gout, urate, and crystal deposition disease

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Prevalence and Influence of Gout in Patients with Advanced Chronic Kidney Disease: Findings of a Large Retrospective Chart Review

Leonard Stern [1], Richard J. Johnson [2], Payam Shakouri [3], Amod Athavale [4], Lissa Padnick-Silver [5], Brian LaMoreaux [5], Brad A. Marder [5,*] and Sreedhar Mandayam [6]

[1] Columbia University Irving Medical Center, Nephrology, New York, NY 10032, USA; ls38@cumc.columbia.edu
[2] Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO 80045, USA
[3] Advanced Kidney Care, Poughkeepsie, NY 12550, USA
[4] Trinity Life Sciences, Waltham, MA 02451, USA
[5] Horizon Therapeutics plc (now Amgen, Inc.), Deerfield, IL 60015, USA; lsilve01@amgen.com (L.P.-S.)
[6] Section of Nephrology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
* Correspondence: bmarder@amgen.com

Abstract: Gout patients have higher mortality, heavier comorbidity burden, and lower quality of life than non-gout patients, but information is sparse on how gout affects advanced CKD patients. This study examined the prevalence and potential health impacts in stage 3–5 CKD patients. Gout was defined as being listed as a comorbidity, ULT use, and/or reported gout symptoms (tophi, >1 flare). Uncontrolled gout was defined as hyperuricemia (serum urate >6 mg/dL) with tophi, ≥2 gout flares/year, or ≥1 swollen/tender joint. This study included 746 patients (55% men, age: 56.2 ± 18.3 years, CKD-duration: 4.0 ± 4.8 years, eGFR: 32.2 ± 15.5 mL/min/1.73 m^2), of which 23% met the gout criteria. Prevalence was highest in patients with stage 3b and 4 CKD. Gout patients had a significantly higher prevalence of cardiovascular comorbidities, CKD-mineral bone disorder, and back pain than non-gout patients. Uncontrolled gout patients had more hypertension, joint issues, chronic pain, febuxostat use, and colchicine use than controlled patients. Compared to those without gout, gout patients had higher rates of cardiovascular and bone diseases, with uncontrolled patients having an even higher burden. In conclusion, these data suggest that identifying and monitoring gout in CKD patients provides health benefits. However, more than one-third of gout patients did not have a formal gout diagnosis in their medical record.

Keywords: gout; uncontrolled gout; chronic kidney disease; comorbidities

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1. Introduction

Gout is a common and potentially debilitating inflammatory arthritis that has been associated with decreased quality of life [1,2], multiple comorbidities [1,3–5], and increased mortality [3]. Patients with compromised renal function are at an increased risk for developing hyperuricemia and gout [6], with a reported gout prevalence of up to 24% in patients with an eGFR <60 mL/min/1.73 m [7,8]. Additionally, patients with hyperuricemia [9–11] and gout [11] are at increased risk for developing CKD. Therefore, better recognition and improved management of patients with coincident gout and CKD may be important to improve patient outcomes. Further, managing hyperuricemia and gout in CKD patients can be particularly challenging because of kidney-related constraints on the use of oral urate-lowering therapy (ULT) [12] and gout flare treatment/prophylaxis [12,13]. Given its commonality in CKD patients, we conducted a comprehensive chart review of patients being seen for CKD care in nephrology clinics. Without revealing this study's intentions, nephrologists practicing in the United States were systematically surveyed to provide data

to examine the prevalence, associated comorbidities, and medical management of gout in a large cohort of patients with moderate to advanced CKD.

2. Methods

This retrospective chart review study was reviewed and approved by the Advarra IRB (registration number: 00000971; Columbia, MD, USA). This study was assigned exempt status, waiving the requirement of informed consent. All study conduct adhered to the tenets of the Declaration of Helsinki.

2.1. Physician and Patient Selection

Nephrologists who had registered on a physician panel representative of the United States healthcare provider population (Toluna, Inc.; Norwalk, CT, USA) were asked to provide de-identified chart data from 4 to 8 patients with stage 3–5 CKD (eGFR < 60 mL/min/1.73 m^2). All physicians had previously expressed interest in contributing to this type of research and were sent an email to gauge interest in providing their clinical perspective and medical record data on advanced CKD patients. Interested physicians responded to the email and were sent a link to the online screening and data collection tool after their identity and medical specialty had been verified using their National Provider Identifier (NPI) number. Gout was not mentioned in the recruitment materials or study objectives to prevent priming respondents about the purpose of this study. All participating physicians were between 3 and 30 years post-fellowship, spent ≥70% of their professional time providing direct patient care, and were managing ≥50 CKD and ≥10 stage 3–5 CKD patients. This study was designed to include ≥75 nephrologists who reported seeing patients with gout and ≥25 nephrologists who reported managing gout themselves. Physicians were asked to choose their most recently seen advanced CKD patients to ensure random selection. Patients were required to have been seen by the responding physician within the 3 months prior to data collection to qualify for inclusion.

2.2. Data Collection

Selected patients had their data anonymously abstracted from the medical charts using a standardized data collection form incorporated into the physician survey. This data collection form was designed to maximize data uniformity and programmed to minimize data entry errors by only allowing physicians to provide numbers (within a restricted range), yes/no responses, or check/uncheck responses, as appropriate. For survey questions with pre-defined lists, list items were shown in random order with "don't know" and "other" options also provided at the end of the list. Checking the "other" option allowed reporting physicians to provide further detail via free text response. Because each nephrologist provided their own clinical evaluation of a patient, the patient data included represented the clinical interpretation of each reporting physician.

2.3. Data Analysis

Patient characteristics and available laboratory measures obtained from the medical records were examined and compared between patients who did and did not meet the study gout criteria. Patients were said to have gout if they met any of the following criteria: gout reported as a comorbidity, record of oral urate-lowering therapy (ULT) use, or clinical evidence of gout (visible tophi, ≥2 gout flare). Though some CKD patients are treated with ULTs for asymptomatic hyperuricemia, this practice is not yet universal [14]. Therefore, patients with ULT use but no other gout criteria were classified as having gout to maximize patient identification. Patients were classified as having uncontrolled gout if SU was >6 mg/dL at the most recent visit and at least one of the following features of gout was present: visible (subcutaneous) tophi, ≥2 gout flares in the year prior to data collection, or ≥1 swollen/tender joint.

Patient- and physician-level data were excluded from analyses if physicians "straight-lined" (i.e., entered the same data on similar questions), completed the study instrument

within one-third of the expected completion time, or entered invalid data on any items. Between-group differences were statistically examined using two-tailed unpaired *t*-tests for continuous parameters and two-tailed chi-square tests for categorical parameters. An alpha of 0.05 was used for all statistical comparisons.

3. Results

A total of 1962 nephrologists were emailed to gauge interest in providing clinical perspectives and medical record data on advanced CKD patients. Of these, 443 (23%) responded and were sent a link for screening and data collection. A total of 188 nephrologists satisfied the study inclusion criteria and 115 completed data collection forms, for an overall survey completion rate of 26% (115/443). This response rate was consistent with what was expected for a web-based physician survey [15]. A total of 11 patients of four nephrologists were excluded due to data validity concerns. Therefore, 746 patient charts from 111 nephrologists were ultimately included in data analyses. Physicians were highly experienced, on average, practicing (post-fellowship) for 14.8 ± 7.1 years and seeing 117.7 ± 66.8 CKD patients/month.

3.1. Patient Characteristics

A total of 746 advanced CKD patients were included in the analyses. As summarized in Table 1, 54% were male, the mean patient age was 56.2 ± 18.3 years, and the mean BMI was 31.4 ± 10.9 kg/m^2. The mean eGFR was 32.2 ± 15.5 mL/min/1.73 m^2 and patients had a CKD history of 4.0 ± 4.8 years. End-stage renal disease patients comprised 16% (123/746) and solid organ transplant recipients comprised 8% (61/746; 90% renal transplant) of the study population. The most reported comorbidities included hypertension (80%), diabetes mellitus (44%), obesity (43%), anemia of CKD (38%), CKD-mineral bone disorder (29%), congestive heart failure (16%), ischemic heart disease (16%), and gout (15%).

Table 1. Characteristics of the studied advanced CKD population.

	(N = 746)
Patient age, years, mean ± SD	56.2 ± 18.3
≥65 years	270 (36%)
Male, n (%)	409 (54%)
Race/ethnicity, n (%)	
Caucasian	317 (42%)
Black	213 (29%)
Hispanic	97 (13%)
Asian American	58 (8%)
Multi-racial	24 (3%)
Other *	24 (3%)
Unknown/prefer not to answer	13 (2%)
Solid organ transplant recipient, n (%)	61 (8%)
Renal transplant recipients, n (%)	55/61 (90%)
Time since organ transplant, years, mean ± SD	5.5 ± 5.8
eGFR, mL/min/1.73 m^2, mean ± SD	32.2 ± 15.5
CKD duration, years, mean ± SD	4.0 ± 4.8
CKD stage, n (%)	
Stage 3a	196 (26%)
Stage 3b	240 (32%)
Stage 4	187 (25%)
Stage 5 (ESRD, includes dialysis patients)	123 (16%)
Body mass index, kg/m^2, mean ± SD	31.4 ± 10.9
Gout (as defined by the study criteria †), n (%)	173 (23%)

Table 1. *Cont.*

	(N = 746)
Comorbidities (as listed in the medical record), n (%)	
Hypertension	594 (80%)
Diabetes mellitus	331 (44%)
Obesity (BMI $\geq$ 30 mg/kg^2) (N = 727)	318 (44%)
Anemia of CKD	281 (38%)
CKD-mineral bone disorder	216 (29%)
Congestive heart failure	119 (16%)
Ischemic heart disease	116 (16%)
Gout	110 (15%)
Degenerative joint disease	82 (11%)
Peripheral vascular disease	78 (10%)
Chronic back pain	56 (8%)
Chronic obstructive pulmonary disease	53 (7%)
Chronic pain	50 (7%)
Pulmonary hypertension	34 (5%)

* includes Native American, Native Hawaiian/Pacific Islander, Middle Eastern/North African. † gout study criteria: gout listed as comorbidity, a patient receiving urate-lowering therapy, or clinical evidence of gout noted in the medical record (e.g., visible tophi, gout flare, $\geq$1 swollen/tender joint). SD: standard deviation; eGFR: estimated glomerular filtration rate; CKD: chronic kidney disease; ESRD: end-stage renal disease; BMI: body mass index.

3.2. Comparison of CKD Patients with and without Gout

Of the 746 CKD patients included, 173 (23%) met the study criteria for gout, with the highest prevalence in patients with stage 3b and 4 CKD (both 28%, Figure 1). A total of 110 patients (64%) in the gout group had gout listed as a comorbidity, and 109 (64%) were currently using a ULT. Of the 135 patients in which flare occurrence was known, 40 (30%) had $\geq$1 acute gout flare in the prior year. Of the 131 patients in which gout-related pain was known, 67 (51%) reported having chronic pain.

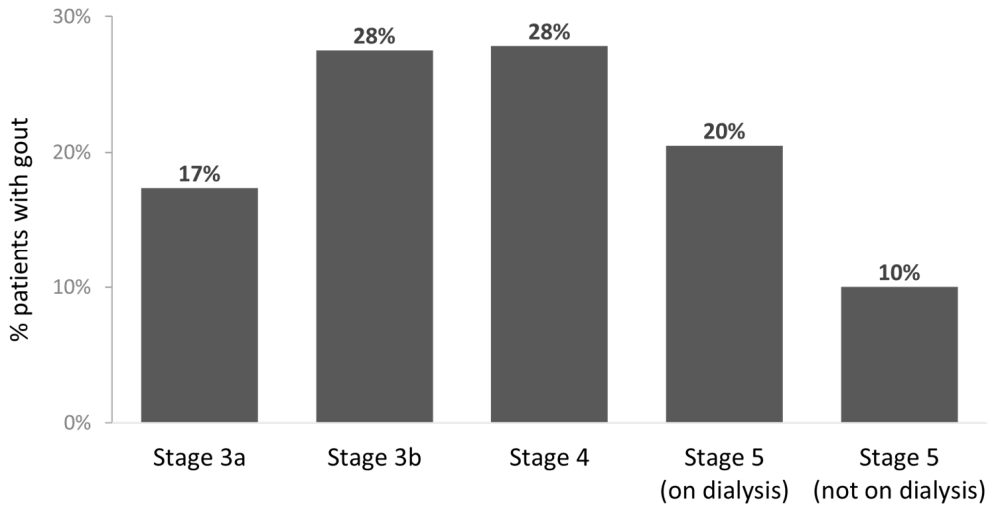

Figure 1. Prevalence of identified gout by CKD stage in a US advanced CKD population. Patients were said to have gout if any of the following were true: gout listed as a comorbidity, urate-lowering therapy use noted, or clinical evidence of gout present (tophi or acute gout flare).

Baseline characteristics of patients with and without gout were similar, but significantly more gout patients had diagnoses of CKD-mineral bone disorder (40% vs. 26%, $p < 0.001$), ischemic heart disease (23% vs. 13%, $p = 0.004$), congestive heart failure (21% vs. 14%, $p < 0.001$), peripheral vascular disease (15% vs. 9%, $p = 0.03$), and chronic back pain (13% vs. 6%, $p = 0.008$; Table 2). Despite similar demographics, mean eGFR, CKD duration, and comorbidity profile, patients with gout had higher HbA1c levels (7.5 $\pm$ 1.40 vs. 7.1 $\pm$ 1.38 mmol/mol, $p = 0.02$) than patients without gout. PTH levels also

tended to be higher in gout patients (172.1 ± 163.1 vs. 155.3 ± 142.1 pg/mL, $p = 0.31$). Further, at the first presentation to the reporting nephrologist, gout patients had shortness of breath (21% vs. 14%, $p = 0.02$), urination changes (15% vs. 7%, $p = 0.001$), and joint symptoms (chronic tenderness, chronic swelling, damage, and/or joint loss of flexibility; 16% vs. 7%, $p < 0.001$) more often.

Table 2. Characteristics of CKD patients with and without gout.

	No Gout (N = 573)	Gout (N = 173)	*p* Value *
Male, n (%)	318 (55%)	91 (53%)	0.50
Patient age, years, mean ± SD	55.6 ± 18.4	58.3 ± 18.1	0.09
≥65 years old, n (%)	198 (35%)	72 (42%)	0.09
Race/ethnicity, n (%) (N = 562, 172)			>0.999
Caucasian	239 (43%)	78 (45%)	
Black	176 (31%)	37 (22%)	
Hispanic	68 (12%)	29 (17%)	
Asian American	39 (7%)	19 (11%)	
Multi-racial	20 (4%)	4 (2%)	
Other †	19 (3%)	5 (3%)	
BMI, kg/m^2, mean ± SD (N = 557, 170)	31.4 ± 10.6	32.0 ± 11.8	0.53
BMI ≥30 kg/m^2, n (%)	244 (44%)	74 (44%)	0.95
eGFR, mL/min/1.73 m^2, mean ± SD	32.2 ± 15.9	32.3 ± 13.9	0.94
Kidney disease duration, years, mean ± SD	4.0 ± 4.6	4.1 ± 5.5	0.81
Comorbidities			
Hypertension (N = 572, 168)	452 (79%)	142 (85%)	0.16
Anemia of CKD	208 (37%)	73 (42%)	0.16
CKD-mineral bone disorder (N = 560, 167)	147 (26%)	69 (40%)	<0.001
Ischemic heart disease (N = 572, 172)	77 (13%)	39 (23%)	0.004
Degenerative joint disease (N = 547, 167)	53 (10%)	29 (17%)	0.01
Diabetes mellitus	250 (44%)	81 (47%)	0.46
Congestive heart failure	82 (14%)	37 (21%)	<0.001
Peripheral vascular disease (N = 562, 163)	53 (9%)	25 (15%)	0.03
COPD (N = 557, 164)	37 (7%)	16 (10%)	0.18
Pulmonary hypertension (N = 546, 157)	26 (5%)	8 (5%)	0.86
Gout listed as comorbidity, n (%) (N = 573, 172)	0	110 (64%)	----
Serum urate, mg/dL, mean ± SD	6.0 ± 1.4	6.6 ± 4.6	0.01
Gout symptoms in the prior year, n (%)			
Acute gout flare ‡ (N = 88, 135)	20 (23%)	80 (59%)	<0.001
Chronic pain (N = 79, 120)	18 (23%)	40 (33%)	0.11
Chronic back pain (82, 117)	15 (18%)	38 (32%)	0.03
Swollen or tender joints (N = 22, 25)	9 (41%)	19 (76%)	0.01

* two-tailed *p*-value, calculated using a *t*-test for continuous parameters and a chi-square test for categorical parameters. BMI, body mass index. † includes Native American, Native Hawaiian/Pacific Islander, Middle Eastern/North African. ‡ ≥2 acute gout flares needed for gout classification.

3.3. Comparison of Patients with Controlled and Uncontrolled Gout

Of the 173 gout patients identified, 23 (13%) met the study criteria for having uncontrolled gout. Of these, five patients (22%) did not have a formal diagnosis of gout (not listed as a comorbidity). Patients with controlled and uncontrolled gout had similar demographics, mean eGFR, and CKD stage distribution (Table 3). However, patients with uncontrolled gout tended to be older, had CKD for longer, and had a different distribution of primary CKD etiology. Comorbidity prevalence was also similar, except that pulmonary hypertension (14% vs. 4%, $p = 0.04$) was present significantly more often, and diabetes (27% vs. 50%, $p = 0.03$) was present significantly less often in patients with uncontrolled gout (Table 3). Patients meeting the criteria for uncontrolled gout experienced ≥2 gout flares in the prior year (48% vs. 26%, $p = 0.0495$) and tended to have degenerative joint

disease (32% vs. 15%, $p = 0.06$) more often than patients with controlled gout. Further, a higher proportion of uncontrolled vs. controlled gout patients were using febuxostat (43% vs. 14%, $p < 0.001$) and colchicine (26% vs. 7%, $p = 0.005$).

Table 3. Characteristics of advanced CKD patients with controlled and uncontrolled gout.

	Controlled Gout (n = 150)	Uncontrolled Gout * (n = 23)	*p*-Value †
Age, years, mean ± SD	57.6 ± 18.3	63.1 ± 16.4	0.17
Male, n (%)	79 (53%)	12 (52%)	0.97
Serum urate, mg/dL, mean ± SD	6.0 ± 1.3	9.7 ± 10.5	0.13
CKD duration, years, mean ± SD	3.9 ± 5.5	5.5 ± 5.1	0.18
eGFR, mL/min/1.73 m^2, mean ± SD	32.3 ± 13.8	32.0 ± 14.6	0.94
CKD stage			0.31
Stage 3a	28 (19%)	6 (26%)	
Stage 3b	58 (39%)	8 (35%)	
Stage 4	46 (31%)	6 (26%)	
Stage 5	18 (12%)	3 (13%)	
Primary CKD etiology, n (%)			<0.001
Gout	2 (1%)	9 (39%)	
Hypertension	65 (43%)	6 (26%)	
Glomerulonephritis	10 (7%)	4 (17%)	
Diabetes mellitus	46 (31%)	4 (17%)	
Hereditary nephritis	3 (2%)	0 (0%)	
Unknown	24 (16%)	0 (0%)	
Comorbidities			
Hypertension (N = 145, 23)	122 (84%)	20 (87%)	0.73
Anemia of CKD	65 (43%)	8 (35%)	0.44
CKD-mineral bone disorder (N = 144, 23)	61 (42%)	8 (35%)	0.49
Ischemic heart disease (N = 149, 23)	31 (21%)	8 (35%)	0.136
Degenerative joint disease (N = 145, 22)	22 (15%)	7 (32%)	0.07
Diabetes mellitus	75 (50%)	6 (26%)	0.03
Congestive heart failure	32 (21%)	5 (22%)	0.97
Pulmonary hypertension (N = 136, 21)	5 (4%)	3 (14%)	0.04
Gout-related medication use (N = 148, 23)			
Colchicine	11 (7%)	6 (26%)	0.005
Any ULT, n (%)	86 (58%)	23 (100%)	<0.001
Allopurinol	66 (45%)	12 (52%)	0.50
Febuxostat	20 (14%)	10 (43%)	<0.001
Pegloticase	1 (0.7%)	2 (9%)	0.006
Probenecid	1 (0.7%)	0 (0%)	0.69

* uncontrolled gout defined as most recent serum urate level ≥6 mg/dL and ≥1 sign of gout present (tophi noted, ≥2 acute gout flares in the prior year, or ≥1 tender or swollen joint). † two-tailed *p*-value determined using *t*-tests for continuous parameters, and chi-square tests for categorical parameters and distributions. ULT: urate-lowering therapy. CKD: chronic kidney disease; SD: standard deviation.

4. Discussion

The current study found that 23% of CKD patients met the study gout criteria. This is in agreement with a large US population database (NHANES) study, which found a gout prevalence of 24% in patients with an eGFR <60 mL/min/1.73 m^2 [8]. Unlike the typical gout population, which is predominantly male, nearly half (47%) of CKD patients with gout were female, indicating that women with CKD may be at similar risk as men for developing gout. We also found that despite similar demographic characteristics and kidney function, gout patients had a higher prevalence of ischemic heart disease and congestive heart failure. These findings are consistent with general population studies showing independent associations between gout and cardiovascular disease [11,16], including coronary artery disease [3,17], coronary artery calcification (CAC) severity [18], and heart failure [11,19]. Because all included patients in the current study had CKD, a well-known risk factor for cardiovascular disease [20], our findings suggest that gout may impose added risk on CKD patients. The possibly synergistic impact of gout and CKD on CAC may contribute as CAC scores are positively correlated with rates of cardiovascular hospitalization and all-cause death [21].

The current study found that CKD patients with gout have higher prevalences of CKD-metabolic bone disease and degenerative joint disease, indicating that these patients may be

particularly vulnerable to bone and joint damage. Prior studies reported higher PTH levels with hyperuricemia in patients with [22–24] and without [24–26] CKD, possibly due to the suppression of 1α-hydroxylase [27]. However, the causative factor in this relationship remains unclear as PTH may inhibit renal urate excretion [24]. Given that approximately one-quarter of CKD patients had gout (both in the current and prior [8] study), monitoring for and properly managing gout may be another important opportunity for improving bone and joint health in CKD patients.

Approximately one in eight patients (13%) who met the study criteria for gout had uncontrolled gout (SU > 6 mg/dL with ≥2 flares in the previous year, tophi, and/or chronic gouty arthritis). Controlled and uncontrolled gout patients had overall similar demographics, comorbidity profile, and kidney function, but uncontrolled gout patients had a higher prevalence of pulmonary hypertension (14% vs. 4%). Patients with uncontrolled gout also had more gout signs than those with the controlled disease, including a higher prevalence of degenerative joint disease and higher incidence of gout flares, also reflected in the significantly higher use of colchicine (26% vs. 7%) and the second-line ULT febuxostat (43.5% vs. 13.5%). Given colchicine's worse toxicity profile in CKD patients, this highlights the need for better preventive care with ULT to minimize the need for flare treatment with potentially harmful anti-inflammatory medications [12]. Further, a recent study revealed that gout patients are at the highest risk for a cardiovascular event in the 120 days following acute gout flare [28].

This study had several limitations, largely resulting from its retrospective and cross-sectional nature. First, observed differences between patients with and without gout cannot be used to determine causality. Therefore, further longitudinal studies examining the influence of gout and its medical management in CKD patients over time are warranted. Second, medical record data were collected via a nephrologist survey and are, therefore, subject to a recall bias. However, physicians were asked to provide data on their most recently seen advanced CKD patients and were not told that this study would focus on gout, both of which should have minimized the impact of such biases on study findings [29]. Third, medical record data were only reported on by each patient's managing physician and were not adjudicated. Therefore, physician judgment may have influenced data accuracy. However, the large number of physician participants and the large number of included patients should have minimized the overall influence of any physician judgment errors. Fourth, nephrologists sometimes use oral ULT to treat asymptomatic hyperuricemia in the absence of gout. Because all patients who used a ULT were assumed to have gout, with nearly three-quarters of gout patients using ULT, it is possible that some non-gout patients were labeled as having gout. However, asymptomatic hyperuricemia in CKD patients is not universally treated [14]. Further, including such patients in the gout group would dilute gout-related differences, resulting in an underreporting of any potential impact on outcomes. It should also be noted that the risks/benefits of ULT use in the CKD population as a whole could not be evaluated here. Fifth, because the criteria for uncontrolled gout required ongoing gout signs/symptoms, it was possible for patients with an SU ≥6 mg/dL to be included in the "controlled gout" population. In fact, approximately one-third of the controlled gout group had an SU between 6 and 7 mg/dL. This limitation could have also led to an underestimation of differences between patients with controlled and uncontrolled gout. Lastly, the number of patients meeting the study criteria for uncontrolled gout was small, and further study is needed on a larger population with coincident advanced CKD and uncontrolled gout.

In conclusion, these data suggest that gout negatively impacts cardiovascular and bone health in patients with advanced CKD, with uncontrolled gout adding additional health burden. Importantly, over one-third of patients with gout signs and symptoms and/or taking a ULT did not have a formal gout diagnosis in the medical record, and over one-third of patients who had a gout diagnosis were not receiving a ULT. In addition to avoiding the painful and debilitating joint sequelae of untreated gout, our data suggest

that improved management of gout in CKD patients could also represent an important opportunity to improve overall patient health and well-being.

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Institutional Review Board Statement: This retrospective study was conducted in accordance with the Declaration of Helsinki, and approved by the Advarra IRB (registration number: 00000971, Columbia, MD; protocol code: Pro00045280, date of approval: 22 July 2020). The study was assigned exempt status, waiving the requirement of informed consent.

Informed Consent Statement: The study was assigned exempt status, waiving the requirement of informed consent.

Data Availability Statement: Horizon is committed to responsibly sharing data from the studies we sponsor. Data may be requested by submitting a research proposal and Statistical Analysis Plan and will be provided following review and approval of the plan and execution of a Data Sharing Agreement. For more information, or to submit a request, please submit to medicalinformation@horizontherapeutics.com.

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Conflicts of Interest: L. Stern has received consulting and speaker fees from Horizon. R. J. Johnson is a consultant and paid speaker for Horizon* and has an ownership interest in Colorado Research Partners LLC and XORTX Therapeutics. P. Shakouri is a consultant for Horizon* and a paid speaker for Horizon* and Relypsa. A. Athavale is an employee of Trinity Life Sciences, who was contracted by Horizon* for assistance with study design, survey design, survey implementation, data collection, and data analysis. B. LaMoreaux and B. Marder are employees of and hold stock in Horizon. S. Mandayam has ownership interest in Medingenii Capital LLC and Prosalus Capital LLC, has received research funding from Travere, Norvartis, Omeros, Roche, Vertex, Equillium, Goldfinch Bio, and Pfizer, is a scientific advisor for US Renal Care and Aurinia, and is a speaker for Otsuka and Alexion. *Horizon (now Amgen, Inc.).

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