (20.0 vs. 7.3%, OR 3.16; all $p \leq 0.006$). The controlled gout group was more likely to seek medical care for unspecified essential hypertension than the uncontrolled group (14.9 vs. 12.4%, OR 0.81, $p = 0.019$).

The uncontrolled gout population used several medications significantly more often than the controlled gout population (Table 3). Allopurinol was used in the vast majority of both the controlled (95.0%) and uncontrolled (91.6%) populations. However, the controlled population was given a higher daily dose (mean of 262.3 vs. 173.4 mg). Both colchicine (34.2 vs. 10.4%) and febuxostat (8.9 vs. 3.8%) were used approximately three times more often in the uncontrolled group than in the controlled group (both $p < 0.001$).

All pain and anti-inflammatory medications examined were highly used by both controlled and uncontrolled gout patients (Table 3). However, prednisone (37.2 vs. 27.4%), methylprednisolone (26.7 vs. 21.5%), and opioids (59.9 vs. 55.5%) were all used significantly more often in the uncontrolled group (all $p \leq 0.003$). The overall use of NSAIDs was similar in both groups (43.8 vs. 41.2%, $p = 0.08$); the uncontrolled group used indomethacin significantly more often than the controlled group (19.4 vs. 5.3%, $p < 0.001$).

All diuretics and anti-hypertensive medications examined (Table 3), with the exception of amlodipine besylate, were used significantly more often in the uncontrolled group (all p ≤ 0.02). Hypokalemic, asthma or COPD, and anticoagulant medications were also used significantly more often in the uncontrolled group (all $p \leq 0.03$). Type II diabetes medications and insulin were used more often in the uncontrolled group (both $p < 0.001$). The proportion of patients using azithromycin and ciprofloxacin was approximately 30% for both medications in both patient groups.

Chronic Kidney Disease

A high proportion of patients had CKD in both patient groups, but uncontrolled gout patients were more likely to have CKD of any stage (49.4 vs. 32.4%, OR 2.04, $p < 0.001$). Additionally, controlled gout patients tended to have less severe kidney disease (Fig. 2). Of patients with CKD, significantly more controlled gout patients had stage 1–3 disease (65.9 vs. 53.7%, $p < 0.001$) and significantly more uncontrolled gout patients had stage 4–5 disease (34.6 vs. 22.2%, $p < 0.001$).

DISCUSSION

Clear, but sometimes discrepant treatment guidelines from multiple organizations exist [6, 9, 32–36], but gout remains an undertreated and often poorly or under-managed disease [37–41]. A recent population-based study indicated that only 33% of gout patients in the United States were on urate-lowering therapies between 2007 and 2014 [2]. Though gout management that specifically targets lowering sUA levels improves gout sequelae (e.g., flares, joint damage, tophi) [42], gout patients have higher levels of hypertension [17–19], cardiovascular disease [24, 43, 44], and kidney disease [15, 27, 45] than patients without gout. However, less has been reported or is known about differences between the controlled and uncontrolled gout populations. The current study of nearly 7000 gout patients was designed to identify any such differences and improve our understanding of gout sequelae, especially with respect to the consequences of not achieving target sUA levels.

We found significantly higher rates of renal disease prevalence and severity, as well as cardiovascular disease and diabetes, in uncontrolled ($\geq$ 8.0 mg/dl) gout patients as compared with controlled ($<$ 6.0 mg/dl) gout patients. Generally, these differences manifested in increased rates of seeking medical care in uncontrolled gout patients. These findings agree with prior studies that found associations

between elevated sUA levels and increased occurrence of cardiovascular disease [46], and events [46, 47], and death [48] and between gout and diabetes [24]. In comparison to the controlled gout group, CKD was more prevalent in the uncontrolled gout group, with a higher proportion having stages 3–5. Previous studies have also shown correlations between sUA levels and risk of renal failure [49] and end-stage renal disease [50]. Smoking was ruled out as a potential confounder in these assessments as approximately 2% of both the controlled and uncontrolled groups were smokers (based on previously validated ICD-9 smoking codes [51]). However, not all physicians use ICD codes to document smoking status and the reported proportion is likely an underestimate for both study groups.

The uncontrolled gout group had nearly double the number of hospitalizations as the controlled gout group. The higher prevalence of multiple comorbidities in the uncontrolled gout population likely underlies this observation. Previously, patients with gout have been reported to have higher rates of hospitalization for cardiorenal complications than patients without gout [52]. However, further research is needed to better understand contributing factors to the increased hospitalization rate observed here in uncontrolled gout patients compared with controlled gout patients.

Differences in medication use between controlled and uncontrolled gout patients were notable. Urate-lowering therapies were used by all patients in both groups. Allopurinol was used by a large proportion of patients in both groups (> 91%), but the average dose of the controlled group was higher than that of the uncontrolled group (262.3 vs. 173.4 mg). The relatively low allopurinol dose in both groups may be representative of allopurinol under-utilization, a known issue that arises from both physician under-prescribing and patient non-compliance [53]. The lower dose in the uncontrolled group may also be representative of claims timing (2007–2016). Prior to 2017, it was not well known that allopurinol dose could be safely increased in patients with renal impairment [54]. Further, allopurinol use with furosemide, which was used in the uncontrolled group more often, can result in an increased sUA via drug–drug interaction [55]. Both colchicine (34.2 vs. 10.4%) and febuxostat (8.9 vs. 3.9%) were used more often in uncontrolled gout patients, but at similar daily doses. These differences were not surprising and likely reflect insufficient allopurinol dosing, poor treatment response, and/or intolerance to higher allopurinol doses. The increased use of colchicine likely reflects increased gout flare severity and frequency in the uncontrolled group. This finding is consistent with prior studies that have shown an increased frequency of gout flares in patients with sUA levels > 6 mg/dl [42, 56–58].

Overall usage of pain and anti-inflammatory medication (corticosteroids, NSAIDs, and opioids) was higher in the uncontrolled group than in the controlled group. Opioid use was significantly higher in uncontrolled gout patients, but only by a narrow margin (59.9 vs. 55.5%). Corticosteroid use was also higher in uncontrolled gout patients (prednisone: 37.2 vs. 27.4%, methylprednisolone: 26.7 vs. 21.3%; both $p < 0.001$). Overall NSAID use was similar between patient groups (uncontrolled: 43.8%, controlled: 41.2%), with the exception of indomethacin, which was used more often in uncontrolled patients (19.4 vs. 5.3%, $p < 0.001$). Because indomethacin, corticosteroids, and opioids are all used to manage pain associated with gout flare, these findings are likely attributable to higher gout flare severity and frequency in the uncontrolled gout group. Increased medication use for gout flares may impact overall patient health, particularly in patients with kidney disease (NSAID nephrotoxicity) and diabetes (corticosteroid-induced hyperglycemia). However, the high use of pain medications in the controlled group indicates that gout patients generally experience high levels of pain (related or unrelated to gout), even when sUA levels meet the urate-lowering therapy target.

Anti-hypertensive medication use was high in both controlled and uncontrolled gout patients. This finding supports the well-known and long-established link between both hyperuricemia and hypertension [59–62] and between gout and hypertension [20, 21, 44]. Lisinopril and amlodipine were used most

commonly and use of both agents was similar in both groups. Hydralazine and isosorbide were used more often in uncontrolled patients, likely reflective of hard to control hypertension and, more speculatively, increased cardiovascular disease, particularly heart failure. All diuretics examined were used significantly more often in the uncontrolled gout population than in the controlled gout population. This may be reflective of the observed higher rates of heart failure and/or the more severe kidney disease in the uncontrolled group.

Our study had several limitations. First, causality of the identified differences between controlled and uncontrolled gout groups cannot be determined with claims data. Second, our gout groups were not age- or sex-matched. This was intentional, and allowed differences between controlled and uncontrolled gout patients, including demographic parameters, to be more easily identified. Both groups had a similar proportion of men and women, but the controlled group was slightly older (72.5 vs. 69.1 years) and had a longer duration in the medical plan (2.67 vs. 1.85 years). This could have skewed our results toward a higher comorbidity/medication use prevalence in the controlled gout group. However other than hyperlipidemia, our uncontrolled gout patients had higher comorbidity rates. Our data were analyzed using both ICD-9 and ICD-10 codes. Therefore, multiple diagnosis codes had to be "bucketed" to accurately obtain the number of patients with a certain condition. It is possible that more obscure ICD codes were unintentionally omitted from our analyses, resulting in an underestimation of some comorbidities. However, our proportion of uncontrolled patients was as expected. Approximately 80% of included patients had a sustained sUA < 6 mg/dl after at least 90 days of oral urate-lowering therapy. This proportion is in agreement with a Veteran's Administration gout registry study showing approximately 75% of patients achieved target sUA [63]. Lastly, it is possible that successful sUA-lowering therapy is a proxy for medical care access and/or quality of medication compliance, both of which would confound our findings. We hope future research will clarify these limitations and hypotheses.

CONCLUSIONS

We present unique findings that identify differences between controlled and uncontrolled gout patients, including higher kidney disease prevalence and severity, as well as, more prevalent diabetes and heart disease in those with uncontrolled gout. Further, gout therapies and stronger analgesic medications, including opioids, were used more frequently in the uncontrolled gout population. These data reinforce and demonstrate that uncontrolled gout is an inadequately treated disease with significant unmet medical needs and worthy of future investigation.

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Disclosures. Megan Francis-Sedlak, Brian LaMoreaux, Lissa Padnick-Silver, and Robert J. Holt are employees of and own stock in Horizon. Alfonso E. Bello has nothing to disclose.

Compliance with Ethics Guidelines. This study used only de-identified patient data that was obtained from an existing database and did not involve the collection, use, or transmittal of

individually identifiable data. Therefore, institutional review board approval for this study was not needed.

Data Availability. The datasets analyzed during the current study are not publicly available. The PearlDiver software (PearlDiver Technologies) was used to access the Humana Claims database. This database is no longer accessible through PearlDiver. Additionally, the license agreement to access these data does not include permission for the authors to share this database.

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