

# Effect of Urate-lowering Therapies on Renal Disease Progression in Patients with Hyperuricemia

Gerald D. Levy, Nazia Rashid, Fang Niu, and T. Craig Cheetham

**ABSTRACT. Objective.** To evaluate the association between hyperuricemia and renal disease progression in a real-world, large observational database study.

**Methods.** We conducted a population-based retrospective cohort study identifying 111,992 patients with hyperuricemia (> 7 mg/dl) from a large medical group. The final cohort were  $\geq 18$  years old, urate-lowering therapy (ULT)-naïve, and had the following laboratory results available: at least 1 glomerular filtration rate (GFR) level before the index date and at least 1 serum uric acid (sUA) level and GFR in the followup 36-month period. The cohort was categorized into 3 groups: never treated (NoTx), ULT time receiving therapy of < 80% (< 80%), and ULT time receiving therapy of  $\geq 80\%$  ( $\geq 80\%$ ). Outcomes were defined as a  $\geq 30\%$  reduction in GFR from baseline, dialysis, or GFR of  $\leq 15$  ml/min. A subanalysis of patients with sUA < 6 mg/dl at study conclusion was performed. Cox proportional hazards regression model determined factors associated with renal function decline.

**Results.** A total of 16,186 patients met inclusion criteria. There were 11,192 NoTx patients, 3902 with < 80% time receiving ULT, and 1092 with  $\geq 80\%$  time receiving ULT. Factors associated with renal disease progression were age, sex, hypertension, diabetes, congestive heart failure, hospitalizations, rheumatoid arthritis, and higher sUA at baseline. Time receiving therapy was not associated with renal outcomes. Patients who achieved sUA < 6 mg/dl had a 37% reduction in outcome events ( $p < 0.0001$ ; HR 0.63, 95% CI: 0.5-0.78).

**Conclusion.** Hyperuricemia is an independent risk factor for renal function decline. Patients treated with ULT who achieved sUA < 6 mg/dl on ULT showed a 37% reduction in outcome events. (First Release April 1 2014; J Rheumatol 2014;41:955–62; doi:10.3899/jrheum.131159)

## Key Indexing Terms:

URIC ACID

CHRONIC KIDNEY DISEASE

HYPERURICEMIA

URATE-LOWERING THERAPY

The prevalence of hyperuricemia and gout in the United States has been steadily increasing. Using data from the US National Health and Nutrition Examination Survey, Zhu, *et al* found a full percentage point increase in the prevalence of gout and a 3-point increase in hyperuricemia from 1988 to 2008<sup>1</sup>. The annual cost of gout in the United States is approaching \$1 billion in direct costs for healthcare and medications. In addition to those costs, millions more are lost in work and productivity<sup>2</sup>. Recent small studies have shown that hyperuricemia leads to progressive renal disease, where use of urate-lowering therapy (ULT) potentially stabilizes or ameliorates renal disease. Animal models suggest a biologic rationale for some of these changes and a possible mechanism for reducing the adverse effects of

hyperuricemia on the kidney. Our study expands on previous work with a much larger observational study performed in a real-world setting.

## MATERIALS AND METHODS

**Study population and design.** We conducted a population-based retrospective cohort study using patient data from Kaiser Permanente Southern California Health Plan (KPSCHP). The KPSCHP has ~3.6 million members, representing 15% of the population in Southern California. The membership closely mirrors the region's population regarding age, race, education, and socioeconomic<sup>3</sup>. KPSCHP maintains longitudinal data on patient demographics, diagnoses, prescriptions, laboratory results, outpatient visits, and hospitalizations in an extensive electronic medical health record. KPSCHP contracts exclusively with the Southern California Permanente Medical Group, a multispecialty medical practice with more than 5532 partner and associate physicians in 14 medical centers and 197 outpatient clinics in Southern California. Our study was approved by the institutional review board for KPSCHP.

All patients in the KPSCHP database with hyperuricemia, defined as a single serum uric acid (sUA) level of > 7 mg/dl, from January 1, 2002, to December 31, 2010, were identified. The first occurrence of sUA level > 7 mg/dl during the study period was designated as the index date. All subjects were required to have at least 12 months of KPSCHP membership with prescription benefits prior to the index date. Enrollment gaps of  $\leq 30$  days were considered continuous enrollment. All subjects met the following inclusion criteria: age  $\geq 18$  years at the index date, ULT-naïve (allopurinol, febuxostat, probenecid) for at least 12 months prior to index date; and laboratory results for at least 1 glomerular filtration rate (GFR) level in the

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6 months prior to the index date. During followup, defined as the index date plus 3 months to 36 months, patients had to have at least 1 GFR level and 1 sUA. Patients were followed for up to 3 years, ending no later than either December 31, 2011, the last GFR during the followup period, a study outcome, disenrollment, or death, whichever came first. Figure 1 shows the time line.

Patients were excluded if they had a history of dialysis, chronic kidney disease stage 4 (CKD4), CKD5, organ transplants, active cancer, human immunodeficiency virus, proteinuria, glomerulonephritis, or nephrolithiasis. GFR or sUA levels that were recorded from emergency room visits or hospital stays were excluded from the analysis because those levels can fluctuate significantly and often return to normal after the acute event has resolved. Baseline characteristics of age, sex, comorbid conditions, concomitant medication use, and renal risk factors were captured in the 12 months prior to the index date. Other factors such as time receiving ULT treatment and outcomes related to renal disease progression were evaluated during the postindex period. The cohort was divided into 3 groups: never treated, including patients who filled only 1 prescription (NoTx), < 80% time receiving therapy (< 80%), and ≥ 80% time receiving therapy (≥ 80%). Time receiving therapy was defined as  $100 \times [(\text{total days receiving ULT treatment}) / \text{total days of followup}]$ .

**Study outcomes.** The primary outcome in our study was renal disease progression, defined as any of the following: a reduction in GFR from baseline of ≥ 30%; initiation of dialysis; or GFR below 15 ml/min per 1.73 m<sup>2</sup> during the followup period. Subjects were further analyzed as to whether a final sUA < 6 mg/dl had an effect on outcome.

**Statistical analyses.** We compared baseline characteristics between ULT treatment groups versus the NoTx group using the Kruskal-Wallis test for continuous variables and the chi-square statistic for categorical variables. For study outcomes, a multivariate Cox proportional hazards model was used to estimate the HR for development of the renal disease progression. In the proportional hazards model we controlled for factors that are associated with the development of renal insufficiency such as age, heart disease, heart failure, hypertension (HTN), diabetes, concomitant prescribed medications (colchicine, nonsteroidal antiinflammatory drugs, or corticosteroids), and sUA levels at baseline. A p value ≤ 0.05 was used to indicate statistical significance. All data were analyzed using SAS version 9.2 (SAS Institute).

## RESULTS

We identified 111,992 patients with hyperuricemia with sUA > 7 mg/dl. Figure 2 provides detailed information on patient disposition after applying the inclusion and

exclusion criteria. The number of subjects was reduced because of the requirement of preindex and postindex date laboratory tests (GFR in the 6 months prior to the index date and both GFR and sUA in the followup period). This reduced the number of patients available for evaluation by 54,604, to a final cohort of 16,186 patients. In about 11% of the cohort, GFR was not calculated by the Kaiser laboratory, therefore the modification of diet in renal disease equation was used to obtain GFR<sup>4</sup>.

Applying the time on therapy calculation yielded 11,192 patients in the NoTx group, 3902 in the < 80% group, and 1092 in the ≥ 80% group. The baseline characteristics of the cohort are shown in Table 1. The ≥ 80% group patients were older and sicker, with a higher percentage of patients identified with gout than the NoTx and < 80% group. The ≥ 80% group were more likely to start ULT and did so earlier than the < 80% group. The median time to start ULT was 16 days in the ≥ 80% group compared to 159 days in the < 80% group. At 12 weeks, 91% of patients in ≥ 80% group were taking ULT compared to 39% patients in the < 80% group. Patient outcomes for the treatment groups are shown in Table 2. There were significant differences for outcome events, sUA levels at baseline, sUA last value, net decrease in sUA levels over the course of the study, and percentage of patients achieving sUA level of < 6 mg/dl. sUA levels dropped from the index date in all groups, with the largest change, 3.1 mg/dl, seen in the ≥ 80% group (p < 0.0001). In the ≥ 80% group, over 53% achieved sUA < 6 mg/dl compared to only 27.9% in the < 80% group and 21.9% in the NoTx group.

Table 3 shows the multivariate Cox proportional hazards model values with statistically significant predictors of renal decline for female sex (HR 1.49, 95% CI 1.25–1.78; p < 0.0001), increasing age (HR 1.03, 95% CI 1.01–1.04; p < 0.0001), higher sUA at baseline (HR 1.11, 95% CI 1.04–1.19; p < 0.0027), diabetes (HR 1.96, CI 1.64–2.35; p < 0.0001), HTN hypertension (HR 1.50, 95% CI

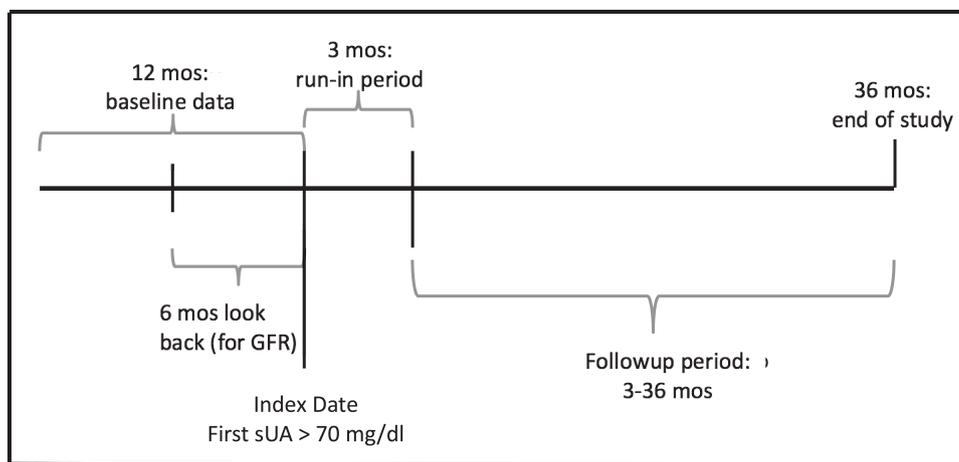


Figure 1. Study time line. GFR: glomerular filtration rate; sUA: serum uric acid.

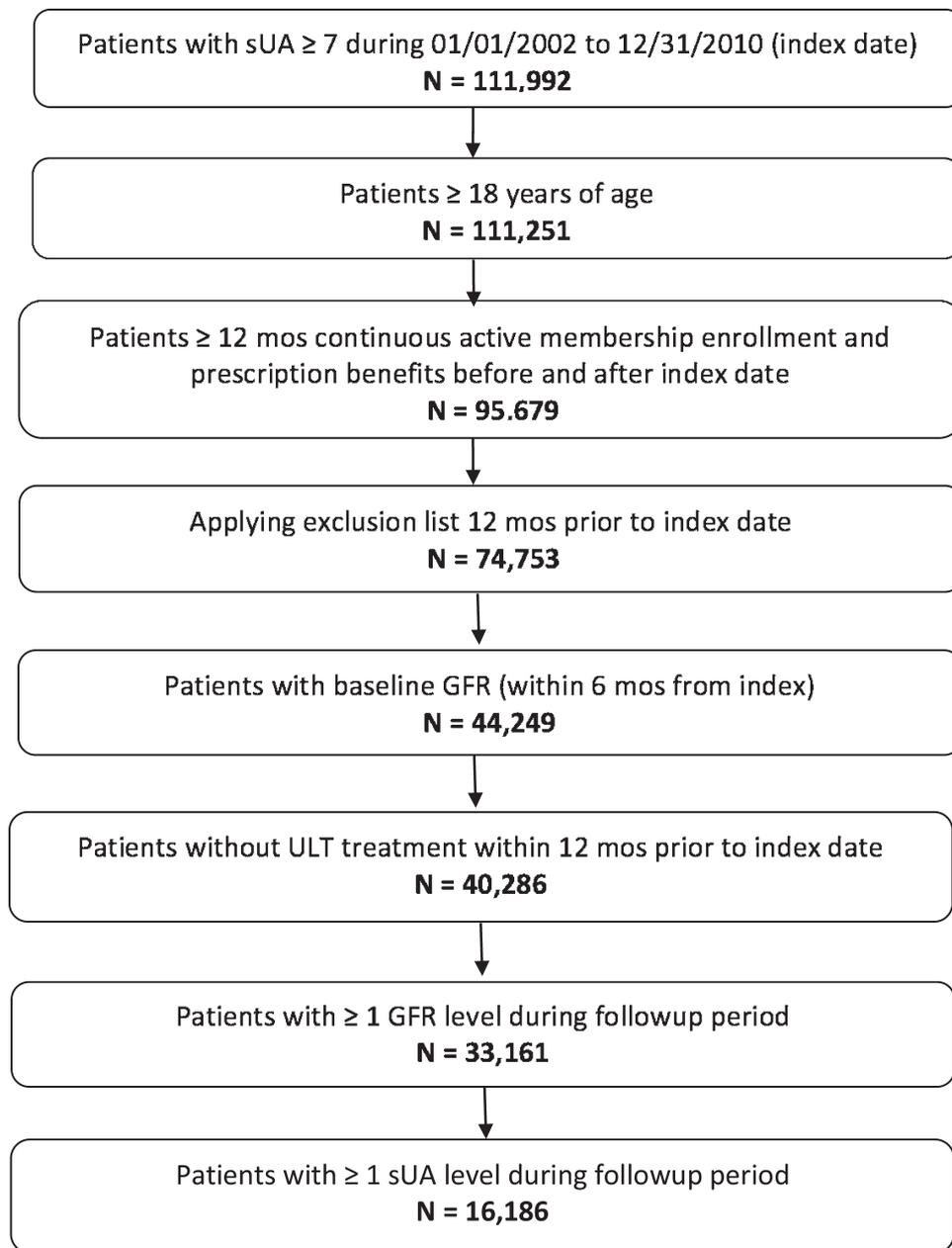


Figure 2. Details of the study sample. GFR: glomerular filtration rate; sUA: serum uric acid; ULT: urate-lowering therapy.

1.17–1.92;  $p < 0.0015$ ), congestive heart failure (HR 1.39, 95% CI 1.04–1.84;  $p < 0.0256$ ), and hospitalizations (HR 1.33, 95% CI 1.12–1.59;  $p < 0.0014$ ). In the  $\geq 80\%$  group there was not an increased risk for renal outcomes (HR 1.08, 95% CI 0.76–1.52;  $p = 0.68$ ). Clinically, the most significant finding was those patients who achieved sUA  $< 6$  mg/dl who showed a 37% reduction in outcome events (HR 0.63, 95% CI 0.5–0.78;  $p < 0.0001$ ).

## DISCUSSION

We evaluated the effect of ULT on renal disease progression and the factors associated with renal disease progression in patients with hyperuricemia. We found that patients who achieved an sUA of  $< 6$  mg/dl with ULT were 37% less likely to have renal disease progression. This is consistent with previous smaller studies on hyperuricemia and renal disease. Iseki, *et al*<sup>5</sup> screened 6403 patients from the

Table 1. Patient baseline characteristics for treatment groups.

Characteristics	Never Taking Therapy, n = 11,192	< 80% Time Taking Therapy, n = 3902	≥ 80% Time Taking Therapy, n = 1092	Total Patients, n = 16,186	p
No. days during followup, mean (SD)	746.9 (275.89)	804.8 (253.31)	751.7 (279.25)	761.2 (271.95)	
Male, n (%)	6802 (60.8)	2746 (70.4)	739 (67.7)	10287 (63.6)	< 0.001
Age, yrs, mean (SD)	57.6 (14.10)	60.8 (12.63)	65.0 (11.38)	58.9 (13.76)	< 0.001
Age, yrs, n (%)					< 0.001
≤ 50	3346 (29.9)	796 (20.4)	116 (10.6)	4258 (26.3)	
51–60	2985 (26.7)	1068 (27.4)	243 (22.3)	4296 (26.5)	
61–70	2713 (24.2)	1117 (28.6)	380 (34.8)	4210 (26)	
> 70	2148 (19.2)	921 (23.6)	353 (32.3)	3422 (21.1)	
Race, n (%)					< 0.001
White	4913 (43.9)	1455 (37.3)	580 (53.1)	6948 (42.9)	
Black	2103 (18.8)	858 (22)	158 (14.5)	3119 (19.3)	
Hispanic	1641 (14.7)	508 (13)	92 (8.4)	2241 (13.8)	
Asian	1171 (10.5)	651 (16.7)	146 (13.4)	1968 (12.2)	
Other	1364 (12.1)	430 (11.0)	116 (10.7)	1910 (11.8)	
Laboratory data, mean (SD)					
sUA level, mg/dl, index date	8.1 (1.02)	8.9 (1.30)	9.2 (1.43)	8.3 (1.20)	< 0.001
GFR, ml/min/1.72 m <sup>2</sup>	70.5 (16.07)	67.1 (16.10)	61.7 (16.07)	69.1 (16.26)	< 0.001
Initial ULT, n (%)					
Allopurinol	0 (0)	3830 (98.2)	1080 (98.9)	4910 (98.3)	
Febuxostat	0 (0)	4 (0.1)	0 (0)	4 (0.1)	
Probenecid	0 (0)	68 (1.7)	12 (1.1)	80 (1.6)	
Days taking therapy, mean (SD)	0 (0)	268.1 (202.64)	689.4 (262.07)	360.3 (278.23)	
Comorbidities of population, n (%)					
CV-related diseases	1475 (13.2)	627 (16.1)	235 (21.5)	2337 (14.4)	< 0.001
Diabetes mellitus	2251 (20.1)	754 (19.3)	278 (25.5)	3283 (20.3)	< 0.001
Dyslipidemia	5192 (46.4)	1913 (49)	625 (57.2)	7730 (47.8)	< 0.001
Gout	1732 (15.5)	1583 (40.6)	465 (42.6)	3780 (23.4)	< 0.001
Heart failure	430 (3.8)	221 (5.7)	104 (9.5)	755 (4.7)	< 0.001
Hypertension	7484 (66.9)	2849 (73)	895 (82)	11228 (69.4)	< 0.001
Obesity	3848 (34.4)	876 (22.5)	267 (24.5)	4991 (30.8)	< 0.001
Osteoarthritis	1827 (16.3)	691 (17.7)	254 (23.3)	2772 (17.1)	< 0.001
Rheumatoid arthritis	109 (1)	41 (1.1)	17 (1.6)	167 (1)	0.19
Concomitant medications, n (%)					
Corticosteroids	1542 (13.8)	693 (17.8)	197 (18)	2432 (15)	< 0.001
Colchicine	710 (6.3)	688 (17.6)	226 (20.7)	1624 (10)	< 0.001
NSAID	5030 (44.9)	2418 (62)	582 (53.3)	8030 (49.6)	< 0.001
Hospitalizations, n (%)	3366 (30.1)	1139 (29.2)	320 (29.3)	4825 (29.8)	0.54
Gout diagnosis at index date	1665 (14.9)	1838 (41)	464 (43.1)	3967 (23.7)	

sUA: serum uric acid; GFR: glomerular filtration rate; ULT: urate-lowering therapy; CV: cardiovascular; NSAID: nonsteroidal antiinflammatory drug.

Okinawa General Health Maintenance Association for hyperuricemia (> 8 mg/dl) and then followed them over a 2-year period for the development of renal failure, defined as a serum creatinine level  $\geq 1.4$  in men and  $\geq 1.2$  in women. The relative risk of progression from normal serum creatinine to elevated ( $\geq 1.4$  in men and  $\geq 1.2$  in women) was 2.91 (1.79–4.75) in men and 10.39 (1.91–56.62) in women. Obermayr, *et al*<sup>6</sup> followed 21,475 healthy volunteers for 7 years to evaluate the potential for incident kidney disease based on elevation of sUA. For patients with mild to moderate hyperuricemia ( $\geq 7$ –8.9 mg/dl), the OR for incident kidney disease was 1.74 (1.45–2.09), and in those with marked hyperuricemia (> 9 mg/dl), the OR for incident

renal disease was 3.12 (2.29–4.25). Weiner, *et al* also found that elevated sUA levels were a risk factor for incident kidney disease (a decrease in GFR of  $\geq 15$  ml/min/1.73 m<sup>2</sup> or an increase in creatinine of  $\geq 0.4$  mg/dl)<sup>7</sup>. Talaat and el Sheikh reported that withdrawing allopurinol from 50 patients with stage 3 and 4 CKD caused worsening of HTN and acceleration of loss of renal function<sup>8</sup>. These studies support an association between elevated sUA levels and renal dysfunction.

Small human studies have explored whether treatment with ULT can slow or reverse the adverse effects of hyperuricemia on the kidney. Gibson evaluated 59 patients taking colchicine who were then randomized to colchicine only or

Table 2. Patient outcomes for treatment groups.

Patient Outcomes	Never Taking Therapy, n = 11,192	< 80% Time Taking Therapy, n = 3902	≥ 80% Time Taking Therapy, n = 1092	Total Patients, n = 16,186	p
Primary outcome, n (%)	350 (3.1)	188 (4.8)	42 (3.8)	580 (3.6)	< 0.0001*
Primary outcome category, n (%)	n = 350	n = 188	n = 42	n = 580	0.33*
30% reduction in GFR level from baseline	347 (99.1)	185 (98.4)	42 (100)	574 (99)	
GFR level < 15 ml/min/1.72 m <sup>2</sup> or dialysis	3 (0.9)	3 (1.6)	0 (0)	6 (1)	
Median followup, days	812	885	822	831	
Development of other outcomes, n (%)	n = 11,192	n = 3902	n = 1092	n = 16,186	< 0.0001*
Development of cancer	40 (0.4)	24 (0.6)	4 (0.4)	68 (0.4)	
Death	146 (1.3)	42 (1.1)	9 (0.8)	197 (1.2)	
Glomerular nephritis	813 (7.3)	348 (8.9)	135 (12.4)	1296 (8)	
Other transplant	10 (0.1)	1 (0)	1 (0.1)	12 (0.1)	
No outcomes	10176 (90.9)	3485 (89.3)	940 (86.1)	14601 (90.2)	
sUA level	n = 11,192	n = 3902	n = 1092	n = 16,186	
sUA level, mg/dl, at baseline	8.1 (1.02)	8.9 (1.30)	9.2 (1.43)	8.3 (1.20)	< 0.0001**
sUA level, mg/dl, mean (SD) last value	7.2 (1.58)	7.2 (1.76)	6.0 (1.40)	7.1 (1.64)	< 0.0001**
Net decrease in sUA	0.9 (1.59)	1.7 (1.98)	3.1 (1.78)	1.2 (1.82)	< 0.0001**
At goal, < 6 mg/dl, n (%)	2447 (21.9)	1088 (27.9)	584 (53.5)	4119 (25.4)	< 0.0001**

\*Fisher's exact test, comparing never treated vs ≥ 80%. \*\*Kruskal-Wallis test. sUA: serum uric acid; GFR: glomerular filtration rate.

allopurinol plus colchicine over a 2-year period. In the colchicine-only control group, 12/33 (37%) had a decline in GFR by ≥ 10 ml/min/1.73 m<sup>2</sup> compared to 2/26 (9%) in the allopurinol group with similar decrease in GFR<sup>9</sup>. Siu, *et al* screened patients with stable renal disease for hyperuricemia defined as sUA > 7.6 mg/dl. After excluding patients with gout, renal stones and advanced renal disease, they identified 54 patients who were then randomly assigned to treatment with active allopurinol management or control (usual therapy)<sup>10</sup>. In the treatment group, 21/25 patients (84%) had stable renal function versus 14/26 (54%) in the control group, and 3/25 (12%) of patients in the treatment group had worsening renal function versus 11/26 (42.3%) in the control group. In the study by Goicoechea, *et al*, patients with hyperuricemia were randomly assigned to either low-dose (100 mg) allopurinol or placebo. The GFR in the treated group improved by 1.3 ml/min/1.73 m<sup>2</sup> compared to a decline in the control group of 3.3 ml/min/1.73 m<sup>2</sup>, p = 0.0001<sup>11</sup>. A retrospective US Veterans Administration study of 100 patients with hyperuricemia (sUA ≥ 7 mg/dl) compared patients who received an average of 221 mg/day of allopurinol to those with hyperuricemia that was not treated (controls). The active group showed reduction in sUA compared to controls (p < 0.001), with a significant improvement in creatinine clearance of 12.9 ml/min compared to controls (p = 0.037)<sup>12</sup>. Kanbay, *et al* found that treating patients with a 3-month course of allopurinol improved sUA, blood pressure, C-reactive protein, and GFR compared to the control group (p < 0.05)<sup>13</sup>. They found that hyperuricemia may increase blood pressure and decrease GFR and recommended early treatment with allopurinol in the management of CKD. These studies suggest

that kidney disease is potentially reversible and the changes may occur relatively soon after starting ULT. That is the reason we started our evaluation at the index date plus 3 months and then followed the patients for 36 months.

The use of ULT to prevent kidney disease has biological foundations in animal studies from the number of direct effects that hyperuricemia has on the kidney. Mazzali, *et al* used a uricase inhibitor, oxonic acid, to induce hyperuricemia in rats<sup>14</sup>. Tubulo-interstitial changes were seen without crystals on light microscopy. Importantly, rats that received allopurinol showed less renal fibrosis and a normalization of blood pressure. Kang, *et al* showed similar findings in rats treated with oxonic acid, with half of the group receiving concomitant allopurinol. The allopurinol group did not show renal hypertrophy, glomerulosclerosis, and interstitial fibrosis compared to the control rats<sup>15</sup>.

Our study has several strengths. We were able to study a large and diverse population of insured members, with expanded criteria to include not just patients with a gout diagnosis but all patients with an elevated sUA. This is underscored by the fact that only 41% (2048/4994) of the patients taking ULT had a gout diagnosis. We followed patients for the time period most likely to show changes, from 3 months post index date to 3 years (median 27 months), with a conservative definition of worsening renal function based on a decline in GFR of ≥ 30 ml/min per 1.73 m<sup>2</sup> renal failure or onset of dialysis.

Several weaknesses need to be considered when interpreting our results. As an observational study, we did not have all the data points one might like. Patients were eligible with a single elevated sUA value and a single sUA and GFR in the followup period. We also lost a significant number of

Table 3. Factors associated with reaching an outcome from Cox proportional hazards model.

Patient Characteristics	HR	95% CI	p
Female sex	1.49	1.25–1.78	< 0.0001
Age, yrs	1.03	1.02–1.04	< 0.0001
Race			
White reference group	1.00	1.00	
Black	0.85	0.64–1.14	0.2868
Hispanic	1.05	0.85–1.31	0.6406
Asian	0.94	0.71–1.24	0.6473
Other	1.41	1.07–1.86	0.0141
Time taking therapy			
< 80% vs never taking therapy	1.27	1.05–1.55	0.0142
≥ 80% vs never taking therapy	1.08	0.76–1.52	0.6815
Laboratory data			
Baseline sUA level	1.11	1.04–1.19	0.0027
sUA at goal vs not at goal	0.63	0.50–0.78	< 0.0001
Baseline GFR level	1.01	0.99–1.01	0.1211
Comorbidities			
CV-related diseases	1.15	0.93–1.42	0.2130
Diabetes mellitus	1.96	1.64–2.35	< 0.0001
Dyslipidemia	0.92	0.77–1.12	0.3942
Gout	0.99	0.81–1.24	0.9922
Heart failure	1.39	1.04–1.84	0.0256
Hypertension	1.50	1.17–1.92	0.0015
Obesity	0.96	0.79–1.18	0.7068
Osteoarthritis	1.05	0.86–1.29	0.6181
Rheumatoid arthritis	1.46	0.84–2.54	0.1857
Concomitant medications			
Corticosteroids	0.92	0.73–1.17	0.4923
Colchicine	1.08	0.82–1.42	0.5823
NSAID	0.85	0.72–1.01	0.0692
Hospitalizations	1.33	1.12–1.59	0.0014
Role of therapy and treat to target goal < 6 mg/dl			
< 80% time receiving drug vs no TX	1.27	1.05–1.55	0.01
≥ 80% time receiving drug vs no TX	1.08	0.76–1.52	0.68
sUA at goal vs not at goal	0.63	0.5–0.78	< 0.0001

sUA: serum uric acid; GFR: glomerular filtration rate; CV: cardiovascular; NSAID: nonsteroidal antiinflammatory drug; TX: treatment.

patients who did not have laboratory tests for serum creatinine and sUA during the followup period and were therefore not eligible for the analysis. It is possible that this introduced a bias into the study if those patients had characteristics that made them more or less likely to have an outcome. With few data points, a number of patients in the NoTx group showed reductions in their sUA over time. This likely represents variation of the sUA test as it relates to hydration, diet, and other factors. Future studies may use more stringent criteria, with multiple values for identifying patients who are hyperuricemic. Patients with a single prescription were considered NoTx because it was not possible to determine whether any tablets were taken and a single prescription over the 36-month followup period was not considered significant. We selected an 80% time receiving treatment criterion for the analysis based on the belief that patients needed to be taking ULT on a regular basis for benefits to accrue. In sensitivity analyses we selected several different cutpoints for time receiving

therapy (i.e., 60%, 50%) and the results remained the same (data not shown). In epidemiologic studies, compliance of 80% is a commonly used threshold.

All treatment groups had patients whose final sUA was < 6 mg/dl including the NoTx group. This group started with a lower initial sUA compared to the other 2 groups and it is possible that variation in the testing may account for the small number with a terminal value < 6 mg/dl (22% in the NoTx group vs 53% in the ≥ 80% group). We did not evaluate patients with CKD4 and CKD5 for several reasons. Many physicians are reluctant to push ULT to target dosing, even with dosage guidance from a recent paper by Stamp and Chapman<sup>16</sup>. Dosing of ULT with GFR < 30 ml/min/1.73 m<sup>2</sup> is more complex, and in the KPSCHP system more than 90% of patients who are hyperuricemic are treated by primary care physicians. The raw data show that patients with more advanced renal disease experienced more outcome events — 4.8% in CKD3 compared to 2.7% in CKD1. Within each CKD band those patients who achieved

sUA < 6 mg/dl had fewer outcome events than those who did not (Table 4). Body mass index values were not available within our database until 2007, leaving the diagnosis of obesity dependent on physician coding. Our finding that obesity was not a predictor of renal decline is probably due to the incomplete data as opposed to a true finding. Other authors have found obesity to be an independent predictor of hyperuricemia and gout<sup>7,17,18</sup>. Finally, owing to the “observational” nature of our study and the lack of paired laboratory tests, the initial pool of over 111,000 subjects was reduced to a final cohort of 16,186 subjects. With improvements in documentation it is possible for future studies to have significantly less patient loss, making more of them available for analysis.

The results showed that patients in the  $\geq 80\%$  group did not benefit from ULT therapy (HR 1.08, 95% CI 1.05–1.55), but for those patients whose sUA was < 6 mg/dl there was a significant reduction in the progression of renal disease (HR 0.63, 95% CI 0.5–0.78;  $p < 0.0001$ ). We chose < 6 mg/dl to be consistent with the recently released American College of Rheumatology Treat to Target guidelines for the prevention of gout attacks<sup>19</sup>. Our study explores the potential benefit of initiating ULT on renal disease progression and confirms earlier, smaller studies showing that sUA is an independent and potentially reversible risk factor for progressive renal function decline. Patients who achieved sUA < 6 mg/dl showed a 37% reduction in outcome events defined as GFR decline of  $\geq 30\%$  or endstage renal disease. Physicians traditionally wait for a second gout attack before initiating ULT with the idea of sparing the patient 1 to 2 years of medication. Our study and others have shown that hyperuricemia is not a benign condition.

In addition to reduction in gout attacks there may be potential renal and cardiac benefits with treatment of hyperuricemia<sup>20</sup>. The preponderance of evidence suggests that ULT should be considered at the time of the first confirmed gout attack and possibly in patients with significant hyperuricemia. Randomized controlled trials are required to determine whether the adverse effects of hyperuricemia are reversible at more severe kidney disease (CKD4/CKD5) and whether the risk/benefit calculation favors treating asymptomatic hyperuricemia.

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Table 4. Baseline renal function group by outcome, then goal. Except for p values, data are n (%).

	CKD3 (30–60)** 4803 (29.7)	CKD2 (60–89)** 8212 (50.7)	CKD1 (> 89)** 3171 (19.6)	Total 16,186	p*
Outcome? Yes	231 (4.8)	264 (3.2)	85 (2.7)	580 (3.6)	0.52
Had sUA < 6	39 (16.9)	51 (19.3)	19 (22.4)	109 (19.8)	
Had sUA $\geq$ 6	192 (83.1)	213 (80.7)	66 (77.6)	471 (81.2)	
Outcome? No	4572 (95.2)	7948 (96.8)	3086 (97.3)	15,606 (96.4)	< 0.0001
Had sUA < 6	1036 (22.7)	2054 (25.8)	920 (29.8)	4010 (25.7)	
Had sUA $\geq$ 6	3536 (77.3)	5894 (74.2)	2166 (70.2)	11,596 (74.3)	

\*Chi-squared test. CKD: chronic kidney disease; sUA: serum uric acid. \*\* ml/min 1.73 m<sup>2</sup>.

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