Factors Influencing Allopurinol Initiation in Primary Care

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ABSTRACT

Despite guidance on appropriate initiation, urate-lowering therapy is prescribed for only a minority of patients with gout. Electronic health records for 8,142 patients with gout were used to investigate the effect of age, sex, comorbidities, number of consultations, and meeting internationally agreed eligibility criteria on time to allopurinol initiation. Time to first prescription was modeled using multilevel Cox proportional hazards regression. Allopurinol initiation was positively associated with meeting eligibility criteria at diagnosis of gout, but negatively associated with becoming eligible after diagnosis. Managing gout as a chronic disease, with regular reviews to discuss allopurinol treatment, may reduce barriers to treatment.

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INTRODUCTION

Despite recent reports that 44% of primary care patients with gout fulfil guideline indications for urate-lowering therapy at diagnosis, and that 87% become eligible within 5 years, only a minority of those eligible patients with gout commence treatment.[1-3] This study investigated factors influencing initiation of allopurinol for treatment of gout in primary care.

METHODS

Primary care electronic health records (EHRs) from the Clinical Practice Research Datalink (CPRD) were analyzed for 8,386 patients with a diagnosis of gout. These patients were originally the gout cohort of a larger retrospective matched-cohort study investigating gout and risk of vascular disease.[4] All patients having gout in that study were eligible for this analysis, but 244 patients were excluded because of missing prescription data, resulting in a study population of 8,142 gout patients. Patients were older than 50 years with an incident diagnosis of gout between 1987 and 1999 to allow 10 years of follow-up.

The outcome of interest was time to first prescription of allopurinol (the most commonly used urate-lowering therapy in the United Kingdom). Putative factors that might be associated with allopurinol prescribing and potential confounders were: age, sex, exposure to alcohol (categorized into ever exposed, never exposed, or missing), body mass index (normal ≤25, overweight >25, or missing), burden of comorbidities (Charlson Comorbidity Index),[5] total number of general practitioner consultations during follow-up for any reason (quartiles), number of gout-related consultations (continuous) and meeting criteria for urate-lowering therapy, derived from the European League Against Rheumatism and the American College of Rheumatology guidelines) (2 or more gout attacks in 12 months, nephrolithiasis, chronic kidney disease, diuretic therapy or tophi) at diagnosis of gout or during follow-up.[5,6]

Time from the date of the first coded entry for gout (baseline) in the EHR to the date of issue of the first prescription for allopurinol was modeled using multilevel Cox proportional hazards regression. Patients not prescribed

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allopurinol were censored at the earliest of 10 years follow-up, transfer out, or death.

Putative factors of interest were identified from the EHR and entered into a full model. Shared frailty was used to account for clustering of prescribing behavior by practice allowing subject-specific interpretation of model coefficients. A significant likelihood ratio test statistic confirmed the variation in allopurinol initiation times among practices. The proportional hazards assumption was tested using generalized linear regression of the scaled Schoenfeld residuals on functions of time. Where a nonzero slope indicated a violation of the proportional hazards assumption, time-dependent covariates were generated by creating interactions of the predictors and a function of survival time. These time-varying covariates were included in the final model and time-varying effects were accommodated using the tvc() option in Stata 14 (StataCorp LP).

Table 1. Sample Characteristics (N = 8,142)

	Allopurinol Prescribed n = 3,283	Allopurinol Not Prescribed n = 4,859
Male, %, (No.)	70.9 (2,327)	67.9 (3,300)
Mean age at diagnosis of gout, y[a]	65.4 (SD 10.2)	66.9 (SD 11.1)
Eligible for allopurinol, %, (n)		
At baseline	34.7 (1,139)	27.1 (1,320)
Ever	25.4 (835)	34.7 (1,684)
Criteria by which eligible for allopurinol, %, (No.)[b]		
Not eligible	39.4 (1,294)	37.7 (1,832)
CKD	2.8 (92)	4.1 (197)
Diuretic therapy	40.7 (1,336)	47.5 (2,310)
≥2 gout attacks in 12 months	14.2 (466)	7.8 (381)
Tophi	1.3 (41)	0.9 (43)
Urolithiasis	1.6 (54)	2.0 (96)
Exposure to alcohol, %, (No.)[c]		
Never exposed to alcohol	11.9 (392)	13.2 (641)
Exposed to alcohol	76.3 (2,506)	71.6 (3,479)
Not recorded	11.7 (385)	15.2 (739)
BMI, %, (n)		
BMI ≤25kg/m[b]	19.1 (626)	24.1 (1,173)
BMI >25kg/m[b]	64.9 (2,129)	56.1 (2,724)
Not recorded	16.1 (528)	19.8 (962)
Charlson comorbidity score at gout diagnosis, mean	1.7 (SD 1.9)	0.8 (1.2)
Consultation for gout during follow-up, median No. (IQR)	2 (1-11)	1 (1-10)
Consultation for any reason during follow-up, median No. (IQR)	42 (4-279)	88 (8-440)

ACR = American College of Rheumatology; BMI = body mass index; CKD = chronic kidney disease; EULAR = European League Against Rheumatism; IQR = interquartile range; SD = standard deviation.

[a] Cohort older than 50 years.

[b] Eligibility according to the EULAR and ACR guidelines.[5,6]

[c] Exposure to alcohol measured as ever exposed/never exposed or not recorded closest to the date of diagnosis of gout.

RESULTS

Sample characteristics are displayed in Table 1. Median follow-up time available for the cohort was 31 months (interquartile range [IQR] 8-64 months). Median time to first prescription of allopurinol was 8 months (IQR 0-41 months).

Those eligible for allopurinol at baseline were more likely to receive it (hazard ratio [HR] = 1.41; 95% CI, 1.29-1.54) than ineligible patients. Those who became eligible following their diagnosis of gout were less likely to receive an allopurinol prescription than those eligible at baseline (HR = 0.77; 95% CI, 0.69-0.85).

Factors associated with time to allopurinol prescription are shown in Table 2. The hazard ratios for the time-varying covariates reflect how the risk is changing per unit time. For example, for sex and chronic kidney disease (CKD) the risk increases by 0.07% and decreases by 1% respectively.

The time-varying covariates indicate a change in the strength of the association with each additional unit of time; for example, for every additional month of follow-up the hazard ratio for allopurinol initation in men increased by 0.007 (0.004-0.01).

DISCUSSION

Those meeting the internationally agreed-upon eligibility criteria for urate-lowering therapy,[5,6] particularly at diagnosis, were more likely to receive allopurinol, suggesting that it is not lack of awareness of guidelines which underlies suboptimal prescribing, as has been reported elsewhere.[1,7] The short median time to first prescription of allopurinol, a positive association with eligibility at diagnosis, and the negative association with becoming eligible after diagnosis suggest decisions to initiate allopurinol are made early. When considered alongside the positive association between allopurinol initiation and recurrent consultations for gout, an eligibility criterion that by definition can only be met after diagnosis, it may be that clinicians are more likely to offer, or patients may be more likely to accept allopurinol after multiple acute attacks. Such was not the case for recurrent consultations for any reason which was negatively associated with allopurinol initiation, further suggesting that the presence of other eligibility criteria is not

reviewed as part of ongoing care, particularly in the presence of other comorbidities.

Evidence suggests that general practitioners perceive gout management to be acute rather than preventive[8] and assumes that patients would prefer treatment for an acute attack rather than long-term prophylactic medication.[7] For reasons that remain unclear, men are thought to be reluctant to consider long-term urate-lowering therapy[9] and were less likely to be prescribed allopurinol in this study, although conflicting results have been reported elsewhere.[1] There is also evidence that patient preferences may change,[10] suggesting a more structured chronic disease management for gout to revisit these preferences may remove some barriers to allopurinol treatment.

Study limitations included the inability to account for patient and clinician preferences in allopurinol-prescribing decisions, serum uric acid levels, and reliance on physician coding to identify gout cases, risking potential misclassification.

Our findings suggest that more frequent chronic disease reviews to revisit patient preferences and eligibility for allopurinol may reduce barriers to successful treatment of gout. Further research should focus on understanding patient and prescriber preferences in allopurinol prescribing and why patients who become eligible for allopurinol after diagnosis do not receive it.

Table 2. Adjusted Hazard of Receiving an Allopurinol Prescription

	Hazard Ratio	95% CI
Eligible for allopurinol (ever)		
Not eligible	1 [referent]	1 [referent]
CKD	3.48	2.31-5.26
Diuretic therapy	2.49	2.10-2.94
≥2 Consultations for gout in 12 months	3.88	3.22-4.68
Tophi	2.10	1.10-4.00
Urolithiasis	2.33	1.44-3.78
Age at diagnosis of gout[a]	1.00	0.99-1.01
Male	0.59	0.51-0.69
Overweight (BMI >25kg/m[b])		
Not overweight (BMI ≤25kg/m[b])	1 [reference]	1 [reference]
Overweight	1.14	1.02-1.27
Not recorded	0.88	0.74-1.04
Exposure to alcohol		
Never exposed	1 [reference]	1 [reference]
Ever exposed to alcohol	1.07	0.93-1.24
Not recorded	0.80	0.65-0.99
Charlson comorbidity score[a]	0.84	0.81-0.88
Number of consultations for gout[a] (during entire follow-up)	1.05	1.02-1.08
Number of consultations for any reason (during entire follow-up)		
Quartile 1 (0-34)	1 [reference]	1 [reference]
Quartile 2 (34-64)	0.44	0.37-0.61
Quartile 3 (65-119)	0.20	0.16-0.24
Quartile 4 (≥120)	0.07	0.05-0.09
Time-varying covariates[c]		
Male	1.007	1.004-1.011
Number of consultations for gout[a] (during entire follow-up)	1.002	1.001-1.002
Number of consultations for any reason (during entire follow-up)		
Quartile 1 (0-34)	1 [reference]	1 [reference]
Quartile 2 (34-64)	1.005	1.001-1.009
Quartile 3 (65-119)	1.009	1.005-1.037
Quartile 4 (≥120)	1.015	1.012-1.020
Eligible for allopurinol (ever)		
Not eligible	1 [referent]	1 [referent]
CKD	0.990	0.982-0.999
Diuretic therapy	0.991	0.988-0.994
≥2 consultations for gout in 12 mo	0.985	0.980-0.989
Tophi	0.994	0.979-1.008
Urolithiasis	0.990	0.982-0.999

ACR = American College of Rheumatology; BMI = body mass index; CKD = chronic kidney disease; EULAR = European League Against Rheumatism.

Note: Model is adjusted for all listed variables and clustering by practice.

[a] Denotes a continuous variable.

[b] Eligibility according to the EULAR and ACR guidelines.[5,6]

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