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Allopurinol Initiation and All-Cause Mortality Among Patients With Gout and Concurrent Chronic Kidney Disease:

A Population-Based Cohort Study

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See also: *Web-Only Supplement*

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Abstract

Background: Two recent randomized clinical trials of escalating doses of allopurinol for the progression of chronic kidney disease (CKD) reported no benefits but potentially increased risk for death. Whether the risk could occur in patients with gout and concurrent CKD remains unknown.

Objective: To examine the relation of allopurinol initiation, allopurinol dose escalation, and achieving target serum urate (SU) level after allopurinol initiation to all-cause mortality in patients with both gout and CKD.

Design: Cohort study.

Setting: The Health Improvement Network U.K. primary care database (2000 to 2019).

Participants: Patients aged 40 years or older who had gout and concurrent moderate-to-severe CKD.

Measurements: The association between allopurinol initiation and all-cause mortality over 5-year follow-up in propensity score (PS)-matched cohorts was examined. Analysis of hypothetical trials were emulated: achieving target SU level (<0.36 mmol/L) versus not achieving target SU level and dose escalation versus no dose escalation for mortality over 5-year follow-up in allopurinol initiators.

Results: Mortality was 4.9 and 5.8 per 100 person-years in 5277 allopurinol initiators and 5277 PS-matched noninitiators, respectively (hazard ratio [HR], 0.85 [95% CI, 0.77 to 0.93]). In the target trial emulation analysis, the HR of mortality for the achieving target SU level group compared with the not achieving target SU level group was 0.87 (CI, 0.75 to 1.01); the HR of

mortality for allopurinol in the dose escalation group versus the no dose escalation group was 0.88 (CI, 0.73 to 1.07).

Limitation: Residual confounding cannot be ruled out.

Conclusion: In this population-based data, neither allopurinol initiation, nor achieving target SU level with allopurinol, nor allopurinol dose escalation was associated with increased mortality in patients with gout and concurrent CKD.

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Gout is the most common form of inflammatory arthritis (1), and its incidence and prevalence have increased during the past few decades (2–8). The cornerstone of long-term management of gout is urate-lowering therapy. Rheumatology treatment guidelines for gout recommend a treat-to-target approach of lowering serum urate (SU) level to below 0.36 mmol/L for all patients with recurrent gout flares, tophi, or radiographic joint damage due to gout (9–12). The most widely used urate-lowering medication is allopurinol (13), which is started at a low dose, increased over weeks to months to achieve the SU level target, and continued indefinitely (9, 11, 14). Besides its urate lowering effect, several observational studies also examined the relation of allopurinol use to the risk for death in patients with gout; the results, however, are inconclusive (15–23).

Chronic kidney disease (CKD) is a comorbidity present in 20% or more of patients with gout (24, 25). Moreover, many studies have found that hyperuricemia is associated with an increased risk for incident CKD and its sequelae (26–28); thus, SU has been considered a potential therapeutic target for halting the progression of CKD. Recently, results from 2 randomized controlled trials (RCTs) showed no renal function–preserving benefits of allopurinol in patients with renal disease but without gout (29, 30). Neither trial set SU level–based inclusion criterion; participants’ mean SU levels were 0.49 mmol/L and 0.36 mmol/L at enrollment, respectively. Unexpectedly, both trials and pooled analyses indicated that allopurinol was associated with a 2-fold increased risk for death in patients with renal disease (31, 32).

Whether allopurinol use will increase mortality in patients with both gout and CKD remains unknown. We did a population-based cohort study to assess the relation of allopurinol initiation to mortality in patients with gout and concurrent moderate-to-severe CKD. In addition, we conducted 2 cohort studies emulating RCTs to examine the effects of achieving target SU level with allopurinol and allopurinol dose escalation on mortality.

METHODS

Data Source

We used data from The Health Improvement Network (THIN), an electronic health records database from general practitioners (GPs) in the United Kingdom. It consists of approximately 17 million persons in the United Kingdom. The computerized information includes sociodemographic characteristics, anthropometric characteristics, lifestyle factors, and details from visits to GPs (that is, prescriptions, diagnoses from specialist referrals,

hospital admissions, and results of laboratory tests). The Read classification system is used to code specific diagnoses (33), whereas a dictionary based on the Multilex classification system is used to code drugs (34). The validity of THIN for use in clinical and epidemiologic research studies has been shown in a previous study (35). The scientific review committee for THIN (21SRC003) and the institutional review board at Xiangya Hospital approved this study, with waiver of informed consent. This study followed the recommendations of the RECORD (REporting of studies Conducted using Observational Routinely-collected Data) statement and the extension RECORD-PE for pharmacoepidemiology studies (36).

Study Design and Cohort Definition

We included patients who were 40 to 89 years old, had gout and concurrent moderate-to-severe CKD from 1 January 2000 to 1 January 2018, and had at least 1 year of continuous enrollment with GPs before entering the study. The diagnosis of gout was based on the presence of at least 1 Read code for gout (37–39). Moderate-to-severe CKD (stage 3) was identified by either estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m² on at least 2 occasions more than 90 days apart within 1 year, with no intervening eGFR of 75 mL/min/1.73 m² or greater, or at least 1 Read code for CKD stage 3 to 5, hemodialysis, or peritoneal dialysis (39). The date of the first allopurinol prescription was assigned as the index date for allopurinol initiators, hereafter called the initiators, and a random date within that time block was assigned as the index date for noninitiators. Persons were excluded if they had cancer (including cancer of the cervix in situ and nonmelanoma skin cancer) or kidney transplant before the index date, or had no SU measure before the index date, or were prescribed other urate-lowering medication (for example, febuxostat, probenecid, benzbromarone, and sulphinyprazole) during the 1 year before the index date.

First, we did a propensity score (PS)–matched cohort study to compare mortality in initiators versus noninitiators. We calculated PS for initial prescription of allopurinol using logistic regression within each 1-year time block, and persons with missing covariate data for PS calculation were excluded from this analysis. For each initiator, we identified a nonallopurinol initiator within the same time block using a PS greedy matching algorithm (40) (Figure 1). Persons who were PS matched in the early accrual time blocks were ineligible to be included in the later accrual time blocks (see Supplement section 1.1 for details, available at [Annals.org](https://www.annals.org)).

Second, we emulated analyses of hypothetical target trial using a cloning, censoring, and weighting approach to assess the effect of either achieving target SU levels or allopurinol dose escalation on mortality in initiators using observational data (41–43) (Figure 1). We created a data set with 2 copies of each initiator at baseline and assigned each of the replicates to either 1 of the intervention groups (that is, achieving target SU level group vs. not achieving target SU level group, allopurinol dose-escalation group vs. no allopurinol dose escalation group). We allowed for a grace period of 1 year after allopurinol initiation for persons to achieve the target SU level or escalate the allopurinol dose (14, 44) (see Supplement section 1.2 for details, available at [Annals.org](https://www.annals.org)).

Assessment of Outcome

The outcome was all-cause mortality over the 5 years after the index date. The death date recorded in THIN is linked to the National Health Service; thus, a change in vital status to “dead” is immediately updated in the person’s electronic health record.

Assessment of Covariates

We obtained covariate information before the index date on sociodemographic characteristics (age, sex, socioeconomic deprivation index score, and region), anthropometric characteristics (body mass index), lifestyle factors (smoking status and alcohol consumption), CKD severity (grades 3 to 5), SU level, and comorbidities (congestive heart failure, myocardial infarction, stroke, hypertension, angina, diabetes mellitus, hyperlipidemia, chronic obstructive pulmonary disease, ischemic heart disease, pneumonia or infection, varicose veins, depression, and lupus). Medication use (that is, antihypertensive drug, statin, antidiabetic drug, diuretics, aspirin, systemic corticosteroid, topical corticosteroid, nonsteroidal anti-inflammatory drugs, nitrates, and colchicine) was identified by at least 1 prescription during the 1 year before the index date. Serum creatinine level was obtained from the database before the index date. The eGFR was calculated from serum creatinine levels using the Modification of Diet in Renal Disease formula (45). We identified the presence of comorbidities using Read codes, as recorded by GPs. Finally, we calculated the number of visits to a GP and hospital admissions during the 1 year before the index date.

Statistical Analysis

The baseline characteristics of initiators were compared with those of PS-matched noninitiators using standardized differences. Person-years of follow-up for each participant were calculated as the amount of time from the index date to the first of the following events: death, disenrollment from a GP practice participating in THIN, 5 years of follow-up, or the end of the study (30 April 2019). We computed mortality rates and plotted cumulative incidence curves of death for initiators and noninitiators, respectively. We estimated the absolute rate difference in mortality between the 2 comparison groups. We obtained the hazard ratio (HR) of mortality for the allopurinol initiation using Cox proportional hazards models and the SE of the HR using “sandwich estimation” (46). We tested the proportional hazards assumption using the Kolmogorov supremum test (47). When the proportional hazards assumption was violated, we conducted a weighted Cox regression to obtain a weighted average HR (48). We did 7 sensitivity analyses to assess the robustness of the study findings. First, we did an as-treated analysis to account for nonadherence to treatment under investigation by censoring the follow-up when either initiators discontinued allopurinol treatment (that is, no prescription refill for allopurinol after a period of more than 60 days) or noninitiators started treatment with either allopurinol or febuxostat. Second, we did an analysis among persons who were enrolled in THIN for at least 1 year and developed gout during the follow-up. Third, we multiplied imputed missing data values of covariates (that is, body mass index, smoking status, alcohol drinking, socioeconomic deprivation index score, and eGFR) using a sequential regression method. To minimize random error, we imputed 5 data sets, did the PS matching, calculated the HRs and their 95% CIs from each

imputed data set, and averaged these measures using the Rubin rule (49). Fourth, we did an analysis in participants whose gout diagnosis was defined by Read code plus receiving medication for gout (that is, colchicine or nonsteroidal anti-inflammatory drugs). This definition had a positive predictive value of 90% in the General Practice Research Database (50), in which 60% of participants overlap with THIN. Fifth, we introduced a 60-day lag time to exclude participants who died within the 60 days after the index date. Sixth, we calculated the E-value to quantitatively evaluate the minimum residual confounding effect that would nullify an association observed in the primary analyses (51). Finally, we assessed the robustness of our findings using other PS-matching methods (that is, optimal matching, 1: up to 2 matching, 1:up to 3 matching, and 1:up to 4 matching).

We emulated a hypothetical target trial to assess the effect of achieving target SU level with allopurinol, defined as any updated SU measurement less than 0.36 mmol/L within 1 year after allopurinol initiation, on mortality using observational data. Each initiator was assigned to both the achieving target SU level group and the not achieving target SU level group. We divided the follow-up time into 5 one-year time blocks starting from allopurinol initiation. Replicates assigned to the achieving target SU level group were censored at 1 year after allopurinol initiation if they did not achieve the target SU level. Replicates assigned to the not achieving target SU level group were censored if they achieved the target SU level at any time within 1 year after allopurinol initiation. Because censoring may lead to potential selection bias, we used inverse probability weights to account for censoring (42). The denominator of the inverse probability weight was the probability that a replicate adhered to his or her assigned group using the logistic regression, which consisted of the baseline covariates described earlier (see the Assessment of Covariates section). We fitted a pooled logistic regression model for mortality, including an indicator for achieving target SU level, year of follow-up (linear and quadratic term), and baseline confounders in the weighted population (52, 53). The odds ratio generated from this model approximated the HR because the outcome is rare. We used a robust SE to compute 95% CI for HR estimates. We estimated absolute 5-year mortality by fitting the pooled logistic models with product terms between the achieving target SU level indicator and the year of follow-up variables. The models' predicted values were then used to estimate mortality from baseline (52). The mortality curves were standardized to the baseline variables (54). We used a nonparametric bootstrap with 100 samples to compute the 95% CI for absolute estimates. We took the same approach to assess the effect of allopurinol dose escalation versus no dose escalation within 1 year after initiation of allopurinol treatment on mortality (Supplement sections 1.1 and 1.2; Appendix Figure 1, available at [Annals.org](https://annals.org)).

All analyses were done using SAS software, version 9.4 (SAS Institute), and a 2-sided *P* value of 0.05 or less was considered statistically significant for all tests.

Role of the Funding Source

The funding source had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

RESULTS

Time-Stratified PS-Matched Cohorts

As shown in the Appendix Table (available at [Annals.org](#)), before PS matching, initiators had a higher SU level; a lower eGFR; a higher prevalence of prescriptions of diuretics, systemic corticosteroids, nonsteroidal anti-inflammatory drugs, and colchicine; and more GP visits than noninitiators (noninitiators could be included in more than 1 recruitment time block before PS matching). After PS matching, the characteristics between the 2 comparison cohorts were well balanced, with all standardized differences less than 0.10 (Table 1). Among 5277 PS-matched initiators and noninitiators, the mean age was 74 years, and 40% were women. The mean values of body mass index, SU, and eGFR were 30.2 kg/m², 0.52 mmol/L, and 47.5 mL/min/1.73 m², respectively. The final mean levels of SU during 5-year follow-up were 0.42 mmol/L (SD, 0.13) and 0.48 mmol/L (SD, 0.12) in initiators and noninitiators, respectively. The final mean levels of eGFR during 5-year follow-up were 47.2 mL/min/1.73 m² (SD, 16.8) and 46.1 mL/min/1.73 m² (SD, 16.5) in initiators and noninitiators, respectively.

Mortality was lower in initiators than in noninitiators (Figure 2). As shown in Table 2, 811 deaths (incidence rate, 4.9 per 100 person-years) occurred during 5 years of follow-up in initiators and 922 deaths (incidence rate, 5.8 per 100 person-years) occurred in their comparators. In initiators, compared with noninitiators, the rate difference of mortality was -0.9 (95% CI, -1.4 to -0.4) per 100 person-years and the HR of mortality was 0.85 (CI, 0.77 to 0.93). The proportional hazard assumption was violated, and the weighted average HR of mortality for initiators was 0.88 (CI, 0.80 to 0.97). Results from all sensitivity analyses also showed that initiators had a modestly lower mortality than noninitiators (Table 2). The E-value was 1.63 (CI, 1.36 to 1.92), indicating that the relation of potential residual confounders to both allopurinol initiation and death must be 1.63 or greater to nullify the modestly protective association between allopurinol initiation and mortality seen in the primary analyses. Similar results were also seen when other PS-matching methods were used to control for confounding (data not shown).

Target Trial Emulation in Allopurinol Initiators

In 5277 initiators, 1484 achieved the target SU level within 1 year after the index date. The median value of initial allopurinol dose was 100 mg/d (range, 100 to 300 mg/d), the median value of final allopurinol dose was 300 mg/d (range, 100 to 900 mg/d), and the final mean level of SU during the 5-year follow-up was 0.30 mmol/L (SD, 0.08) in participants who achieved the target SU level. In 3793 participants who did not achieve the target SU level within 1 year after the index date, about 33% discontinued treatment after the first prescription. The median value of either initial or final allopurinol dose was 100 mg/d (range, 100 to 300 mg/d for initial dose; range, 100 to 900 mg/d for final dose), and the final mean level of SU during the 5-year follow-up was 0.47 mmol/L (SD, 0.11). For achieving target SU level, compared with not achieving target SU level, the difference in 5-year mortality was -1.6 percentage points (CI, -3.6 to -0.5 percentage points) and the HR was 0.87 (CI, 0.75 to 1.01) (Table 3; Appendix Figure 2, available at [Annals.org](#)).

In 5277 initiators, we excluded 1581 (30%) participants who did not have information on initial dose of allopurinol. In the remaining 3696 initiators, 773 increased their allopurinol dose within 1 year after the index date. In the allopurinol dose escalators, the median value of initial allopurinol dose before the dose escalation was 100 mg/d (range, 100 to 300 mg/d), and the corresponding value of final allopurinol dose after the dose escalation was 300 mg/d (range, 150 to 600 mg/d). The final mean SU level during the 5-year follow-up was 0.35 mmol/L (SD, 0.10). In the allopurinol nondose escalators, the final mean SU level was 0.39 mmol/L (SD, 0.11) during the 5-year follow-up. Compared with no dose escalation, the difference in 5-year mortality for dose escalation was -1.4 percentage points (CI, -3.7 to 0.4 percentage points), and the corresponding HR was 0.88 (CI, 0.73 to 1.07) (Table 3; Appendix Figure 3, available at [Annals.org](https://annals.org)).

DISCUSSION

In this large database of GP electronic health records from the United Kingdom, allopurinol initiation was associated with a modestly lower mortality compared with nonallopurinol use in participants with both gout and moderate-to-severe CKD. In addition, emulating a target RCT in allopurinol initiators, we showed that a treat-to-target approach of lowering SU level with allopurinol does not seem to increase mortality in participants with both gout and CKD.

Many observational studies have found that persons with hyperuricemia are at an increased risk for incident and progressive renal disease compared with the general population (26, 55, 56). However, findings from Mendelian randomization studies do not support a causal relationship between SU levels and renal function (57–59). In addition, despite potential renoprotective benefits suggested in previous observational studies (39, 60–64) and earlier RCTs (65–69), 2 large-scale, recent RCTs (the CKD-FIX [Controlled trial of slowing of Kidney Disease progression From the Inhibition of Xanthine oxidase] [29] and the PERL [Preventing Early Renal Loss in Diabetes] trials [30]) reported no protective effect of allopurinol on renal function deterioration in patients with either stage 3 or 4 CKD without gout or in those with both type 1 diabetes and early-to-moderate diabetic kidney disease. Furthermore, both trials reported that mortality was numerically higher in the allopurinol treatment group than in the placebo group, with pooled analysis showing a relative risk of 2.07 (CI, 0.98 to 4.34; $P=0.06$) (31, 32).

Although some previous studies found that allopurinol use was associated with lower mortality in patients with gout or persons with hyperuricemia (15–18), others have not confirmed this (19, 20). A recent meta-analysis found that several studies that reported a protective effect of allopurinol use on mortality may have immortal time bias or immeasurable time bias (21). The meta-analysis of studies that did not have such biases found a null association (21). Nevertheless, no previous study has assessed the effect of allopurinol initiation on mortality, specifically in patients with both gout and CKD. Our study found that neither allopurinol use, nor achieving target SU level, nor allopurinol dose escalation with allopurinol seem to increase mortality in participants with gout and concurrent CKD. These findings provide empirical evidence that adopting current gout treatment guidelines does not seem to have a detrimental effect on mortality in patients with both gout and CKD.

Two strengths of our study merit comment. First, owing to ethical and logistic difficulties, it is likely infeasible to conduct an RCT to assess whether allopurinol use increases mortality in participants with both gout and CKD. Using a real-world, population-based electronic database and a study design emulating a RCT, we showed that the strategy of achieving target SU level with allopurinol did not show a detrimental effect on mortality in patients with both gout and CKD. These findings are pertinent to the management of gout in the context of CKD. Second, we assessed both absolute and relative effects of allopurinol initiation, achieving target SU level via allopurinol, and allopurinol dose escalation on mortality and evaluated the effect using both intention-to-treat and as-treated approaches. All results were consistent, indicating the robustness of our study findings.

Our study has some limitations. First, although we used rigorous approaches to control for confounding, some covariates, such as disease severity; causes of CKD (for example, IgA nephropathy); and finer geographic areas across England, Northern Ireland, Scotland, or Wales, may not be well captured in THIN; thus, residual confounding cannot be ruled out. For example, we were unable to adjust for severity of various comorbidities. More frail and sicker patients may be less likely to be prescribed and continue their “preventive medication” (for example, allopurinol), particularly for nonimmediately fatal conditions, or physicians may be reluctant to escalate the allopurinol dose for those patients. Consequently, residual confounding due to severity of comorbidities could lead to a potentially biased protective effect of allopurinol on mortality. Second, allopurinol initiators and those who achieved target SU levels may have received better health care for their overall health needs than their comparators, which could also lead to lower mortality. Third, previous studies have reported that allopurinol use was associated with a decreased risk for cardiovascular mortality compared with nonuse (70) but a modestly increased risk for cardiovascular events compared with probenecid initiators (71). However, owing to a lack of recent data on cause-specific mortality in THIN, we were unable to assess the effect of allopurinol use on the risk for cardiovascular mortality in participants with both gout and CKD.

Our findings are clinically relevant in gout care because CKD is a common comorbidity of gout, and allopurinol is most commonly used with escalating doses to achieve and maintain a SU target below a subsaturation point of urate crystals, which will eventually decrease gout flare frequency and tissue urate crystal burden (72–74). However, the findings from 2 recent RCTs that allopurinol use may increase mortality in participants without gout but with CKD have raised concerns about whether a treat-to-target approach of lowering SU level would be safe for patients with gout and concurrent CKD. To that end, our findings provide reassurance that such a strategy does not have an apparent detrimental effect on mortality in patients with both gout and CKD (9–12).

In conclusion, in this population-based data, neither allopurinol initiation, nor achieving target SU level with allopurinol, nor allopurinol dose escalation was associated with an increased risk for death in patients with gout and concurrent CKD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

Appendix

Appendix Table.

Baseline Characteristics of Patients With Gout and CKD by Allopurinol Initiator and Noninitiator Status Before PS Matching

Characteristic	Allopurinol Initiators	Noninitiators*	Standardized Difference [†]
Patients, <i>n</i>	6962	64 353	–
Demographic characteristic			
Mean age (SD), <i>y</i>	73.9 (9.1)	74.9 (9.0)	0.050
Mean socioeconomic deprivation index (SD) [‡]	2.7 (1.3)	2.6 (1.3)	0.017
Female, %	40.0	32.3	0.074
Mean body mass index (SD), <i>kg/m</i>²	30.2 (5.8)	29.4 (5.4)	0.071
Mean SU level (SD), <i>mmol/L</i>	0.54 (0.11)	0.42 (0.12)	0.471
Mean estimated glomerular filtration rate (SD), <i>mL/min/1.73 m</i>²	46.6 (15.1)	50.2 (14.8)	0.114
Lifestyle factors, %			
Drinking			0.018
None	20.8	19.2	
Past	3.7	3.9	
Current	75.5	76.9	
Smoking			0.001
None	49.0	49.3	
Past	45.0	44.5	
Current	6.1	6.2	
Region, %			0.061
England	77.0	82.5	
Northern Ireland	5.6	5.5	
Scotland	8.3	4.3	
Wales	9.1	7.7	
Stage of CKD, %			0.005
Stage 3	95.6	95.6	
Stage 4	3.4	3.2	
Stage 5	1.0	1.2	
Comorbidity, %			
Congestive heart failure	21.2	14.1	0.087
Hypertension	81.9	81.5	0.005
Chronic obstructive pulmonary disease	10.1	9.0	0.017

Characteristic	Allopurinol Initiators	Noninitiators*	Standardized Difference [†]
Myocardial infarction	15.6	14.6	0.013
Angina	20.5	20.7	0.002
Diabetes	29.1	30.4	0.014
Hyperlipidemia	25.5	25.2	0.004
Ischemic heart disease	35.2	33.3	0.018
Pneumonia or infection	9.3	9.7	0.007
Stroke	7.6	8.4	0.015
Transient ischemic attack	6.4	7.4	0.018
Varicose veins	10.5	10.7	0.002
Depression	10.2	9.6	0.010
Lupus	0.3	0.4	0.007
Medication, %[§]			
Angiotensin-converting enzyme inhibitors	54.7	48.7	0.058
β -receptor inhibitor	49.1	41.9	0.069
Calcium-channel blockers	35.8	39.7	0.039
Statin	62.4	61.1	0.013
Antidiabetic	20.2	19.9	0.003
Anticoagulants	20.0	16.1	0.048
Aspirin	41.2	41.5	0.003
Thiazide diuretics	31.8	21.3	0.114
Loop diuretics	46.0	29.7	0.163
Potassium-sparing diuretics	14.9	8.8	0.089
Systemic corticosteroid	23.3	14.0	0.116
Topical corticosteroid	14.7	14.1	0.007
Nitrates	14.5	12.4	0.031
Nonsteroidal anti-inflammatory drugs	70.4	51.4	0.203
Colchicine	49.5	12.2	0.411
Mean Health care use (SD)[§]			
Hospitalizations	0.6 (1.4)	0.6 (1.4)	0.018
General practice visits	10.2 (7.9)	7.9 (7.7)	0.143
Specialist referrals	0.8 (1.3)	0.7 (1.2)	0.039

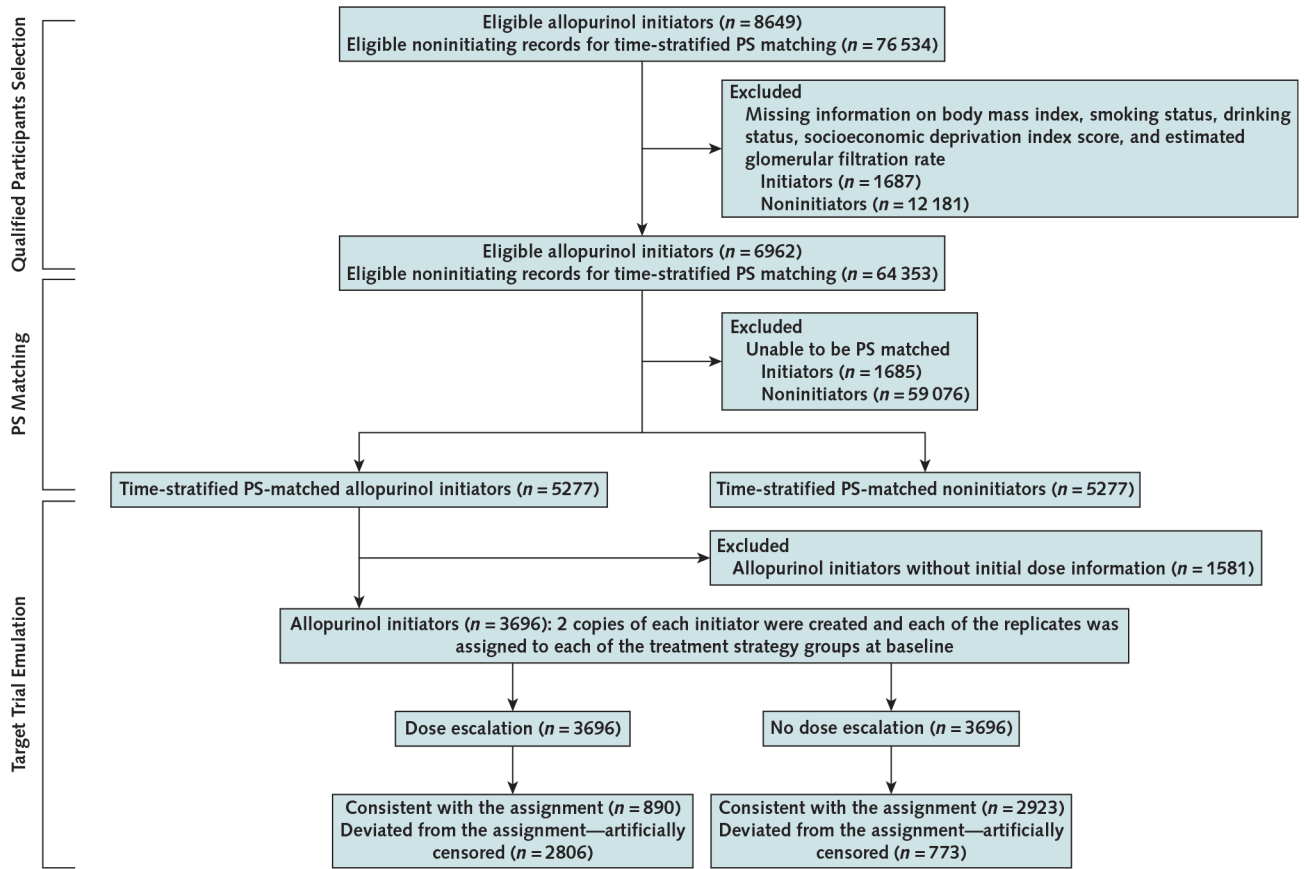
CKD = chronic kidney disease; PS = propensity score; SU = serum urate.

* The number for noninitiators represents the number of records (i.e., participants could be included in more than 1 recruitment time block).

[†]We used generalized estimating equations to calculate the standardized differences accounting for correlation among the duplicated participants.

[‡]The socioeconomic deprivation index was measured by the Townsend deprivation index, which was grouped into quintiles from 1 (least deprived) to 5 (most deprived).

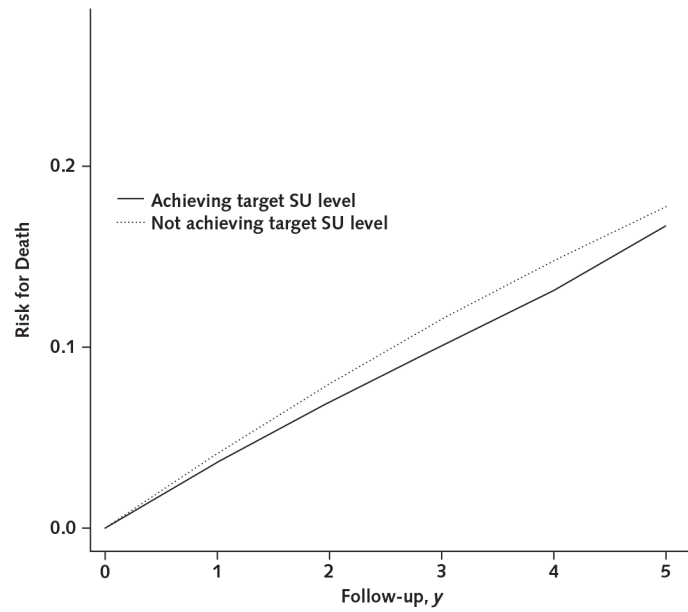
[§]Frequency during the past year.



Appendix Figure 1.

Flow chart of eligible persons for examining the relation of allopurinol initiation and allopurinol dose escalation to all-cause mortality, THIN 2000 to 2019.

PS = propensity score; THIN = The Health Improvement Network.

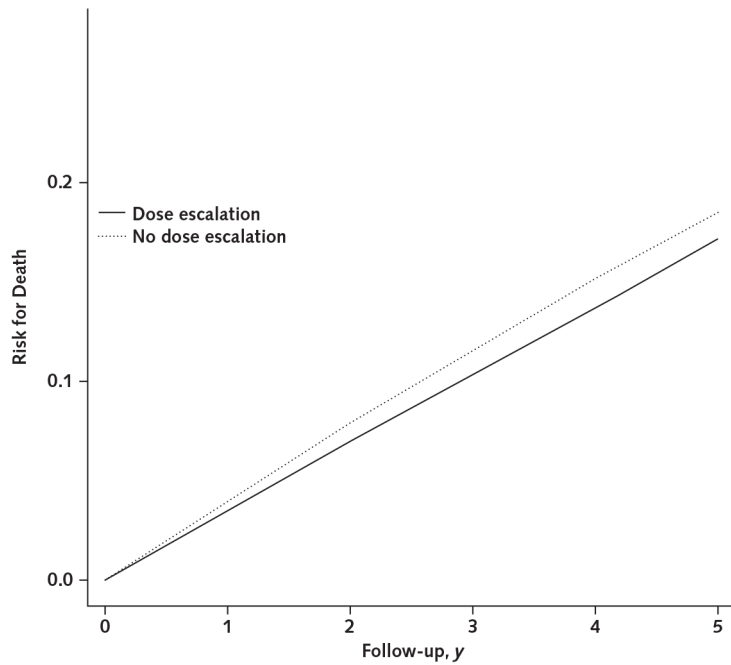


At risk, <i>n</i>	0	1	2	3	4	5
Achieving target SU level	5277	1335	1072	793	592	432
Not achieving target SU level	5277	3194	2539	1974	1475	1085

Appendix Figure 2.

Five-year risk for death between patients achieving target SU level and those not achieving target SU level with allopurinol in the target trial emulation study.

SU = serum urate.



At risk, <i>n</i>	0	1	2	3	4	5
Dose escalation	3696	676	544	423	318	239
No dose escalation	3696	2495	2083	1999	1533	841

Appendix Figure 3.

Five-year risk for death between allopurinol dose escalation and no allopurinol dose escalation in the target trial emulation study.

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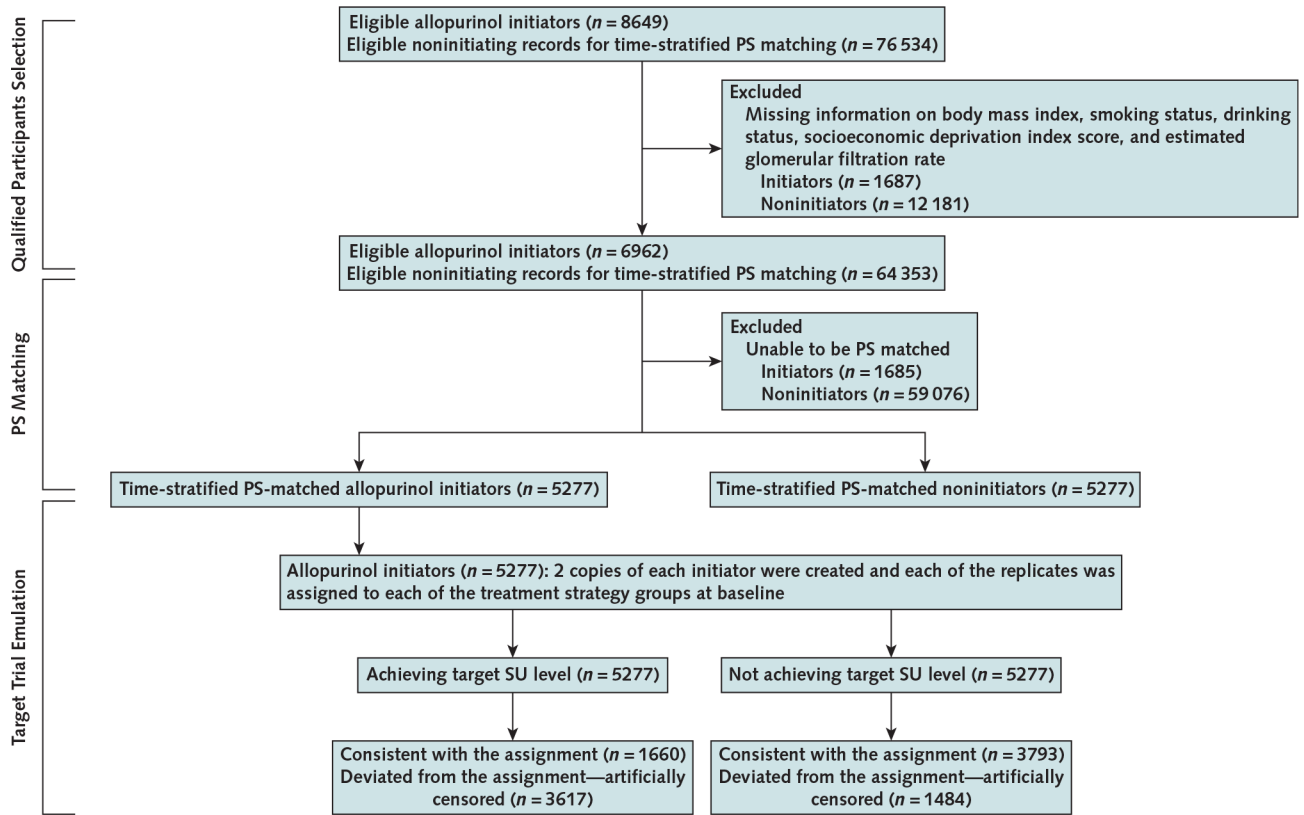
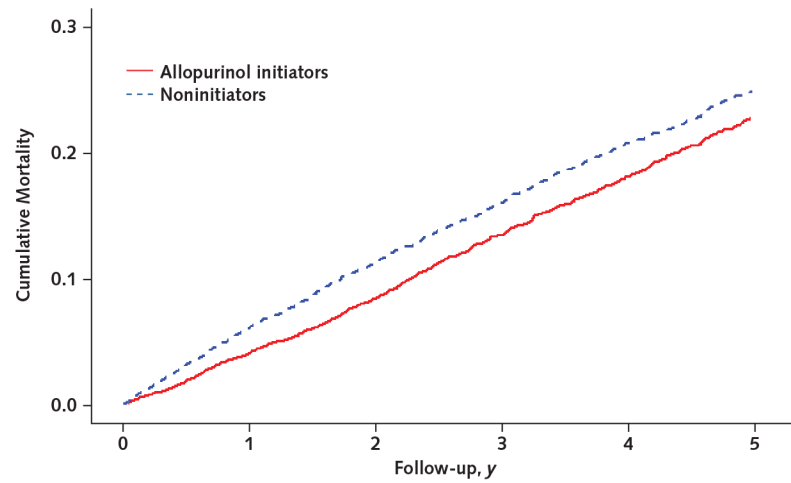


Figure 1. Flow chart of eligible persons for examining the relation of allopurinol initiation and achieving target SU level with allopurinol to all-cause mortality, THIN 2000 to 2019. PS= propensity score; SU= serum urate; THIN= The Health Improvement Network.



At risk, <i>n</i>						
Allopurinol initiators	5277	4529	3612	2767	2070	832
Noninitiators	5277	4383	3447	2659	1975	780

Figure 2. Five-year cumulative mortality between allopurinol initiators and noninitiators in the propensity score–matched study.

Table 1. Baseline Characteristics of Patients With Gout and CKD by PS-Matched Allopurinol Initiator and Noninitiator Status

Characteristic	Allopurinol Initiators	Noninitiators	Standardized Difference
Patients, n	5277	5277	-
Demographic characteristic			
Mean age (SD), y	73.9 (9.0)	74.0 (9.6)	0.008
Mean socioeconomic deprivation index score (SD) *	2.7 (1.3)	2.7 (1.3)	0.013
Female, %	38.8	39.8	0.021
Mean body mass index (SD), kg/m ²	30.2 (5.7)	30.1 (5.8)	0.015
Mean SU level (SD), mmol/L	0.52 (0.10)	0.52 (0.10)	0.041
Mean estimated glomerular filtration rate (SD), mL/min/1.73 m ²	47.5 (14.0)	47.5 (14.1)	0.001
Lifestyle factors, %			
Drinking			0.009
None	20.4	20.8	
Past	3.7	3.8	
Current	75.9	75.5	
Smoking			0.013
None	49.3	48.7	
Past	44.6	44.9	
Current	6.1	6.3	
Region, %			<0.001
England	78.2	78.2	
Northern Ireland	5.2	5.2	
Scotland	8.0	8.0	
Wales	8.6	8.6	
Stage of CKD, %			0.036
Stage 3	96.0	95.7	
Stage 4	3.0	3.5	
Stage 5	0.9	0.7	
Comorbidity, %			<0.001
Congestive heart failure	19.3	19.3	

Characteristic	Allopurinol Initiators	Noninitiators	Standardized Difference
Hypertension	81.6	81.0	0.014
Chronic obstructive pulmonary disease	9.7	10.1	0.011
Myocardial infarction	15.3	15.2	0.005
Angina	20.0	19.9	0.001
Diabetes	29.1	28.5	0.012
Hyperlipidemia	25.6	24.3	0.029
Ischemic heart disease	34.3	33.5	0.017
Pneumonia or infection	9.3	9.8	0.017
Stroke	7.6	7.5	0.003
Transient ischemic attack	6.7	6.5	0.005
Varicose veins	9.8	11.1	0.044
Depression	10.2	10.4	0.007
Lupus	0.3	0.3	0.007
Medication, %[†]			
Angiotensin-converting enzyme inhibitors	53.6	53.8	0.004
β -receptor inhibitor	47.7	47.1	0.013
Calcium-channel blockers	36.1	36.3	0.003
Statin	62.0	60.7	0.027
Antidiabetic	20.0	19.8	0.005
Anticoagulants	19.0	20.1	0.026
Aspirin	41.2	40.1	0.022
Thiazide diuretics	31.5	31.8	0.006
Loop diuretics	42.3	42.7	0.008
Potassium-sparing diuretics	13.3	13.6	0.007
Systemic corticosteroid	21.5	21.6	0.005
Topical corticosteroid	14.5	14.1	0.014
Nitrates	13.9	13.9	0.001
Nonsteroidal anti-inflammatory drugs	68.8	70.5	0.037
Colchicine	43.8	44.4	0.012
Mean Health care use (SD)[‡]			
Hospitalizations	0.6 (1.3)	0.6 (1.4)	0.011

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Characteristic	Allopurinol Initiators	Noninitiators	Standardized Difference
General practice visits	9.8 (7.4)	9.9 (9.7)	0.019
Specialist referrals	0.8 (1.2)	0.8 (1.3)	0.003

CKD = chronic kidney disease; PS = propensity score; SU = serum urate.

* The socioeconomic deprivation index was measured by the Townsend deprivation index, which was grouped into quintiles from 1 (least deprived) to 5 (most deprived).

[#] Frequency during the past year.

Table 2. Relation of Allopurinol Initiation to All-Cause Mortality in Patients With Gout and CKD in the PS-Matched Cohort Study

Analysis	Allopurinol Initiators/Noninitiators				Rate Difference* per 100 Person-Years (95% CI)	Hazard Ratio [†] (95% CI)
	Patients, n	Deaths, n	Mean Follow-up, y	Rate per 100 Person-Years		
Primary analysis	5277/5277	811/922	3.1/3.0	4.9/5.8	-0.9 (-1.4 to -0.4)	0.85 (0.77 to 0.93)
As-treated analysis [‡]	5277/5277	318/599	1.5/2.0	4.1/5.7	-1.6 (-2.3 to -1.0)	0.72 (0.63 to 0.82)
Incident gout cases	4313/4313	643/698	3.1/3.0	4.8/5.4	-0.6 (-1.1 to 0.0)	0.89 (0.80 to 0.99)
Missing data imputation [§]	5980/5980	926/1067	3.1/3.0	4.9/5.9	-1.0 (-1.5 to -0.5)	0.83 (0.76 to 0.91)
Redefined gout cases	4714/4714	704/783	3.1/3.0	4.8/5.6	-0.8 (-1.3 to -0.2)	0.86 (0.78 to 0.96)
60-d lag analysis	5226/5226	771/882	3.0/2.9	4.9/5.8	-0.9 (-1.4 to -0.4)	0.84 (0.76 to 0.93)

CKD = chronic kidney disease; PS = propensity score.

*The rate in allopurinol initiators minus the rate in noninitiators.

[†]The rate in the allopurinol initiators divided by the rate in noninitiators.

[‡]This analysis censored the follow-up at the time when allopurinol initiators discontinued the allopurinol treatment (i.e., no prescription refill for allopurinol with a period of more than 60 d) or noninitiators started treatment (initiated with allopurinol or febuxostat).

[§]We imputed 5 data sets and did the PS matching for each imputed data set. Patients, deaths, mean follow-up, rate, rate difference, and hazard ratio refer to the average value of the 5 imputed data sets.

Table 3.

Relations of Achieving Target SU Level (<0.36 mmol/L) and Allopurinol Dose Escalation to All-Cause Mortality in Allopurinol Initiators With Gout and CKD in the Target Trial Emulation Studies

Variable	Achieving Target SU Level /Not Achieving Target SU Level	Dose Escalation/ No Dose Escalation
Patients, <i>n</i>	5277/5277	3696/3696
Weighted deaths, <i>n</i>	660/754	483/518
Weighted risk over 5 y, %	13.2/14.8	13.9/15.2
Inverse probability weighting risk difference, % (95% CI)	-1.6 (-3.6 to -0.5)	-1.4 (-3.7 to 0.4)
Inverse probability weighting hazard ratio (95% CI)	0.87 (0.75 to 1.01)	0.88 (0.73 to 1.07)

CKD = chronic kidney disease; SU = serum urate.

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