Factors Influencing the Effectiveness of Allopurinol in Achieving and Sustaining Target Serum Urate in a US Veterans Affairs Gout Cohort

Jasvinder A. Singh, Shuo Yang, and Kenneth G. Saag

ABSTRACT. ***Objective.*** To assess factors associated with the ability to achieve and maintain target serum urate (SU) with allopurinol in patients with gout.

Methods. We used US Veterans Affairs (VA) databases from 2002–2012. Eligible patients had ≥ 1 inpatient or ≥ 2 outpatient visits with a diagnostic code for gout, filled a new index allopurinol prescription, had at least 1 posttreatment SU level measured, and met the 12-month observability rule. Treatment successes were defined as the achievement of postindex SU < 6 mg/dl (success 1) and postindex SU < 6 mg/dl that was sustained (success 2).

Results. Of the 198,839 unique patients with allopurinol use, 41,153 unique patients (with 47,072 episodes) and 17,402 unique patients (with 18,323 episodes) were eligible for analyses for success 1 and success 2; 42% each achieved (success 1) or achieved and maintained postindex SU < 6 mg/dl (success 2). In multivariable-adjusted models, factors associated with significantly higher odds of both outcomes were older age, normal body mass index, Deyo-Charlson index score of 0, rheumatologist as the main provider rather than non-rheumatologist, midwestern US location for the healthcare facility, a lower hospital bed size, military service connection for medical conditions of 50% or more (a measure of healthcare access priority), longer distance to the nearest VA facility, and lower preindex SU.

Conclusion. We identified novel factors associated with maintaining SU < 6 mg/dl based on a theoretical model. Several potentially modifiable factors can be targeted by individual/provider/systems interventions for improving successful achievement and maintenance of target SU in patients with gout. (J Rheumatol First Release February 1 2020; doi:10.3899/jrheum.190522)

Key Indexing Terms:
GOUT ALLOPURINOL EFFECTIVENESS TARGET SERUM URATE PREDICTORS

From the Birmingham Veterans Affairs Medical Center; Department of Medicine at the School of Medicine, and Department of Epidemiology at the School of Public Health, University of Alabama at Birmingham, Birmingham, Alabama, USA.

This study was funded by the US National Institute of Arthritis, Musculoskeletal and Skin Diseases P50 AR060772 grant that also support efforts for Dr. Singh (Project PI) and Dr. Saag (main PI). The authors are ready to share the data with colleagues, after obtaining appropriate permissions from institutional review boards at the Birmingham VA Medical Center and the University of Alabama at Birmingham, related to their privacy and data-sharing policies. JAS has received consultant fees from Crealta/Horizon. JAS owns stock options in Amarin and Viking Pharmaceuticals Inc. JAS is a member of the Veterans Affairs Rheumatology Field Advisory Committee. JAS is the editor and the Director of the UAB Cochrane Musculoskeletal Group Satellite Center on Network Meta-analysis. JAS is a member of the executive of OMERACT, an organization that develops outcome measures in rheumatology and receives arms-length funding from 36 companies. He is also supported by the resources and the use of facilities at the VA Medical Center at Birmingham, Alabama, USA. KGS serves as a consultant for Amgen, Merck, and Radius and receives funding from Amgen and Merck.

J.A. Singh, MBBS, MPH, Birmingham Veterans Affairs Medical Center, and Department of Medicine at the School of Medicine, and Department of Epidemiology at the School of Public Health, University of Alabama at Birmingham; S. Yang, MS, Department of Epidemiology at the School of Public Health, University of Alabama at Birmingham;
K.G. Saag, MD, MSc, Department of Medicine at the School of Medicine, University of Alabama at Birmingham.

Address correspondence to J.A. Singh, University of Alabama, Faculty Office Tower 805B, 510 20th St. South, Birmingham, Alabama 35294, USA. E-mail: Jasvinder.md@gmail.com

Accepted for publication August 2, 2019.

Failure to achieve and maintain target serum urate (SU) is a critical shortcoming of current gout management[1,2,3]. Fewer than 50% of patients treated with allopurinol, an effective and inexpensive urate-lowering therapy (ULT), achieve target SU < 6 mg/dl[1,4]. Maintenance of target SU is associated with lower risk of gout flares and tophi and lower healthcare costs[4–10] and is recommended by every treatment guideline[11-17].

A single US Veterans Affairs (VA) center study (n = 643; 253 with SU; 39%) reported that a lower medical comorbidity load was associated with higher odds of reaching the target SU < 6 mg/dl[1]. In claims database studies, factors associated with higher likelihood of achieving target SU < 6 mg/dl were older age, female sex, higher allopurinol dose, and the absence of kidney disease (n = 3363; 2059 had SU; 61%)[18]; higher allopurinol adherence (n = 18,243; 4277 with SU; 23%)[19]; and female sex, older age, white race, rheumatologist care, and higher allopurinol start dose and adherence

(n = 9581 incident users)[20]. These studies had important limitations. All studies except 2[1,20], used prevalent user design, which tends to bias estimates and overestimate adherence. None examined factors associated with maintaining target SU, the main goal recommended by gout guidelines[11,21,22]. Most studies examined demographic and clinical characteristics (i.e., predisposing factors), but none evaluated gout severity (i.e., need factors), or important system-level or healthcare access factors, such as region, rural location, distance to the medical center, etc. (i.e., enabling factors)[1,18,19,20]. Therefore, significant knowledge gaps remain. No conceptual model was invoked in any of these studies. Andersen's Behavioral Model of need, enabling, and predisposing factors[23,24] offers a potential solution to improve our understanding of associated factors.

We examined the data from the VA healthcare system[25,26], the largest integrated healthcare system in the United States. It provides care to 6 million participants annually[26]. We hypothesized that in patients with gout who are taking allopurinol, the needs, enabling, and predisposing factors based on Andersen's model[23,24] would be associated with a patient's ability to achieve and maintain target SU < 6 mg/dl; and the initial allopurinol dose and previous allopurinol use in the baseline year would also be associated independently with these outcomes.

MATERIALS AND METHODS

Study cohort and eligibility and data sources. We used the VA national databases from 2002 to 2012[27,28,29], which are reliable for demographics and most common diagnoses[30] and valid for specific diagnoses[31]. The Institutional Review Board (IRB) at the University of Alabama at Birmingham (X120928002) and the Birmingham VA Medical Center (01487) approved the study. The IRB waived the need for informed consent for this database study. We followed the Strengthening of Reporting in Observational studies in Epidemiology (STROBE) guidelines[32].

Patients were eligible if they had ≥ 1 inpatient or ≥ 2 outpatient visits with an International Classification of Diseases, 9th ed (ICD-9) code 274.x for gout, were treated with allopurinol, had a postindex SU level taken, and met the 12-month observability period (i.e., for each 12 months, there must be an ICD-9 code 274.x recorded in the system). Index allopurinol prescription was defined as no allopurinol exposure in the previous 121 days. This included a 91-day clearance period and a 30-day grace period between prescriptions, because patients often have a small stock of medication, especially with the 90-day prescriptions, the most common day supply at the VA. A gap of > 30 days between any 2 allopurinol prescriptions was considered the end of an episode and led to the beginning of another drug exposure period.

Patient demographic and comorbidity data were obtained from the VA Patient Treatment File and Outpatient Clinic tables. Results of SU tests were obtained from each Veterans Health Information Systems and Technology Architecture system accessed, using VA Informatics and Computing Infrastructure (VINCI)[33]. Medication data were obtained through the Decision Support System's Pharmacy National Data Extract, which contains records for all inpatient and outpatient prescriptions, including every medication filled and refilled from all VA facilities (number of days' supply, dose, number of pills, and the start and end date for medication filling and refills). Provider factors were obtained from the MedSAS Outpatient provider data. Systems factors [VA location, bed size, community-based outpatient clinic (CBOC) vs VA clinic, etc.] were obtained from the VA planning systems support group office and VINCI.

Outcome. We examined 2 key outcomes of success: (1) achieving target SU < 6 mg/dl postindex allopurinol prescription [(i.e., during the followup at any time 14 days or after the index allopurinol prescription (success 1)]; and (2) maintaining target SU < 6 mg/dl [i.e., meeting the previous definition and having all subsequent (≥ 2) SU levels < 6 mg/dl postindex prescription during the followup, with at least 1 day between laboratory assessments (success 2)].

Associated factors: covariates and potential confounders. We examined the following factors, as they mapped to the Andersen's Model[23,24].

Predisposing factors included these patient characteristics: age (in yrs), sex, race/ethnicity (white, Hispanic, black or African American, other, and unknown), body mass index, and marital status (single, married, divorced, widowed, and unknown). Comorbidity was assessed using the Deyo-Charlson index[34], a validated measure consisting of 17 comorbidities, examined as summation score and categorized as 0, 1, or 2 or more comorbidities.

Enabling factors were provider factors [i.e., the main provider of gout care categorized by provider specialty as rheumatologists versus other (non-rheumatologist; including primary care)].

System factors were the location of the VA facility (rural vs urban, affiliation with a teaching hospital, yes or no), outpatient clinic type (CBOC vs VA medical center vs both vs other), VA facility bed size (categorized into ≤ 50, 51–100, 101–200, and > 200), and region (mid-Atlantic, Midwest, Northeast, South, and West).

Healthcare access factors included the distance to the nearest VA medical center as a measure of accessibility, an important predictor of outcomes[35,36]. It was calculated as the straight-line miles from the centroid of the patient's residential postal code to the nearest VA site, as previously. Military service connection and means test were also included, because both were significant predictors of SU monitoring in our previous VA study[37]. Military service connection is an indicator of access to care. It ranges from 0% to 100% and is awarded for conditions that begin during or result from active military duty[38]. Veterans with ≥ 50% service connection do not have co-payments for medical care or prescriptions, and get priority in VA healthcare access. Means test measures household income and assets and is completed yearly by most veterans[39]. Categories are AN (most needy but not service-connected), AS (most needy and service connected), and C (not most needy).

Regarding medication factors: allopurinol start dose was calculated as unit dose × quantity divided by days' supply based on the first and last filled prescription and categorized as ≤ 100, 101–200, 201–300, and > 300 mg/day. We also examined any previous allopurinol use in the 1-year baseline.

Need factors were disease severity factors: duration of gout, assessed as the time from meeting the definition (1 inpatient ICD-9 code or 2 or more outpatient ICD-9 codes) to the beginning of the index allopurinol prescription; and preindex SU level, categorized as < 6, 6 to < 8, 8 to < 10, 10 to < 12, and ≥ 12 mg/dl.

Statistical analyses. We compared the characteristics of patients who did or did not receive a post-allopurinol SU test as well as did or did not achieve success 1 or 2, using chi-square/comparison of proportions test or t test as applicable. We used multivariable-adjusted logistic regression models to assess whether needs, enabling, and predisposing factors were associated with the ability to achieve target SU < 6 mg/dl (Model 1a) and to achieve and maintain SU < 6 mg/dl in gout patients taking allopurinol (Model 1b). We reported OR and 95% CI. We performed sensitivity analyses by (1) replacing Deyo-Charlson individual comorbidities in the main model with a score (0, 1, ≥ 2; model 2a, 2b); and (2) additionally adjusting the main model for allopurinol use in the baseline 1-year and the starting allopurinol dose (model 3a, 3b). We performed exploratory analyses by additionally adjusting the main model for allopurinol variables including the start and the end dose, use in the baseline 1-year, dose escalation (normal, fast, slow, none), and medication possession ratio (MPR; model 4a, 4b), calculated as the medication supply actually received by the patient divided by medication supply that could have been received.

RESULTS

Cohort characteristics. Of the 627,693 patients with gout, 198,839 patients (310,695 episodes) had a new allopurinol prescription and at least 12 months of observability (Figure 1). Of these, 41,153 patients (47,072 episodes) and 17,402 patients (18,323 episodes) contributed to the analyses for achieving target SU (success 1) or maintaining target SU (success 2), respectively.

The study cohort for achieving target SU (success 1) had a mean age of 66.8 years, body mass index (BMI) of 33.6 kg/m^2, were male (99%), and white (61%; Table 1). Comorbidities were common and were higher compared to patients who did not get a postindex prescription SU test (Table 2). Characteristics were similar for the 2 study cohorts for achieving target SU (success 1; Table 3) or maintaining target SU (success 2; Table 4).

Unadjusted characteristics of patients achieving or maintaining target SU. For the success 1 cohort, the mean followup duration was 784.8 days (~26 mos; SD 810.3 days). The mean time to achieving target SU was 273.3 days (~9 mos; SD 303.5 days) and mean allopurinol dose was 193.5 mg/day (SD 104 mg/day; Table 1). Only 42% patients each achieved target SU (success 1: 17,284/41,153 patients; 19,535 episodes) or achieved and maintained target SU (success 2: 7,309/17,402 patients; 18,323 episodes). Unadjusted characteristics are shown in Tables 3 and 4. Mean (SD) preindex SU was lower in patients reaching versus not reaching target SU during followup: 7.8 (2.2) versus 8.9 (2.0) mg/dl for achieving target SU (success 1); and 8.1 (2.2) mg/dl versus 9.2 (2.1) mg/dl for achieving and maintaining target SU (success 2).

Multivariable-adjusted correlates of achieving or maintaining target SU. Factors associated with significantly higher odds of achieving target SU < 6 mg/dl (success 1) were older age, male sex, white race, rheumatologist as the main provider of gout care, a lower hospital bed size of ≤ 50 or 101–200 (compared to > 200), Midwest location for the healthcare facility, and the presence of comorbidities (rheumatologic disease, peptic ulcer disease, diabetes with complications and severe liver disease; Table 3). Medical comorbidities (heart disease, diabetes, and renal disease), preindex SU higher than 8 mg/dl (vs 6 to < 8), and longer gout duration were significantly associated with lower odds of achieving target SU (Table 3).

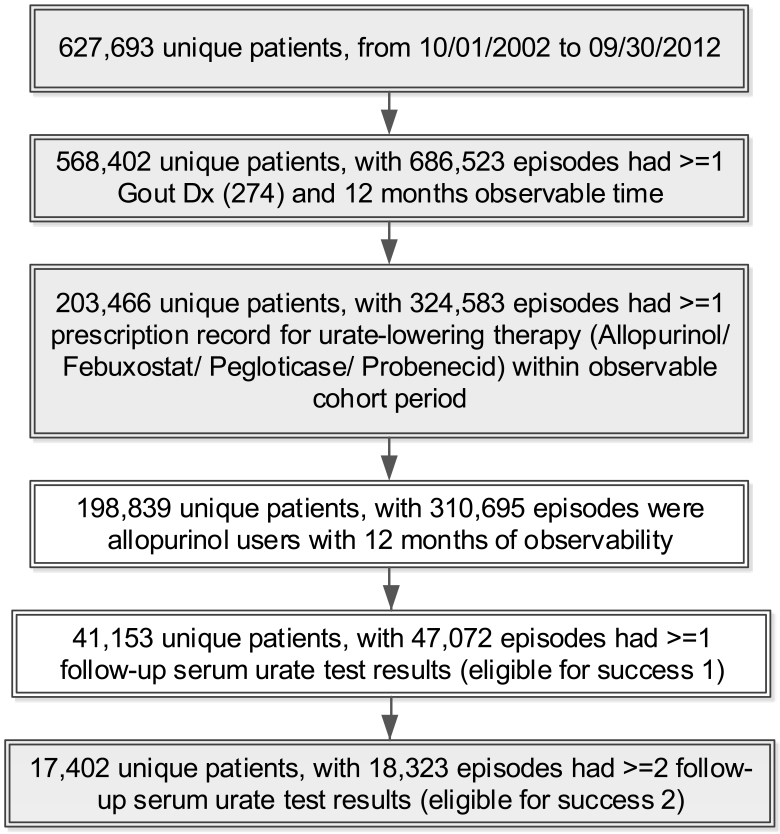

Figure 1. Cohort selection flowchart. The flowchart shows the selection of a sample for the study, based on eligibility criteria. We examined 41,153 people with gout for achievement of target serum urate (success 1) and 17,402 people with gout for achievement and maintenance of target serum urate (success 2).

Table 1. Selected characteristics of overall sample and the study cohort.

Characteristics	Total Sample, n = 310,695 Episodes N (%) or mean (SD)	Study Cohort with At Least 1 Postindex SU Measurement, n = 47,072 Episodes N (%) or mean (SD)
Male sex	307,992 (99.1)	46,659 (99.1)
Race/ethnicity		
White	196,479 (63.2)	28,572 (60.7)
Black	65,664 (21.1)	11,376 (24.2)
Hispanic	11,928 (3.8)	2527 (5.4)
Other	19,444 (6.3)	2810 (6.0)
Unknown	17,180 (5.5)	1787 (3.8)
Age, mean (SD)	67.5 (11.8)	66.8 (11.5)
BMI, kg/m^2, mean (SD)	33.5 (7.5)	33.6 (7.6)
Marital status		
Married	184,084 (59.5)	26,687 (57.0)
Divorced	67,217 (21.7)	10,694 (22.8)
Single	32,037 (1034)	5535 (11.8)
Widowed	25,916 (8.4)	3946 (8.4)
Deyo-Charlson comorbidity index score, mean (SD)	1.4 (1.6)	1.6 (1.7)
Main provider type		
Any physician	163,131 (52.5)	23,564 (50.1)
Nursing	31,405 (10.1)	3887 (8.3)
Physician assistant or nurse practitioner	28,258 (9.1)	3863 (8.2)
Other	87,901 (28.3)	15,758 (33.5)
Provider specialty		
Rheumatology	8140 (2.6)	2543 (5.4)
Others	302,555 (97.4)	44,529 (94.6)
Veterans Integrated Service Network		
Northeast	28,846 (9.3)	6685 (14.2)
Mid-Atlantic	69,414 (22.3)	13,620 (28.9)
South	93,584 (30.1)	10,612 (22.6)
Midwest	65,957 (21.2)	5045 (10.7)
West	52,872 (17.0)	11,106 (23.6)
Affiliated to university hospital (yes)	290,131 (93.4)	42,787 (90.9)
Outpatient clinic type		
CBOC	62,822 (20.2)	8525 (18.1)
VAMC	43,420 (14.0)	29,107 (61.8)
VAMC and CBOC	16,347 (5.3)	2193 (4.7)
Other	43,420 (14.0)	7247 (15.4)
Operating beds, mean (SD)	162.7 (94.7)	169.6 (94.4)
Operating VAMC bed size		
> 200	93,847 (30.2)	15,812 (33.6)
≤ 50	42,073 (13.5)	7471 (15.9)
> 50 to ≤ 100	56,082 (18.1)	5815 (12.4)
> 100 to ≤ 200	118,693 (38.2)	17,974 (38.2)
Distance from closest VA facility within network, miles, mean (SD)	13.3 (13.9)	12.6 (15.3)
Distance from closest VA medical center within network, miles, mean (SD)	44.3 (78.6)	47.8 (124.1)
Rural location of the VA facility	162,420 (52.4)	22,405 (47.7)
Means test category		
Most needy but not service-connected	104,088 (33.5)	16,961 (36.0)
Most needy and service-connected	123,729 (39.8)	19,800 (42.1)
Not most needy	68,367 (22.0)	8252 (17.5)
Other	14,489 (4.7)	2055 (4.4)
Daily allopurinol dose, mg/day, mean (SD)		
Start daily dose	206.1 (119.6)	192.7 (105.2)
End daily dose	215.4 (118.8)	213.4 (116.2)
Average dose	200.8 (106.6)	193.5 (103.8)
Followup time, days (censored by event), mean (SD)	524.3 (536.5)	273.3 (303.5)
Time to achieve target SU < 6 mg/dl, days, mean (SD)	—	179 (102)
Medication possession ratio (censored by event), mean (SD)	0.8 (0.2)	0.9 (0.1)

Bold text denotes statistically significant $p < 0.05$ between the overall sample and that with at least 1 postindex SU. SU: serum urate; BMI: body mass index; VA: Veterans Affairs; VAMC: VA Medical Center clinic; CBOC: community-based outpatient clinic.

Table 2. Comorbidity characteristics of overall sample and the study cohort.

Characteristics	Overall Sample, n = 310,695	Study Cohort without SU Test Postindex Filled Allopurinol Prescription, n = 263,623	Study Cohort with At Least 1 SU Test Postindex Filled Allopurinol Prescription, n = 47,072
Deyo-Charlson index comorbidities			
Myocardial infarction	9841 (3.2)	8063 (3.1)	1778 (3.8)
Coronary heart disease	38,989 (12.5)	32,111 (12.2)	6878 (14.6)
Peripheral vascular disease	25,655 (8.3)	21,266 (8.1)	4389 (9.3)
Cerebrovascular disease	23,948 (7.7)	20,012 (7.6)	3936 (8.4)
Dementia	1693 (0.5)	1447 (0.6)	246 (0.5)
Chronic pulmonary disease	52,886 (17.0)	44,339 (16.8)	8547 (18.2)
Rheumatologic disease	5052 (1.6)	3993 (1.5)	1059 (2.3)
Peptic ulcer disease	4780 (1.5)	4050 (1.5)	730 (1.6)
Mild liver disease	2435 (0.8)	2004 (0.8)	431 (0.9)
Diabetes	108,283 (34.9)	90,891 (34.5)	17,392 (37.0)
Diabetes with complications	27,629 (8.9)	22,561 (8.6)	5068 (10.8)
Paraplegia	855 (0.3)	697 (0.3)	158 (0.3)
Renal disease	20,556 (6.6)	16,112 (6.1)	4444 (9.4)
Malignancy	34,221 (11.0)	28,532 (10.8)	5689 (12.1)
Severe liver disease	830 (0.3)	701 (0.3)	129 (0.3)
Malignant neoplasm without specification of site	1631 (0.5)	1350 (0.5)	281 (0.6)
AIDS	912 (0.3)	705 (0.3)	207 (0.4)
Cancer	34,443 (11.1)	28,721 (10.9)	5722 (12.2)
Hepatic coma	175 (0.1)	145 (0.1)	30 (0.1)
Deyo-Charlson comorbidity index score, mean (SD)	1.4 (1.6)	1.3 (1.6)	1.6 (1.7)

Data are n (%) unless otherwise indicated. Bold text denotes Deyo-Charlson comorbidities that were statistically significant between the 2 groups with an unadjusted p value of < 0.05. SU: serum urate.

Factors associated with significantly higher odds of maintaining target SU < 6 mg/dl (success 2; at least 2 SU levels at target postindex prescription) were white race, rheumatologist as the main provider, a lower hospital bed size such as 101–200 (ref > 200 beds), and a normal BMI (Table 4). These were associated with lower odds: medical comorbidities (heart disease, mild liver disease, diabetes, renal disease, malignancy and malignant neoplasm without specification of site), being single, a southern US location for the healthcare facility (vs Midwest), and a preindex SU level higher than 8 mg/dl (vs 6 to < 8).

In sensitivity analysis (model 2), a higher Deyo-Charlson comorbidity index score ≥ 2 was associated with lower likelihood of achieving or maintaining target SU (Figure 2).

Analyses of effect modification including allopurinol dose and use variables, overall and in explaining racial differences in achieving or maintaining target SU. In multivariable-adjusted models adjusted additionally for previous allopurinol use and start dose, compared to start dose of ≤ 100 mg/day, higher allopurinol doses were associated with higher odds and allopurinol use in the baseline 1-year with lower odds of achieving or maintaining target SU (Supplementary Tables 1 and 2, available with the online version of this article). In exploratory analyses, normal or fast allopurinol escalation (compared to no escalation), higher allopurinol end dose, and higher allopurinol medication possession ratio were associated with higher odds of both outcomes, with higher allopurinol start dose being only borderline significant (Supplementary Table 3, available with the online version of this article).

Although in the main analysis African Americans had significantly lower adjusted odds of achieving target SU (OR 0.94, 95% CI 0.89–0.99) and similar odds of maintaining target SU (OR 1.02, 95% CI 0.93–1.11), after adjusting for the rate of allopurinol dose escalation and MPR they had significantly higher odds of achieving target SU (OR 1.16, 95% CI 1.09–1.23) and maintaining target SU (OR 1.22, 95% CI 1.11–1.34; Supplementary Table 3, available with the online version of this article). Further analyses revealed that this effect modification was due to allopurinol MPR.

DISCUSSION

To our knowledge, no study to date has examined factors associated with maintaining target SU. Our comprehensive, national cohort study performed robust analyses that controlled for patient, provider, systems, medication, and disease severity factors and advances the understanding of factors associated with target SU. Patients who saw rheumatologists (< 3% of patients) as the main providers for gout care were more likely to achieve target SU and to maintain target SU. A better quality of gout care with a rheumatology provider[1] and higher odds of target SU achievement with a rheumatologist provider[20] explain our findings. This may be due to the prioritization of gout management during a

Table 3. Unadjusted and adjusted analyses of patients with gout for achievement of target SU of < 6 mg/dl.

Characteristics	Achieved Target SU, n = 19,535 Episodes	Did Not Achieve Target SU, n = 27,537 Episodes	Achieved Target SU, **Unadjusted Model,** OR (95% CI)	Achieved Target SU, **Adjusted Model,** OR (95% CI)
Male sex (ref, female)	19,321 (98.9)	27,338 (99.3)	**1.51 (1.24–1.85)**	**1.63 (1.32–2.01)**
Race				
White	12,387 (63.4)	16,185 (58.8)	REF	REF
Black	4413 (22.6)	6963 (25.3)	**0.84 (0.80–0.88)**	**0.94 (0.89–0.99)**
Hispanic	873 (4.5)	1654 (6.0)	**0.70 (0.64–0.76)**	**0.77 (0.70–0.85)**
Other	1097 (5.6)	1713 (6.2)	**0.83 (0.76–0.90)**	**0.80 (0.73–0.88)**
Unknown	765 (3.9)	1022 (3.7)	0.96 (0.87–1.07)	0.94 (0.84–1.05)
Age, mean (SD)	67.7 (11.1)	66.2 (11.7)	**1.01 (1.01–1.01)**	**1.01 (1.01–1.01)**
Marital status				
Married	11,267 (57.6)	15,420 (56.0)	REF	REF
Divorced	4372 (22.4)	6322 (23.0)	**0.95 (0.90–0.99)**	1.02 (0.97–1.08)
Single	2143 (11.0)	3392 (12.3)	**0.87 (0.82–0.93)**	0.99 (0.92–1.06)
Widowed	1676 (8.6)	2270 (8.2)	0.78 (0.58–1.06)	0.89 (0.65–1.22)
Unknown	77 (0.4)	133 (0.5)	1.02 (0.95–1.10)	0.95 (0.88–1.02)
Deyo-Charlson comorbidities				
Myocardial infarction	674 (3.5)	1104 (4.0)	**0.85 (0.77–0.94)**	0.93 (0.83–1.04)
Coronary heart disease	2254 (11.5)	4624 (16.8)	**0.65 (0.62–0.69)**	**0.75 (0.70–0.80)**
Peripheral vascular disease	1744 (8.9)	2645 (9.6)	**0.93 (0.87–0.99)**	0.95 (0.88–1.02)
Cardiovascular disease	1684 (8.6)	2252 (8.2)	1.07 (0.99–1.14)	1.06 (0.99–1.14)
Dementia	110 (0.6)	136 (0.5)	1.13 (0.87–1.46)	0.96 (0.73–1.26)
Chronic pulmonary disease	3482 (17.8)	5065 (18.4)	0.96 (0.92–1.01)	1.04 (0.98–1.09)
Rheumatologic disease	485 (2.5)	574 (2.1)	**1.21 (1.06–1.37)**	**1.19 (1.04–1.36)**
Peptic ulcer disease	361 (1.9)	369 (1.3)	**1.43 (1.23–1.67)**	**1.33 (1.13–1.56)**
Mild liver disease	169 (0.9)	262 (1.0)	0.90 (0.74–1.10)	0.87 (0.70–1.10)
Diabetes	6837 (35.0)	10,555 (38.3)	**0.88 (0.85–0.92)**	**0.95 (0.90–0.99)**
Diabetes with complications	1962 (10.0)	3106 (11.3)	**0.89 (0.84–0.95)**	**1.09 (1.01–1.17)**
Paraplegia	80 (0.4)	78 (0.3)	**1.44 (1.04–1.98)**	1.31 (0.94–1.85)
Renal disease	1480 (7.6)	2964 (10.8)	**0.69 (0.65–0.74)**	**0.77 (0.71–0.83)**
Malignancy, including leukemia and lymphoma	2548 (13.0)	3141 (11.4)	**1.16 (1.09–1.23)**	1.05 (0.98–1.12)
Severe liver disease	65 (0.3)	64 (0.2)	**1.42 (0.98–2.03)**	**1.67 (1.11–2.51)**
Metastatic solid tumor	134 (0.7)	147 (0.5)	1.31 (1.03–1.66)	1.01 (0.78–1.31)
AIDS	81 (0.4)	126 (0.5)	0.93 (0.70–1.24)	1.08 (0.80–1.46)
Provider specialty[1]				
Rheumatology	1125 (5.8)	1418 (5.2)	REF	REF
Other	18,410 (94.2)	26,119 (94.9)	**0.88 (0.81–0.95)**	**0.79 (0.72–0.86)**
Region of country				
Midwest	2292 (11.7)	2757 (10)	REF	REF
Northeast	3047 (15.6)	3638 (13.2)	1.03 (0.95–1.11)	1.04 (0.95–1.14)
Mid-Atlantic	5604 (28.7)	8016 (29.1)	**0.85 (0.80–0.91)**	**0.89 (0.82–0.96)**
South	4066 (20.8)	6546 (23.8)	**0.74 (0.69–0.80)**	**0.81 (0.75–0.89)**
West	4526 (23.2)	6580 (23.9)	**0.84 (0.78–0.90)**	**0.87 (0.80–0.95)**
Affiliated with university (ref, no)	17,644 (90.3)	25,143 (91.3)	**0.89 (0.84–0.96)**	1.04 (0.95–1.14)
VA clinic type				
VAMC	11,911(61.0)	17,196 (62.5)	REF	REF
CBOC	3655 (18.7)	4870 (17.7)	**1.06 (1.01–1.12)**	1.00 (0.95–1.06)
Other	3131 (16.0)	4116 (15.0)	**1.09 (1.04–1.16)**	1.09 (1.02–1.15)
VAMC and CBOC	838 (4.3)	1355 (4.9)	0.92 (0.84–1.01)	0.86 (0.78–0.95)
Operating beds				
> 200	6213 (31.8)	9599 (34.9)	REF	REF
≤ 50	3257 (16.7)	4214 (15.3)	**1.18 (1.11–1.25)**	**1.13 (1.04–1.22)**
51–100	2492 (12.8)	3323 (12.1)	**1.14 (1.07–1.22)**	1.04 (0.97–1.12)
101–200	7573 (38.8)	10,401 (37.8)	**1.12 (1.07–1.17)**	**1.18 (1.12–1.24)**
Means test[2]				
Most needy but not service-connected	6836 (35.0)	10,125 (36.8)	REF	REF
Most needy and service-connected	8268 (42.3)	11,532 (41.9)	**1.06 (1.02–1.11)**	0.98 (0.85–1.12)
Not most needy	3598 (18.4)	4654 (16.9)	**1.13 (1.07–1.20)**	0.99 (0.93–1.05)
Other	832 (4.3)	1223 (4.4)	0.99 (0.89–1.09)	**0.90 (0.81–0.99)**

Table 3. Continued.

Characteristics	Achieved Target SU, n = 19,535 Episodes	Did Not Achieve Target SU, n = 27,537 Episodes	Achieved Target SU, **Unadjusted Model,** OR (95% CI)	Achieved Target SU, **Adjusted Model,** OR (95% CI)
Duration of gout, mean (SD)	2.2 (2.3)	2.1 (2.2)	1.01 (1.00–1.02)	**0.97 (0.96–0.98)**
Preindex SU level, mg/dl				
< 6	3769 (21.3)	1513 (5.9)	**3.02 (2.81–3.24)**	**3.00 (2.79–3.22)**
6 to < 8	5079 (28.7)	6135 (24.1)	REF	REF
8 to < 10	6169 (34.8)	10,831 (42.5)	**0.69 (0.66–0.72)**	**0.70 (0.66–0.73)**
10 to < 12	2199 (12.4)	5385 (21.1)	**0.49 (0.47–0.53)**	**0.51 (0.48–0.55)**
≥ 12	509 (2.9)	1637 (6.4)	**0.38 (0.34–0.42)**	**0.42 (0.37–0.47)**

Data are n (%) unless otherwise indicated. Bold text denotes statistically significant OR. [1] Provider specialty: other category includes nonphysician rheumatologist, physician assistant, or advanced nurse practitioner; numbers were too small to separate physician assistant or advanced nurse practitioner. [2] Means test is an assessment of socioeconomic status of a veteran. Adjusted model: includes patient factors such as age (in yrs), sex, race/ethnicity (white, Hispanic, black or African American, other, unknown), BMI, marital status, Deyo-Charlson index medical comorbidities, physician factors including provider specialty (rheumatologists vs non-rheumatologist), healthcare access including distance to nearest VA medical center, percent service connection, means test, duration of gout, and preindex SU level. System factors include location of the VA facility (rural vs urban), affiliation to a teaching hospital, outpatient clinic type, VA facility bed size (≤ 50, 51–100, 101–200, and > 200) and region (mid-Atlantic, Midwest, Northeast, South, and West). Factors adjusted in the model that were not significant included location of the VA, percent service connection, and distance to the nearest VA. Unique patients = 17,284 for patients who achieved target SU and 23,869 for patients who did not achieve target SU. C statistic for the adjusted model was 0.66. Rheumatologic diseases include systemic lupus erythematosus, systemic sclerosis, polymyositis, polymyalgia rheumatica, rheumatoid lung, and rheumatoid arthritis. SU: serum urate; VA: Veterans Affairs; VAMC: VA Medical Center clinic; BMI: body mass index; CBOC: community-based outpatient clinic.

rheumatology visit. This finding has potential policy implications for the VA.

We recognize that a multifaceted approach with several policy initiatives is required to address this quality gap. Expanded rheumatology care teams (nurse practitioners, physician assistants, community health workers), and technology-based solutions (tele-health, e-consults, and virtual health communities) may address this problem. This would require provision of more resources for the VA rheumatology workforce. Nurse- or pharmacist-led interventions are effective in improving gout care and outcomes[40,41,42]. Maintaining target SU < 6 mg/dl is associated with reduction in gout flares, resolution of gouty tophi, and improvement in quality of life and function[5,10] and is key to optimal management[11,21,22].

It took a mean of 9 months to achieve target SU. This is longer than might be expected based on the American College of Rheumatology treatment guideline with frequent ULT dose titration[11]. Only 42% of the patients maintained target SU, a key treatment goal recommended by gout guidelines[11–17]. Allopurinol is well-tolerated with few adverse events, which does not explain this low rate of success. Patients prioritized lowering of SU (to target) in gout as an important goal[43], challenging the recent American College of Physicians position to consider treat to symptom control in gout with no SU monitoring as an alternative to treat to target SU[17]. Thus, improvement in rates of target SU achievement and maintenance in gout are needed.

African Americans had lower odds of achieving target SU in models not accounting for allopurinol adherence and gout severity factors, but higher odds of achieving or maintaining target SU, in exploratory analyses. This is a novel insight. It indicates that the lower chance of target SU achievement in African Americans can be explained largely by lower allopurinol adherence, and to a lesser degree by worse baseline disease, lower allopurinol start dose, and improper dose escalation. After accounting for these confounding factors, African Americans with gout have a better SU outcome than whites (Supplementary Table 3, available with the online version of this article). Addressing these modifiable factors has the potential of improving gout outcomes in African Americans and reducing health disparities in gout.

Prior studies lacked a theoretical model and were limited because of inclusion of a select few variables or univariate analysis[1,18,19,20], or they were single-center[1] or a regional sample[20], lacked gout disease severity variables[1,18,19,20], or used a prevalent allopurinol user design (and not incident user design)[18,19]. Using the Andersen model[23,24], we specified *a priori* that system, healthcare access, and disease severity factors (i.e., enabling and predisposing factors, not included in previous studies) in addition to patient and provider factors (need factors) will be associated with target SU outcomes. We found higher odds of target SU achievement in males compared to females in contrast to previous studies[18,20]. Several things may explain these differences: differences in setting (national vs regional sample), population (veterans vs US population), design (incident vs prevalent user design)[18], control for disease severity (disease duration and SU vs SU[20], or neither[18]), and additional covariate adjustment (system and healthcare access vs neither[18,20]).

Our study highlights the role of comorbidities in the

Table 4. Unadjusted and adjusted analyses of patients with gout for achievement and maintenance of target SU of < 6 mg/dl.

Characteristics	Achieved and Maintained Target SU, Episodes = 7462	Did Not Achieve and Maintain Target SU, Episodes = 10,861	Unadjusted Model, OR (95% CI)	Multivariable-Adjusted Model, OR (95% CI)
Male sex (ref, female)	7388 (99.0)	10,772 (99.2)	1.17 (0.85–1.16)	1.31 (0.94–1.82)
Race				
White	4889 (65.5)	6706 (61.7)	REF	REF
Black	1645 (22.1)	2615 (24.1)	**0.88 (0.82–0.95)**	1.02 (0.93–1.11)
Hispanic	314 (4.2)	606 (5.6)	**0.72 (0.62–0.83)**	**0.80 (0.68–0.94)**
Other	374 (5.0)	637 (5.9)	**0.80 (0.70–0.93)**	**0.74 (0.64–0.86)**
Unknown	240 (3.2)	297 (2.7)	1.09 (0.91–1.31)	1.02 (0.84–1.24)
Age, mean (SD)	67.9 (10.8)	66.8 (11.4)	**1.01 (1.01–1.01)**	**1.01 (1.01–1.01)**
Marital status				
Married	4253 (57.0)	6010 (55.3)	REF	REF
Divorced	1702 (22.8)	2481 (22.8)	0.97 (0.90–1.05)	1.02 (0.94–1.10)
Single	787 (10.5)	1382 (12.7)	**0.79 (0.72–0.88)**	**0.86 (0.77–0.96)**
Widowed	696 (9.3)	946 (8.7)	0.86 (0.52–1.43)	0.97 (0.86–1.09)
Unknown	24 (0.3)	42 (0.4)	1.05 (0.94–1.17)	0.96 (0.57–1.64)
Deyo-Charlson comorbidities				
Myocardial infarction	7179 (96.2)	10,367 (95.5)	**0.81 (0.70–0.95)**	0.98 (0.83–1.16)
Coronary heart disease	938 (12.6)	2317 (21.3)	**0.53 (0.48–0.57)**	**0.64 (0.58–0.70)**
Peripheral vascular disease	741 (9.9)	1230 (11.3)	**0.87 (0.78–0.96)**	0.96 (0.86–1.07)
Cerebrovascular disease	697 (9.3)	1042 (9.6)	0.97 (0.88–1.08)	1.01 (0.90–1.13)
Dementia	40 (0.5)	57 (0.5)	0.99 (0.65–1.49)	0.91 (0.59–1.41)
Chronic pulmonary disease	1376 (18.4)	2262 (20.8)	**0.86 (0.80–0.93)**	0.99 (0.91–1.07)
Rheumatologic disease	233 (3.1)	297 (2.7)	1.14 (0.95–1.36)	1.11 (0.92–1.34)
Peptic ulcer disease	157 (2.1)	182 (1.7)	**1.26 (1.01–1.57)**	1.24 (0.98–1.56)
Mild liver disease	65 (0.9)	138 (1.3)	**0.67 (0.49–0.90)**	**0.63 (0.45–0.90)**
Diabetes	2705 (36.3)	4651 (42.8)	**0.77 (0.73–0.82)**	**0.89 (0.82–0.95)**
Diabetes with complications	840 (11.3)	1616 (14.9)	**0.74 (0.68–0.81)**	1.00 (0.90–1.11)
Paraplegia	35 (0.5)	41 (0.4)	1.29 (0.81–2.04)	1.38 (0.85–2.25)
Renal disease	644 (8.6)	1579 (14.5)	**0.57 (0.51–0.62)**	**0.64 (0.58–0.72)**
Malignancy	982 (13.2)	1461 (13.5)	0.98 (0.89–1.07)	**0.88 (0.80–0.97)**
Severe liver disease	26 (0.4)	38 (0.4)	1.03 (0.62–1.71)	1.41 (0.78–2.57)
Malignant neoplasm without specification of site	53 (0.7)	87 (0.8)	0.88 (0.62–1.24)	**0.66 (0.45–0.96)**
AIDS	37 (0.5)	59 (0.5)	0.90 (0.60–1.37)	0.96 (0.62–1.49)
Provider specialty[1]				
Rheumatology	596 (8.0)	749 (6.9)	REF	REF
Other	6866 (92.0)	10,112 (93.1)	**0.85 (0.76–0.95)**	**0.77 (0.68–0.87)**
Region of country				
Midwest	803 (10.8)	995 (9.2)	REF	REF
Northeast	1358 (18.2)	1752 (16.1)	0.98 (0.87–1.11)	0.87 (0.76–1.00)
Mid-Atlantic	2126 (28.5)	2100 (28.6)	**0.87 (0.77–0.97)**	0.96 (0.83–1.11)
South	1416 (19.0)	2427 (22.4)	**0.73 (0.65–0.82)**	**0.76 (0.66–0.88)**
West	1759 (23.6)	2586 (23.8)	**0.85 (0.76–0.96)**	0.89 (0.78–1.03)
Affiliated with university (ref, no)	6774 (90.8)	9971 (91.8)	**0.87 (0.78–0.97)**	0.98 (0.84–1.13)
Outpatient clinic type				
VAMC	4620 (61.9)	6841 (63.0)	REF	REF
CBOC	1335 (17.9)	1802 (16.6)	1.08 (0.99–1.17)	1.00 (0.92–1.10)
Other	1210 (16.2)	1781 (16.4)	1.00 (0.91–1.08)	1.01 (0.92–1.11)
VAMC and CBOC	297 (4.0)	437 (4.0)	0.98 (0.84–1.15)	0.89 (0.75–1.05)
Operating bed size				
> 200	1216 (16.3)	1651 (15.2)	REF	REF
≤ 50	930 (12.5)	1248 (11.5)	**1.14 (1.04–1.26)**	1.05 (0.93–1.19)
51–100	2830 (37.9)	4032 (37.1)	**1.17 (1.06–1.29)**	1.07 (0.95–1.20)
101–200	2486 (33.3)	3930 (36.2)	**1.01 (1.03–1.18)**	**1.17 (1.08–1.26)**
Means test[2]				
Most needy but not service-connected	2685 (36.0)	4085 (37.6)	REF	REF
Most needy and service-connected	3227 (43.3)	4728 (43.5)	1.04 (0.97–1.11)	1.01 (0.81–1.26)
Not most needy	1255 (16.8)	1621 (14.9)	**1.16 (1.06–1.28)**	0.99 (0.89–1.09)
Other	295 (4.0)	426 (3.9)	1.02 (0.87–1.20)	0.95 (0.80–1.13)

Table 4. Continued.

Characteristics	Achieved and Maintained Target SU, Episodes = 7462	Did Not Achieve and Maintain Target SU, Episodes = 10,861	Unadjusted Model, OR (95% CI)	Multivariable-Adjusted Model, OR (95% CI)
Duration of gout, mean (SD)	2.1 (2.2)	2.0 (2.1)	**1.02 (1.01–1.04)**	0.98 (0.97–1.00)
Preindex SU level, mg/dl				
< 6	1237 (17.8)	512 (5.0)	**2.76 (2.44–3.11)**	**2.80 (2.48–3.17)**
6 to < 8	1816 (26.1)	2072 (20.1)	REF	REF
8 to < 10	2637 (37.8)	4280 (41.5)	**0.70 (0.65–0.76)**	**0.72 (0.66–0.78)**
10 to < 12	1010 (14.5)	2559 (24.8)	**0.45 (0.41–0.50)**	**0.49 (0.45–0.54)**
≥ 12	270 (3.9)	881 (8.6)	**0.35 (0.30–0.41)**	**0.44 (0.38–0.52)**

Data are n (%) unless otherwise indicated. Bold text denotes statistically significant OR. [1] Provider specialty: "Other" category includes non-rheumatologist physician, physician assistant, or advanced nurse practitioner; numbers were too small to separate physician assistant or advanced nurse practitioner. [2] Means test is an assessment of socioeconomic status of a veteran. Rheumatologic diseases include systemic lupus erythematosus, systemic sclerosis, polymyositis, polymyalgia rheumatica, rheumatoid lung, and rheumatoid arthritis. Adjusted model: includes patient factors such as age (in yrs), sex, race/ethnicity (white, Hispanic, black or African American, other, unknown), BMI, marital status, Deyo-Charlson index medical comorbidities, healthcare access including distance to nearest VAMC, percent service connection, means test, duration of gout, and preindex SU level. Physician factors include provider specialty (rheumatologists vs non-rheumatologist). System factors include location of the VA facility (rural vs urban), affiliation to a teaching hospital, outpatient clinic type, VA facility bed size (≤ 50, 51–100, 101–200, and > 200) and region (mid-Atlantic, Midwest, Northeast, South, and West). Unique patients = 7309 for patients who achieved and maintained target SU (with 7462 episodes) and 10,389 for patients (with 10,861 episodes) who did not. C statistic for the adjusted model was 0.66. SU: serum urate; BMI: body mass index; VAMC: VA Medical Center clinic; CBOC: community-based outpatient clinic.

achievement of target SU with allopurinol. The presence of 2 or more comorbidities was independently associated with 20% lower odds of maintaining target SU < 6 mg/dl compared to no comorbidities. A linear dose gradient was seen with increasing comorbidity load. This novel finding adds to the current knowledge. We found that heart disease, renal disease, and diabetes were associated with lower odds of achieving or maintaining target SU < 6 mg/dl. Our national sample, controlled using the Deyo-Charlson index, a validated comorbidity index, confirmed previous findings from regional/single-center studies controlled for selected conditions[1,18,19,20]. Although polypharmacy might be associated with higher allopurinol adherence[20], damage from higher comorbidity or specific medications on SU levels might make it more challenging to achieve target SU in people with specific comorbidities or an overall high comorbidity load, as our study and other studies show[1,18,20,44,45]. Future studies should examine whether optimization of comorbidity management can improve gout outcomes.

Geographic region was associated with odds of achieving and maintaining target SU. Compared to the Midwest, patients living in the South were less likely to achieve or to achieve and maintain target SU. Differences in resources, regional economies, and/or patient populations may underlie these differences. Policy makers may need to provide additional VA resources in these US regions to improve gout outcomes. This finding indicates that findings from even well-designed studies limited to 1 US region[20] are unlikely to be generalizable to the entire United States.

We assessed allopurinol start dose and previous allopurinol exposure as potential confounders of achieving or maintaining target SU rather than mediators, because they meet the classic definition of confounders by being associated both with the covariates and the outcome. For example, while adjusting for allopurinol MPR clearly changed the apparent relationship between race and achieving SU targets, it seems more reasonable to infer that adjusting for MPR accounted for the confounding between race and medication adherence than the mediation interpretation that the effect of race on SU adherence "acted through" medication adherence.

Higher allopurinol start doses > 100 mg/day increased the odds of achieving or maintaining target SU by 1.8–3.5–fold, slightly higher than the 1.7–fold found in a previous study[20]. Higher allopurinol end dose, higher allopurinol MPR, and normal or fast allopurinol escalation were also associated with very high odds of achieving or maintaining target SU. This is not surprising because allopurinol is an effective ULT. Most treatment guidelines recommend a low allopurinol starting dose of 100 mg/day and a gradual allopurinol dose escalation, to avoid gout flares and rare allopurinol hypersensitivity. Thus, the pros and the cons of high versus low allopurinol start dose and fast vs normal/slow allopurinol dose escalation must be considered and discussed with an individual patient in a shared decision-making approach. A high allopurinol MPR and higher end dose (i.e., to adequately lower SU) are noncontroversial approaches in gout care.

The study findings must be interpreted considering limitations. The use of ICD-9 codes for the diagnosis of gout and other comorbidities using the VA databases is subject to misclassification bias. However, ICD-9 codes for gout in the VA had high accuracy with sensitivity of 90% and specificity of 100%[37] and VA databases are valid and reliable for several diagnoses[30,31], although other database studies have reported lower accuracy for gout code[46]. Findings from this predom-

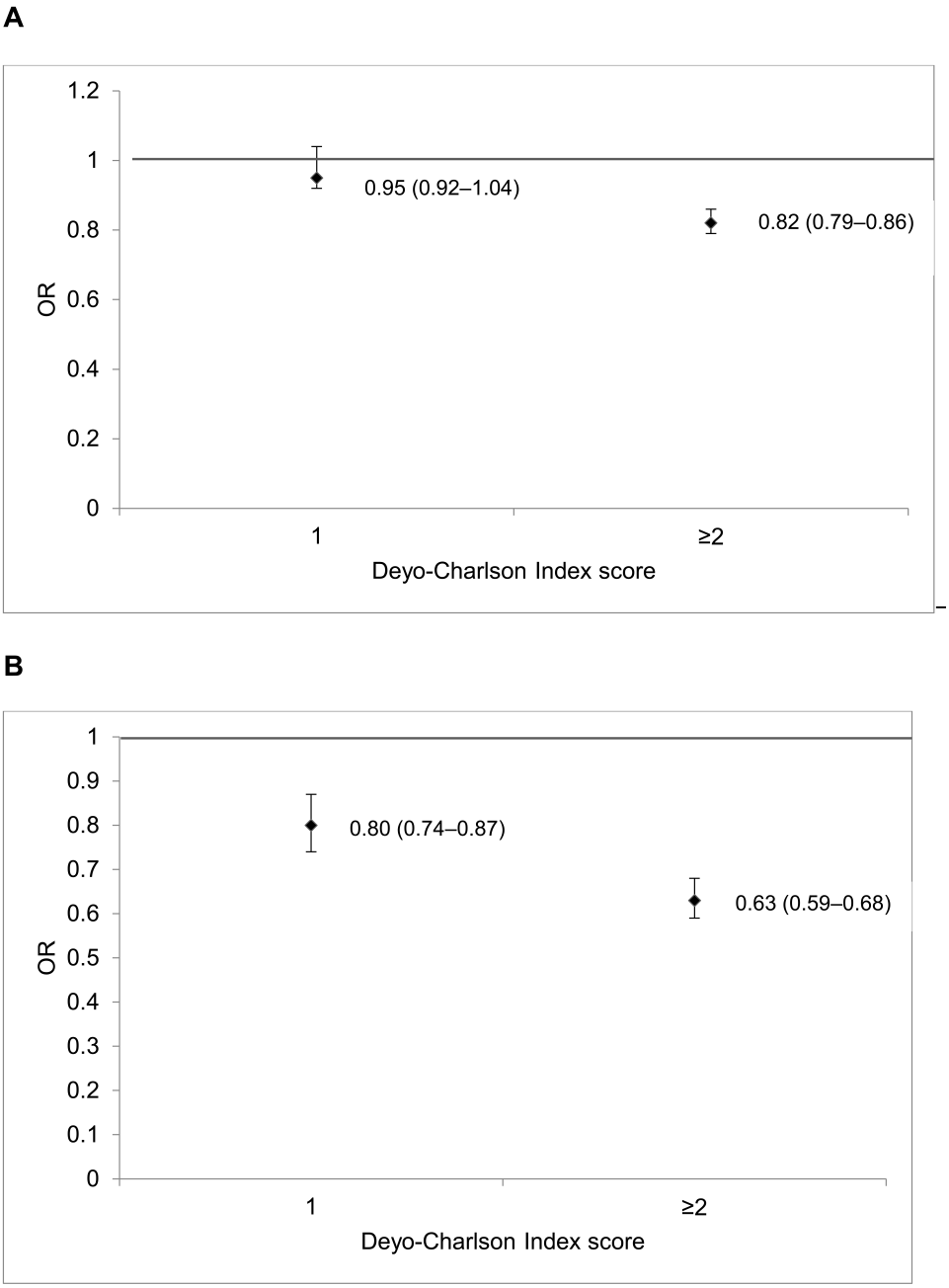

Figure 2. Association of Deyo-Charlson comorbidity index score with achieving or maintaining target serum urate in a multivariable-adjusted model. A. Association of Deyo-Charlson comorbidity index score with the odds of achieving target serum urate. B. Association of Deyo-Charlson comorbidity index score with the odds of achieving and maintaining of target serum urate. Reference category is Deyo-Charlson comorbidity index score of zero (no comorbidity). OR estimates are shown as diamonds and 95% CI are shown as whiskers. Estimates with 95% CI overlapping the OR of 1 (solid line) are statistically not significant. For example, compared to a score of 0, a Deyo-Charlson comorbidity index score of 2 or more was significantly independently associated with lower odds of achieving or maintaining target serum urate with OR (95% CI) of 0.82 (0.79–0.86) and 0.63 (0.59–0.68), respectively. The results are from model 2, in which the individual Deyo-Charlson comorbidities in the main model (model 1) were replaced with a Deyo-Charlson index score of 0, 1, or ≥ 2.

inantly male veteran population may not be generalizable to women and non-veterans. However, no previous studies have found sex or veteran status as confounders of these associations and the male-predominant VA population made it an excellent clinical laboratory to study gout, also a male-predominant condition. As in any other US healthcare system

(Medicare, Medicaid, etc.), care provided outside the system could not be accounted for in these analyses and may have affected precision. The effect of this missingness on our results is unclear. Our findings are likely not generalizable to other healthcare systems, because systems-level factors can vary. However, identified factors can now be targeted to improve these outcomes nationally for the large VA healthcare system, at a minimum.

Study strengths include the use of an integrated national VA database, a large sample size, an incident allopurinol user design, the use of a theoretical model, inclusion of several important covariates previously not included, examination of several models to test the robustness of findings, and examination of factors associated with maintaining target SU that were not reported previously.

We conducted a comprehensive national study of factors associated with achieving and maintaining target SU < 6 mg/dl in patients with gout, using data from one of the largest integrated national US healthcare systems. We identified key factors independently associated with achieving and maintaining target SU < 6 mg/dl: those of the patient, comorbidity, physician, system, healthcare access, allopurinol dose/adherence, and disease severity. Several characteristics may be amenable to patient/physician/systems–targeted interventions to improve the chances of maintaining target SU < 6 mg/dl in gout in this large national healthcare system. This, in turn, can improve gout outcomes and reduce the patient morbidity and the societal effect of gout.

ACKNOWLEDGMENT

We thank Michael Conner, BS, at Birmingham VA Medical Center for assisting in obtaining and programming the VA data for these analyses, and Jeffrey Foster at the University of Alabama at Birmingham for assistance in drafting tables and figures and proofing this paper for errors. We thank Dr. Joshua Richman at Birmingham VA Medical Center for his advice regarding the statistical analyses.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

REFERENCES

1. Singh JA, Hodges JS, Asch SM. Opportunities for improving medication use and monitoring in gout. Ann Rheum Dis 2009;68:1265-70.
2. Sarawate CA, Brewer KK, Yang W, Patel PA, Schumacher HR, Saag KG, et al. Gout medication treatment patterns and adherence to standards of care from a managed care perspective. Mayo Clin Proc 2006;81:925-34.
3. Mikuls TR, Farrar JT, Bilker WB, Fernandes S, Saag KG. Suboptimal physician adherence to quality indicators for the management of gout and asymptomatic hyperuricaemia: results from the UK General Practice Research Database (GPRD). Rheumatology 2005;44:1038-42.
4. Sarawate CA, Patel PA, Schumacher HR, Yang W, Brewer KK, Bakst AW. Serum urate levels and gout flares: analysis from managed care data. J Clin Rheumatol 2006;12:61-5.
5. Shoji A, Yamanaka H, Kamatani N. A retrospective study of the relationship between serum urate level and recurrent attacks of gouty arthritis: evidence for reduction of recurrent gouty arthritis with antihyperuricemic therapy. Arthritis Rheum 2004;51:321-5.
6. Schumacher HR Jr., Becker MA, Lloyd E, MacDonald PA, Lademacher C. Febuxostat in the treatment of gout: 5-yr findings of the focus efficacy and safety study. Rheumatology 2009;48:188-94.
7. Becker MA, Schumacher HR, MacDonald PA, Lloyd E, Lademacher C. Clinical efficacy and safety of successful longterm urate lowering with febuxostat or allopurinol in subjects with gout. J Rheumatol 2009;36:1273-82.
8. Becker MA, MacDonald PA, Hunt BJ, Lademacher C, Joseph-Ridge N. Determinants of the clinical outcomes of gout during the first year of urate-lowering therapy. Nucleosides Nucleotides Nucleic Acids 2008;27:585-91.
9. Halpern R, Fuldeore MJ, Mody RR, Patel PA, Mikuls TR. The effect of serum urate on gout flares and their associated costs: an administrative claims analysis. J Clin Rheumatol 2009;15:3-7.
10. Sundy JS, Baraf HS, Yood RA, Edwards NL, Gutierrez-Urena SR, Treadwell EL, et al. Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: two randomized controlled trials. JAMA 2011; 306:711-20.
11. Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res 2012;64:1431-46.
12. Khanna D, Khanna PP, Fitzgerald JD, Singh MK, Bae S, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: Therapy and antiinflammatory prophylaxis of acute gouty arthritis. Arthritis Care Res 2012;64:1447-61.
13. Zhang W, Doherty M, Bardin T, Pascual E, Barskova V, Conaghan P, et al. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2006;65:1312-24.
14. Hui M, Carr A, Cameron S, Davenport G, Doherty M, Forrester H, et al. The British Society for Rheumatology guideline for the management of gout. Rheumatology 2017;56:e1-e20.
15. Yamanaka H, Japanese Society of Gout and Nucleic Acid Metabolism. Japanese guideline for the management of hyperuricemia and gout: second edition. Nucleosides Nucleotides Nucleic Acids 2011;30:1018-29.
16. Sivera F, Andres M, Carmona L, Kydd AS, Moi J, Seth R, et al. Multinational evidence-based recommendations for the diagnosis and management of gout: integrating systematic literature review and expert opinion of a broad panel of rheumatologists in the 3e initiative. Ann Rheum Dis 2014;73:328-35.
17. Qaseem A, Harris RP, Forciea MA; Clinical Guidelines Committee of the American College of Physicians. Management of acute and recurrent gout: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2017;166:58-68.
18. Pandya BJ, Riedel AA, Swindle JP, Becker LK, Hariri A, Dabbous O, et al. Relationship between physician specialty and allopurinol prescribing patterns: a study of patients with gout in managed care settings. Curr Med Res Opin 2011;27:737-44.
19. Halpern R, Mody RR, Fuldeore MJ, Patel PA, Mikuls TR. Impact of noncompliance with urate-lowering drug on serum urate and gout-related healthcare costs: administrative claims analysis. Curr Med Res Opin 2009;25:1711-9.
20. Rashid N, Coburn BW, Wu YL, Cheetham TC, Curtis JR, Saag KG, et al. Modifiable factors associated with allopurinol adherence and outcomes among patients with gout in an integrated healthcare system. J Rheumatol 2015;42:504-12.
21. Kiltz U, Smolen J, Bardin T, Cohen Solal A, Dalbeth N, Doherty M,

et al. Treat-to-target (t2t) recommendations for gout. Ann Rheum Dis 2017;76:632-8.
22. Richette P, Doherty M, Pascual E, Barskova V, Becce F, Castaneda-Sanabria J, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis 2017;76:29-42.
23. Andersen R, Newman JF. Societal and individual determinants of medical care utilization in the United States. Milbank Mem Fund Q Health Soc 1973;51:95-124.
24. Andersen RM. Revisiting the behavioral model and access to medical care: does it matter? J Health Soc Behav 1995;36:1-10.
25. Boyko EJ, Koepsell TD, Gaziano JM, Horner RD, Feussner JR. US Department of Veterans Affairs medical care system as a resource to epidemiologists. Am J Epidemiol 2000;151:307-14.
26. Perlin JB, Kolodner RM, Roswell RH. The Veterans Health Administration: quality, value, accountability, and information as transforming strategies for patient-centered care. Am J Manag Care 2004;10:828-36.
27. McGinnis KA, Fine MJ, Sharma RK, Skanderson M, Wagner JH, Rodriguez-Barradas MC, et al. Understanding racial disparities in HIV using data from the veterans aging cohort 3-site study and VA administrative data. Am J Public Health 2003;93:1728-33.
28. Cowper DC, Hynes DM, Kubal JD, Murphy PA. Using administrative databases for outcomes research: select examples from VA health services research and development. J Med Syst 1999;23:249-59.
29. Berlowitz DR, Halpern J. Evaluating and improving pressure ulcer care: The VA experience with administrative data. Jt Comm J Qual Improv 1997;23:424-33.
30. Kashner TM. Agreement between administrative files and written medical records: a case of the Department of Veterans Affairs. Med Care 1998;36:1324-36.
31. Szeto HC, Coleman RK, Gholami P, Hoffman BB, Goldstein MK. Accuracy of computerized outpatient diagnoses in a Veterans Affairs general medicine clinic. Am J Manag Care 2002;8:37-43.
32. STROBE statement. Checklist of items that should be included in reports of cohort studies. [Internet. Accessed October 30, 2019.] Available from: www.strobe-statement.org/fileadmin/Strobe/uploads/checklists/STROBE_checklist_v4_cohort.pdf
33. US Department of Veterans Affairs. VA Informatics and Computing Infrastructure (VINCI). Washington, DC; 2011. [Internet. Accessed October 30, 2019.] Available from: www.hsrd.research.va.gov/for_researchers/vinci
34. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.
35. Goldberg DS, French B, Forde KA, Groeneveld PW, Bittermann T, Backus L, et al. Association of distance from a transplant center with access to waitlist placement, receipt of liver transplantation, and survival among US veterans. JAMA 2014;311:1234-43.
36. Smith SC, Shanks C, Guy G, Yang X, Dowell JD. Social and demographic factors influencing inferior vena cava filter retrieval at a single institution in the United States. Cardiovasc Intervent Radiol 2015;38:1186-91.
37. Singh JA, Hodges JS, Toscano JP, Asch SM. Quality of care for gout in the US needs improvement. Arthritis Rheum 2007;57:822-9.
38. Borowsky SJ, Nelson DB, Fortney JC, Hedeen AN, Bradley JL, Chapko MK. VA community-based outpatient clinics: performance measures based on patient perceptions of care. Med Care 2002;40:578-86.
39. VA Midwest Healthcare Network. VISN 23. [Internet. Accessed January 20, 2020.] Available from: www.visn23.va.gov
40. Doherty M, Jenkins W, Richardson H, Sarmanova A, Abhishek A, Ashton D, et al. Efficacy and cost-effectiveness of nurse-led care involving education and engagement of patients and a treat-to-target urate-lowering strategy versus usual care for gout: a randomised controlled trial. Lancet 2018;392:1403-12.
41. Goldfien R, Pressman A, Jacobson A, Ng M, Avins A. A pharmacist-staffed, virtual gout management clinic for achieving target serum uric acid levels: a randomized clinical trial. Perm J 2016;20:18-23.
42. Ramsubeik K, Ramrattan LA, Kaeley GS, Singh JA. Effectiveness of healthcare educational and behavioral interventions to improve gout outcomes: a systematic review and meta-analysis. Ther Adv Musculoskelet Dis 2018;10:235-52.
43. Singh JA, Edwards NL. Patient perceptions of gout management goals: a cross-sectional Internet survey. J Clin Rheumatol 2019 Jan 4 (E-pub ahead of print).
44. Sheer R, Null KD, Szymanski KA, Sudharshan L, Banovic J, Pasquale MK. Predictors of reaching a serum uric acid goal in patients with gout and treated with febuxostat. Clinicoecon Outcomes Res 2017;9:629-39.
45. Juraschek SP, Kovell LC, Miller ER 3rd, Gelber AC. Gout, urate-lowering therapy, and uric acid levels among adults in the United States. Arthritis Care Res 2015;67:588-92.
46. Harrold LR, Saag KG, Yood RA, Mikuls TR, Andrade SE, Fouayzi H, et al. Validity of gout diagnoses in administrative data. Arthritis Rheum 2007;57:103-8.