Title

Lowering Serum Urate With Urate-Lowering Therapy to Target and Incident Fracture Among People With Gout

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Title: Lowering serum urate with urate-lowering therapy to target and incident fracture among people with gout

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Competing interests
None.

Abstract

Objectives: Gout is associated with a higher risk of fracture; however, the associations of hyperuricemia and urate-lowering therapy (ULT) with the risk of fracture have been inconsistent. We examined whether lowering serum urate (SU) levels with ULT to a target level (i.e., <360 μmol/L) reduces risk of fracture among people with gout.

Method: We emulated analyses of a hypothetical target trial using a "cloning, censoring, and weighting" approach to examine the association between lowering SU with ULT to the target levels and the risk of fracture using data from The Health Improvement Network, a United Kingdom primary care database. Individuals with gout who were 40 years or older and initiated ULT were included in the study.

Results: Among 28,554 people with gout, the 5-year risk of hip fracture was 0.5% for the "achieving the target SU level" arm and 0.8% for "not achieving the target SU level" arm, respectively. The risk difference and hazard ratio for "achieving the target SU level" arm was -0.3% (95% confidence interval [CI]: -0.5% to -0.1%) and 0.66 (95% CI: 0.46 to 0.93), respectively, compared with "not achieving the target SU level". Similar results were observed when the associations of lowering SU level with ULT to the target levels with the risk of composite fracture, major osteoporotic fracture, vertebral fracture, and non-vertebral fracture were assessed.

Conclusions: In this population-based study, lowering the SU level with ULT to the guideline-based target level is associated with a lower risk of incident fracture in people with gout.

Introduction

Fractures are a leading cause of morbidity and mortality worldwide (1). The formidable social and economic burden of fracture, especially in the elderly, make its prevention a major public health goal (2, 3). Gout is the most common inflammatory arthritis and its prevalence and incidence have been increasing overtime (4-6). Previous studies have found that gout is associated with a higher risk of fracture; however, the exact mechanism linking gout to fracture remains unclear (7, 8).

Several studies have examined the association between serum urate (SU) levels (regardless of gout status) and the risk of fracture (9-15). Most of these studies evaluated the relation of levels of SU either continuously or categorically (e.g., quartiles or quintiles) to the risk of fracture; the results were inconsistent (9-14). One study assessed the association between hyperuricemia and the risk of fracture and reported that the risk of hip fracture was higher among men with hyperuricemia than those with normouricemia (15). A few studies also examined the relation of urate-lowering therapy (ULT) to the risk of fracture (16-19); however, the results were inconsistent. In addition, none of these studies specifically examined the effect of lowering the SU with ULT to the target levels (i.e., <360 μmol/L) on the risk of fracture.

Randomized clinical trials have assessed the effect of treat-to-target SU with ULT to below 360 μmol/L on the risk of recurrent gout flares, tophi, or radiographic joint damage for people with gout (20-22); however, these studies were unable to evaluate the effect of lowering SU with ULT to target levels on the risk of fractures owing to the limited statistical power. Using a population-based electronic medical

records database, we conducted a cohort study emulating analyses of a hypothetical target trial to examine the effect of lowering SU with ULT to the target level (i.e., <360 μmol/L) on the risk of fracture among people with gout.

Method

Data source

We used data from The Health Improvement Network (THIN) (now called IQVIA Medical Research Database), an electronic health records database from general practitioners (GPs) in the United Kingdom (UK). The THIN consist of approximately 17 million individuals in the UK. The computerized information includes socio-demographics, anthropometric characteristics, lifestyle factors, and details from visits to GPs (i.e., prescriptions, diagnoses from specialist referrals, hospital admissions, and results of laboratory tests). The READ classification system is used to code specific diagnoses, whereas a dictionary based on the Multilex classification system is used to code drugs. The validity of THIN for use in clinical and epidemiological research studies has been demonstrated in a previous study (23, 24). The scientific review committee for THIN database and the institutional review board at Xiangya Hospital approved this study with a waiver of informed consent. This study followed the recommendations of the STROBE initiative for reporting observational studies in epidemiology.

Study design and cohort definition

We included participants who were 40 to 89 years old, had gout between 1 January 2000 and 31 October 2021, and had at least one year of continuous enrollment with GPs prior to entering the study (**eFigure 1**). The diagnosis of gout was based on the

presence of at least one gout Read code (24-26). Of them, we identified ULT initiators (i.e., allopurinol, febuxostat, probenecid, benzbromarone, or sulphinpyrazone) based on the first record of ULT prescription after the diagnosis of gout. The first ULT prescription date was assigned as each participant's index date. Persons were excluded if they had cancer or any fracture before the index date, or had missing values of body mass index (BMI), drinking status, smoking status, socioeconomic deprivation index score, SU, and estimated glomerular filtration rate (eGFR) before the index date.

We emulated analyses of a hypothetical target trial using a "cloning, censoring, and weighting" approach to evaluate the effect of "achieving the target SU levels (i.e., <360 μmol/L)" on the risk of fracture in ULT initiators using observational data (24, 27-29). We created a data set with two clones of each initiator at baseline and assigned each of the clones to either one of the intervention arms (i.e., achieving the target SU level arm vs. not achieving the target SU level arm). For example, we assigned one clone to the "achieving the target SU level" arm (i.e., achieving the target SU during one year after the index date) and the other clone to the "not achieving the target SU level" arm (i.e., not achieving the target SU during one year after the index date). "Cloning" makes two comparison groups compatible with their observed data at time zero (**Figure 1**). We allowed for a grace period of one year after ULT initiation for individuals to achieve the target SU level (21). If clones deviated from their assigned strategy during the first year of follow-up, they would be artificially censored. Specifically, clones assigned to the "achieving the target SU level" arm were censored if they did not achieve the target SU at the end of the first year of follow-up, and clones assigned to the "not achieving the target SU level" arm

were censored if they achieved the target SU at during the first year of follow-up. During the grace period, if an individual experienced an incident fracture or loss to follow-up or died before achieving the target SU, that person was considered consistent with his/her assignment in both arms (or clones) and contributed the outcome to each of the assigned arms (**Figure 1**). The key protocol components are shown in **eTable 1**.

Assessment of outcome

The primary outcome was hip fracture (30, 31). Secondary outcomes were composite fracture (fractures at any site) (27), major osteoporotic fracture (hip, vertebral, wrist, and humerus fracture), vertebral fracture, and non-vertebral fracture (32, 33). We defined fracture outcomes using Read codes as per previously published studies (27, 31, 34). Positive predictive values were 91.0% for hip fracture and 88.1% for vertebral fracture (34), respectively.

Assessment of covariates

Covariates prior to the index date were obtained from THIN. These included socio-demographics (age, sex, and socioeconomic deprivation index score, and region), anthropometric characteristics (BMI), lifestyle factors (smoking status and drinking status), SU, gout duration, comorbidities (hypertension, venous thromboembolism, myocardial infarction, stroke, pneumonia or infection, hyperlipidaemia, varicose veins, depression, chronic obstructive pulmonary disease, fall, osteoporosis, atrial fibrillation, osteoarthritis, diabetes, and chronic kidney disease) prior to the index date, as well as medication use (disease-modifying antirheumatic drugs, antihypertensive drug, antidiabetic drug, statin, anticoagulants, aspirin, non-steroidal

anti-inflammatory drugs [NSAIDs], opioids, nitrates, colchicine, diuretics, systemic corticosteroid, proton pump inhibitor, and antiosteoporosis drugs [i.e., bisphosphonates, denosumab, alendronate, ibandronate, risedronate, zoledronic acid, teriparatide, and hormone replacement therapy]) within one year before the index date. Serum creatinine was obtained from the database before the index date. The eGFR was calculated from serum creatinine values using the Modification of Diet in Renal Disease (MDRD) formula (35). Finally, we calculated the number of visits to a GP and hospital admissions within one year before the index date.

Statistical analysis

We created a dataset with two copies of each ULT initiator at baseline. Each initiator was assigned to both "achieving the target SU level" and "not achieving the target SU level" arms. We divided the follow-up time into five one-year time blocks starting from ULT initiation. Replicates assigned to the "achieving the target SU level" arm were artificially censored one year after ULT initiation if they did not achieve the target SU level. Replicates assigned to the "not achieving the target SU level" arm were artificially censored if they achieved the target SU level before developing fracture or at any time within one year after ULT initiation. Because artificial censoring may lead to potential selection bias we used inverse probability weights (IPW) to account for censoring (28). The denominator of the IPW was the probability that a replicate adhered to his/her assigned arm (i.e., uncensored) using the logistic regression which consisted of the baseline covariates described above (see **Assessment of covariates**) and the time-varying covariates (i.e., BMI, eGFR, lifestyle factors, comorbidities, medication use, and healthcare utilization) between the index date and the date of artificial censoring. Participants were followed until the first

occurrence of the following events: incident fracture, death, disenrollment from a GP practice participating in THIN, five years of follow-up, or the end of the study (31 October 2021). We compared the risk of fracture between two weighted comparison groups using a pooled logistic regression model including an indicator for "achieving the target SU level", and adjusting for the year of follow-up (linear and quadratic term), baseline confounders and time-varying confounders in the weighted population (36, 37). The odds ratio generated from this model approximated the HR because the outcome is rare (37). We used a robust standard error (SE) to compute 95% CI for HR estimates. We estimated the absolute risk difference of fracture over five years by fitting the pooled logistic models with product terms between the "achieving the target SU level" indicator and the year of follow-up variables. The models' predicted values were then used to estimate the risk of fracture from baseline (36). The risk curves were standardized to the baseline variables (38). We used a nonparametric bootstrap analysis with 20 samples to compute the 95% CI for absolute estimates.

We performed several sensitivity analyses to assess the robustness of the study findings. First, we calculated the E value to quantitatively evaluate the minimum residual confounding effect that would nullify an association observed in the primary analyses (39). Second, we performed an analysis among subjects who were enrolled in THIN for at least one year and developed gout during the follow-up (i.e., people with incident gout). Third, we performed an analysis in participants whose gout diagnosis was defined by Read code plus receiving medication for gout (i.e., colchicine or NSAIDs). This definition had a positive predictive value of 90% in the General Practice Research Database (40), in which 60% of participants overlap with THIN. Fourth, we performed an analysis exclusively in participants initiating

allopurinol to achieve the target SU level. Fifth, we performed an analysis among participants who received the anti-inflammatory treatment (i.e., corticosteroid, colchicine or NSAIDs) during the one year before the index date. Sixth, to evaluate whether there is a SU concentration-dependent relation of achieving the target SU level to the risk of hip fracture, we performed an analysis by creating three replicates for each initiator at baseline and assigning the three replicates to one of the following intervention arms: achieving the target SU<300 μmol/L (i.e., recommended in the previous BSR/BHPR guideline) (41), achieving the target SU of 300-360 μmol/L, and not achieving the target SU during one year after the index date, and comparing the risk of fracture among the three comparison groups using the same approach. Finally, we examined the relation of achieving the target SU levels with ULT to the risk of traumatic injury, a control outcome for which we expected a null association.

All analyses were conducted using SAS software, version 9.4 (SAS Institute Inc), and a two-sided P value ≤ 0.05 was considered statistically significant for all tests.

Results

We identified 73,206 participants who met the inclusion criteria and initiated ULT during the study period. Of them, we excluded 44,652 initiators who had cancer, or any fracture prior to the index date, or missing values of BMI, drinking status, smoking status, socioeconomic deprivation index score, SU, and eGFR. The final study cohort consisted of 28,554 participants (**eFigure 1**). The mean age was 65.3 years and 23.7% were women. The mean values of BMI and SU were 30.3 kg/m^2 and 510.3 μmol/L, respectively. The baseline characteristics of the remaining participants

are shown in **Table 1**.

Of 28,554 ULT initiators, 8,390 achieved the target SU level within one year after the index date. The mean of the final SU level during the five-year follow-up was 311.2 μmol/L and 454.4 μmol/L among individuals who achieved the target SU level and individuals who did not achieve the target SU level within one year after the index date, respectively. Baseline SU level, eGFR, BMI, socioeconomic deprivation index, osteoarthritis, diabetes, prescription with statin, NSAIDs, nitrate, antiosteoporosis drugs, antihypertensive drugs, corticosteroids, or aspirin were the most important predictors for adherence to "achieving the target SU level". Baseline SU level, eGFR, BMI, osteoarthritis, stroke, fall, prescription with statin, NSAIDs, opioids, nitrate, antiosteoporosis drugs, antihypertensive drugs, corticosteroids, proton pump inhibitor, diuretics, or aspirin were the most important predictors for adherence to "not achieving the target SU level". The C statistics for predicting the adherence of "achieving the target SU level" and "not achieving the target SU level" was 0.73 and 0.76, respectively. The distribution of the estimated weights for adherence is shown in **eFigure 2**. After IPW, baseline characteristics were well balanced between the two comparison groups with all standardized mean differences<0.1 (**eTable 2**). The mean follow-up time was 3.6 years for the "achieving the target SU level" arm and 3.5 years for the "not achieving the target SU level" arm, respectively.

As shown in **Figure 2**, the 5-year risk of hip fracture was lower for the "achieving the target SU level" arm (0.5%) compared with the "not achieving the target SU level" arm (0.8%). The 5-year risk difference of hip fracture for the "achieving the target SU level" arm compared with the "not achieving the target SU

level" arm was -0.3% (95% CI: -0.5% to -0.1%), and the HR was 0.66 (95% CI: 0.46 to 0.93) (**Table 2**). The prevented fraction of achieving the target SU level with ULT for hip fracture was 37.5%, suggesting that of eight hip fracture cases that occurred among 1000 participants in the "not achieving the target SU levels" arm over five years, three cases can be prevented if participants reached the "target SU levels with the ULT". The E-value was 2.40 (95% CI: 1.36 to 3.77), indicating that the relation of potential residual confounder(s) to both "achieving the target SU level" and risk of hip fracture must be ≥ 2.40 to nullify the protective association between "achieving the target SU level" and risk of hip fracture observed in the primary analyses. Results from the sensitivity analyses conducted among participants with incident gout, among those whose gout diagnosis was defined by Read code plus receiving medication for gout, among those initiating with allopurinol, and among those who received the anti-inflammatory treatment (i.e., corticosteroid, colchicine or NSAIDs) during one year before the index date also showed that "achieving the target SU level" was associated with a lower risk of hip fracture compared with "not achieving the target SU level", with HR being 0.63 (95% CI: 0.43 to 0.92), 0.65 (95% CI: 0.45 to 0.95), 0.64 (95%CI: 0.45 to 0.92), and 0.67 (95%CI 0.47 to 0.96), respectively (**Table 2**). Moreover, compared with the "not achieving the target SU" arm, the protective effects for hip fracture were similar in the "achieving the target SU<300 μmol/L" arm and the "achieving the target SU of 300-360 μmol/L" arm, with the HRs being 0.67 (95%CI 0.43 to 1.06) and 0.61 (95%CI 0.41 to 0.90), respectively. However, the number of participants in the "achieving the target SU<300 μmol/L" arm was small in the current study; thus, it would be valuable to study the SU concentration-dependent effect and the risk of fracture in the larger scale studies. We did not observe significant association between "achieving the target SU level" with ULT and the risk

of traumatic injury (HR 0.90, 95%CI 0.63 to 1.29) (**eTable 3**).

Similar results were also observed for the effect of lowering SU with ULT to the target levels on the secondary outcomes. As shown in **Figure 3** and **Table 3**, the 5-year risks of composite fracture (risk difference -0.5%, 95% CI: -0.8% to 0.0%; HR 0.87, 95%CI: 0.77 to 0.99), major osteoporotic fracture (risk difference -0.6%, 95% CI: -0.7% to -0.3%; HR 0.73, 95%CI: 0.58 to 0.91), vertebral fracture (risk difference -0.1%, 95% CI: -0.2% to 0.0%; HR 0.59, 95%CI: 0.35 to 0.97), and non-vertebral fracture (risk difference -0.4%, 95% CI: -0.8% to 0.0%; HR 0.88, 95%CI: 0.77 to 0.99) for "achieving the target SU level" arm were all lower than that for "not achieving the target SU level" arm.

Discussion

In this large population-based GP electronic health records database from the UK, lowering SU with ULT to target levels (i.e., <360 μmol/L) among people with gout was associated with a lower risk of hip fracture than not reaching target levels with ULT. Similar results were also observed for the risks of composite fracture, major osteoporotic fracture, vertebral fracture, and non-vertebral fracture. These findings suggest that a "treat-to-target SU level" with ULT may have a beneficial effect on reducing the risk of fracture among people with gout.

Previous studies have investigated the association between ULT use (vs. non-use) and risk of fracture; however, the results were inconsistent. One cohort study reported that allopurinol use was associated with a higher risk of major osteoporotic fractures or hip fracture in both the general population and people with gout (17);

whereas another cohort study of people with gout found a lower risk of fracture in allopurinol users than that in non-users (19). Two other studies failed to show an association of ULT with either the risk of major osteoporotic fracture among people with gout (18) or the risk of hip fracture among older patients undergoing inpatient rehabilitation (16). These studies either included the prevalent allopurinol users in its exposure group (16) which may lead to potential selection bias or used people with gout but not using ULT as a comparison group (17-19), which may be susceptible to confounding by indication. In addition, none of these studies has assessed the effect of lowering SU with ULT to a target level (i.e., <360 μmol/L) on the risk of fracture among people with gout. In the current study, we found that lowering SU to the target level (i.e., <360 μmol/L) within one year after initiation of ULT among people with gout was significantly associated with a decreased risk of fracture, and the findings persisted in various sensitivity analyses.

Several biological mechanisms have been proposed to explain the association between SU levels and the risk of fracture. First, studies have shown that SU may affect bone health through its impact on oxidative stress (42-44). When SU levels are hyperuricemic at supersaturated concentrations, such as that among people with gout (45), the antioxidant properties of SU could be overcome by its pro-oxidant effects, which can contribute to an inflammatory milieu, promote bone resorption, and inhibit bone formation (46-48), and ultimately contribute to the increased risk of fracture. Second, others have found that hyperuricemia could inhibit vitamin D activation by suppressing 1-a-hydroxylase, resulting in a lower 1,25-dihydroxyvitamin D level and higher parathyroid hormone level (49, 50). As a result, hyperuricemia could affect bone remodeling through its effect on either vitamin D or parathyroid hormone levels

or both (51). Although our study could not directly assess the effect of SU on the risk of fracture, the findings appear to suggest that a reduced risk of fracture with ULT among people with gout may be partially through the effect of ULT on lowering SU to the target levels.

Several strengths of our study merit comment. Using a real-world population-based electronic database, we emulated an RCT to compare the risk of fracture in people with gout who achieved the target SU level with those who did not achieve the target SU level with ULT. This causal analysis approach allows us to assess the role of hyperuricemia on the excess fracture risk in people with gout by minimizing both selection bias (i.e., initiators of ULT) and confounding by indication (i.e., all participants received ULT). Furthermore, the effects of "achieving the target SU level" with ULT were consistent across the different outcomes (i.e., hip fracture, composite fracture, major osteoporotic fracture, vertebral fracture, and non-vertebral fracture), indicating that our study findings are robust.

Our study has some limitations. Although we used rigorous approaches to control for confounders by emulating an analysis of an RCT, some covariates, such as disease severity, bone density or any frailty measurements, may not be well captured by the variables available in THIN; thus, we cannot rule out residual confounding. For example, more frail and sicker people may be less likely to continue on "preventive medication", such as ULT, particularly for non-immediately fatal conditions, or physicians may be reluctant to escalate the allopurinol dose for those people. Consequently, residual confounding could lead to a potentially biased protective effect of ULT on the risk of fracture. Nevertheless, the association between

"achieving the target SU level" with ULT and the control outcome, the risk of traumatic injury, was null, lending the specificity to our findings. Second, ULT initiators who achieved target SU levels may have received better healthcare for their overall health needs and have taken ULT longer than their comparators; thus, we cannot separate the effect of quality of healthcare from that of lowering UA. However, when comparing healthcare utilization prior to ULT initiation among individuals who reached the target levels of ULT with those who did not reach the target levels of ULT, no difference was observed between two groups, suggesting the effect of healthcare utilization on the risk of fracture, if existed, may not completely explain the results found in our study. In addition, excluding participants who did not have the SU level before the index date may limit the generalizability of the current findings to a population who might receive less healthcare or experience less severe disease.

In summary, in this population-based data, lowering SU levels with ULT to the guideline-based target level was associated with a lower risk of incident fracture in people with gout.

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Everyone who contributed significantly to the work has been listed.

Author Contributions

Drs. Zhang, Lei and Zeng had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs. Zhang, Lei and Zeng are joint corresponding authors. All authors have read, provided critical feedback on intellectual content, and approved the final manuscript. Concept and design: Lei, Zhang, Zeng, Wei, Choi, Dalbeth, Lane. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Wei, Zeng, Lei, Zhang. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Wei, Wu, Lyu, Zhang. Obtained funding: Wei, Zeng, Lei. Administrative, technical, or material support: Wei, Zeng, Lei, Zhang. Supervision: Lei, Zeng, Zhang.

Conflict of Interest

No conflict of interest for any of the authors.

Ethical approval

This study received approval from the medical ethical committee at Xiangya Hospital (2018091077), with waiver of informed consent.

Scientific approval

This study was approved by the THIN Scientific Review Committee (21SRC003_A1).

Statement

THIN is a registered trademark of Cegedim SA in the United Kingdom and other countries. Reference made to the THIN database is intended to be descriptive of the data asset licensed by IQVIA. This work uses de-identified data provided by patients as a part of their routine primary care.

Disclaimer

The interpretation of these data is the sole responsibility of the authors.

Transparency

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

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Table 1. Baseline characteristics of people with gout

Characteristics	Study Population (n=28,554)
Demographics	
Age, mean (SD), y	65.3 (12.0)
Socioeconomic deprivation index, mean (SD)*	2.7 (1.3)
Female (%)	23.7
BMI, mean (SD), kg/m^2	30.3 (5.6)
Serum urate, mean (SD), umol/L	510.3 (88.5)
eGFR, mean (SD), mL/min/1.73m^2	66.7 (22.2)
Gout duration, mean (SD), y	3.3 (5.0)
Lifestyle factors	
Drinking (%)	
None	13.2
Past	2.8
Current	84.1
Smoking (%)	
None	50.1
Past	40.8
Current	9.1
Region	
England	66.9
Northern Ireland	5.3
Scotland	10.6
Wales	17.2
Comorbidity (%)	
Hypertension	63.2
Venous thromboembolism	3.8
Myocardial infarction	9.6
Stroke	4.4
Pneumonia or infection	7.4
Hyperlipidaemia	20.5
Varicose veins	7.0
Depression	9.6
Chronic obstructive pulmonary disease	6.4
Fall	8.9
Osteoporosis	1.6
Atrial fibrillation	13.2
Osteoarthritis	26.1
Diabetes	18.4
Chronic kidney disease	24.0
Medication (%)[†]	
Antihypertensive	71.0
Antidiabetic	11.4
Statin	45.8
Anticoagulants	11.2
Aspirin	26.5
NSAIDs	71.9

Opioids	13.7
Nitrates	8.4
Colchicine	42.6
Loop diuretics	23.4
Thiazide diuretics	23.9
Potassium-sparing diuretics	7.7
Systemic corticosteroid	16.4
PPIs	43.8
Antiosteoporosis drugs	3.5
DMARDs	1.1
Healthcare utilization, mean (SD)†	
Hospitalizations	0.4 (1.1)
General practice visits	7.5 (6.3)
Specialist referrals	0.6 (1.0)

* The Socio-Economic 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.

BMI, body mass index; n, number; y, years; SD, standard deviation; eGFR, estimated glomerular filtration rate; NSAID, non-steroidal anti-inflammatory drug; PPIs, proton pump inhibitor; DMARDs, disease-modifying antirheumatic drugs.

Table 2. Relations of achieving the target SU level (<360 μmol/L) to hip fracture in people with gout initiating urate-lowering therapy

	Achieving the target SU level	Not achieving the target SU level
Hip fracture		
Target trial emulation (n)	28,554	28,554
Fracture	62	108
Risk over 5 years (%)	0.5	0.7
Risk difference (%, 95%CI)	-0.2 (-0.3, 0.0)	0.0 (reference)
HR (95%CI)	0.77 (0.61, 0.98)	1.00 (reference)
Weighted fracture (n)	105	152
Weighted risk over 5 years (%)	0.5	0.8
IPW risk difference (%, 95%CI)	-0.3 (-0.5, -0.1)	0.0 (reference)
IPW HR (95%CI)	0.66 (0.46, 0.93)	1.00 (reference)
Sensitivity analyses		
Incident gout cases, HR (95% CI)	0.63 (0.43, 0.92)	1.00 (reference)
Re-defined gout cases, HR (95% CI)	0.65 (0.45, 0.95)	1.00 (reference)
Initiating with allopurinol, HR (95% CI)	0.64 (0.45, 0.92)	1.00 (reference)
Received anti-inflammatory treatment, HR (95% CI)	0.67 (0.47, 0.96)	1.00 (reference)

SU, serum uric acid; IPW, Inverse-probability weighting; HR, hazard ratio; n, number; 95% CI, 95% confidence interval.

Table 3. Relations of achieving the target SU level (<360 μmol/L) to composite fracture, major osteoporotic fracture, vertebral fracture, and non-vertebral fracture in people with gout initiating urate-lowering therapy

	Achieving the target SU level	Not achieving the target SU level
Composite fracture		
Target trial emulation (n)	28,554	28,554
Weighted fracture (n)	903	1,003
Weighted risk over 5 years (%)	4.2	4.7
IPW risk difference (%, 95%CI)	-0.5 (-0.8, 0.0)	0.0 (reference)
IPW HR (95%CI)	0.87 (0.77, 0.99)	1.00 (reference)
Major osteoporotic fracture*		
Target trial emulation (n)	28,554	28,554
Weighted fracture (n)	291	360
Weighted risk over 5 years (%)	1.3	1.9
IPW risk difference (%, 95%CI)	-0.6 (-0.7, -0.3)	0.0 (reference)
IPW HR (95%CI)	0.73 (0.58, 0.91)	1.00 (reference)
Vertebral fracture		
Target trial emulation (n)	28,554	28,554
Weighted fracture (n)	40	56
Weighted risk over 5 years (%)	0.2	0.3
IPW risk difference (%, 95%CI)	-0.1 (-0.2, 0.0)	0.0 (reference)
IPW HR (95%CI)	0.59 (0.35, 0.97)	1.00 (reference)
Non-vertebral fracture		
Target trial emulation (n)	28,554	28,554
Weighted fracture (n)	871	964
Weighted risk over 5 years (%)	4.1	4.5
IPW risk difference (%, 95%CI)	-0.4 (-0.8, 0.0)	0.0 (reference)
IPW HR (95%CI)	0.88 (0.77, 0.99)	1.00 (reference)

SU, serum uric acid; IPW, Inverse-probability weighting; HR, hazard ratio; n, number; 95% CI, 95% confidence interval.

*Major osteoporotic fracture included hip, vertebral, wrist and humerus fractures.

Figure legends

Figure 1. Study design of a hypothetical randomized controlled trial ("target trial") on which we modeled our observational data analysis (A); Cloning and censoring in four hypothetical patients (B).

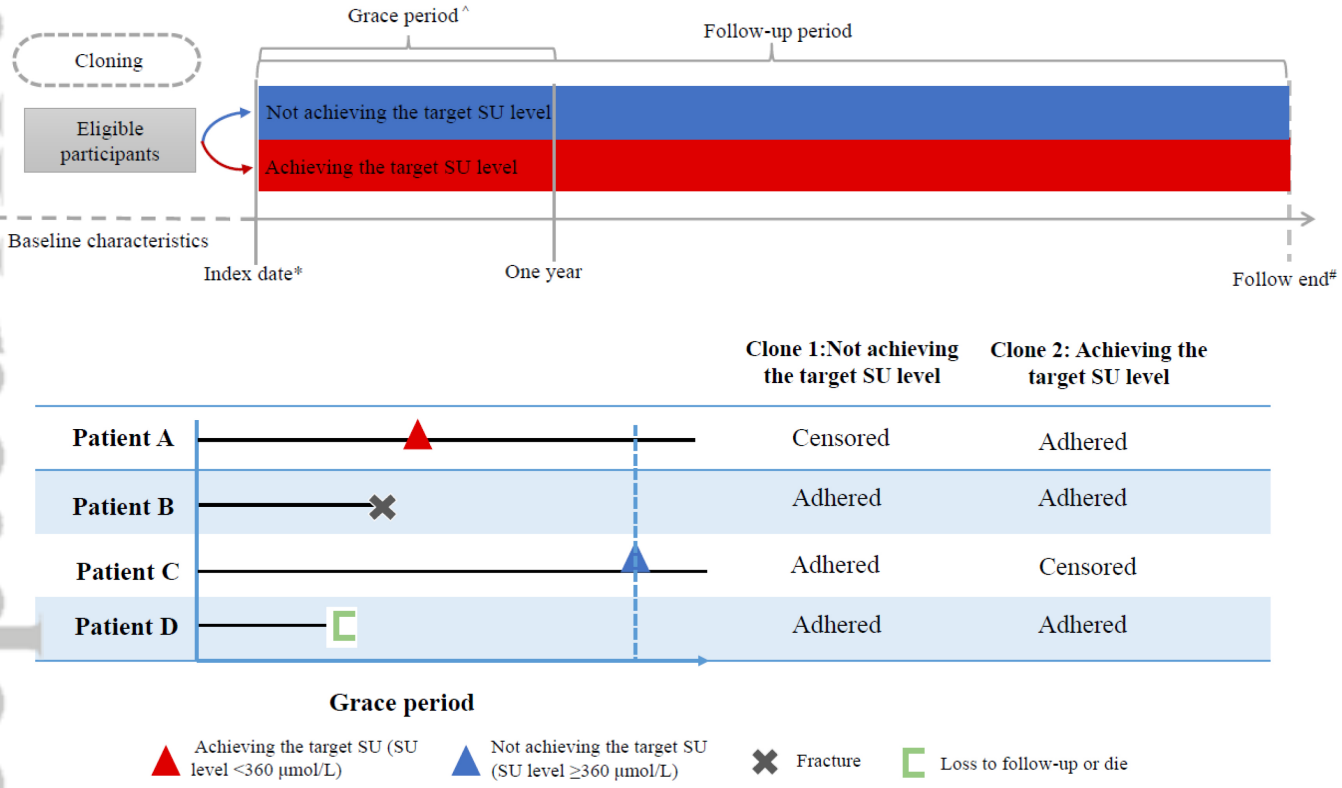
*Index date: the date of urate-lowering therapy initiation.

#Follow end: the date of incident hip fracture, death, disenrollment from a GP practice participating in THIN, 5 years of follow-up, or the end of the study, whichever occurred first.

^ Grace period: participants were given one-year to achieve the target SU level after initiating with urate-lowering therapy. Not achieving the target SU level: SU level ≥360 μmol/L within one year after index date; Achieving the target SU level: SU level <360 μmol/L within one year after index date.

Figure 2. Five-year risk of hip fracture between achieving the target serum urate (SU) level and not achieving the target SU level with urate-lowering therapy in people with gout.

Figure 3. Five-year risk of composite fracture (A), major osteoporotic fracture (B), vertebral fracture (C), and non-vertebral fracture (D) between achieving the target serum urate (SU) level and not achieving the target SU level with urate-lowering therapy in people with gout.



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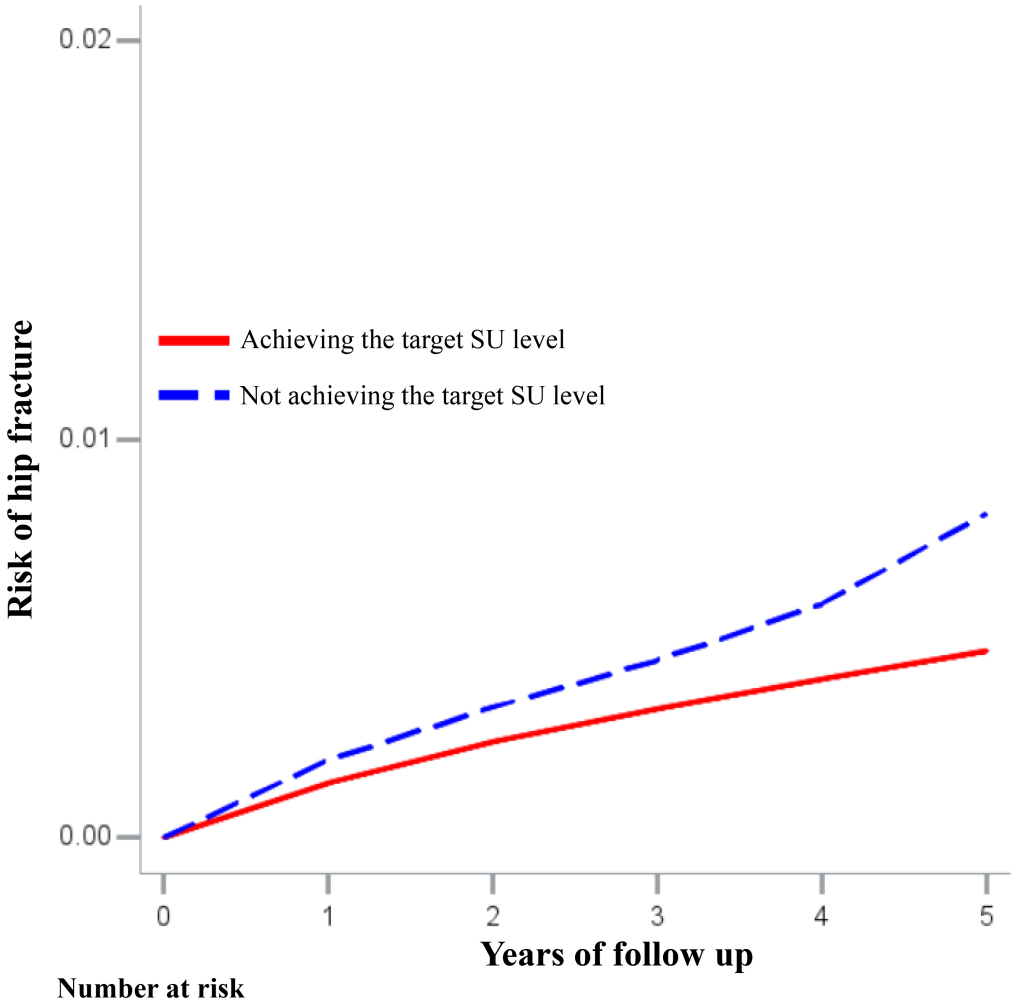
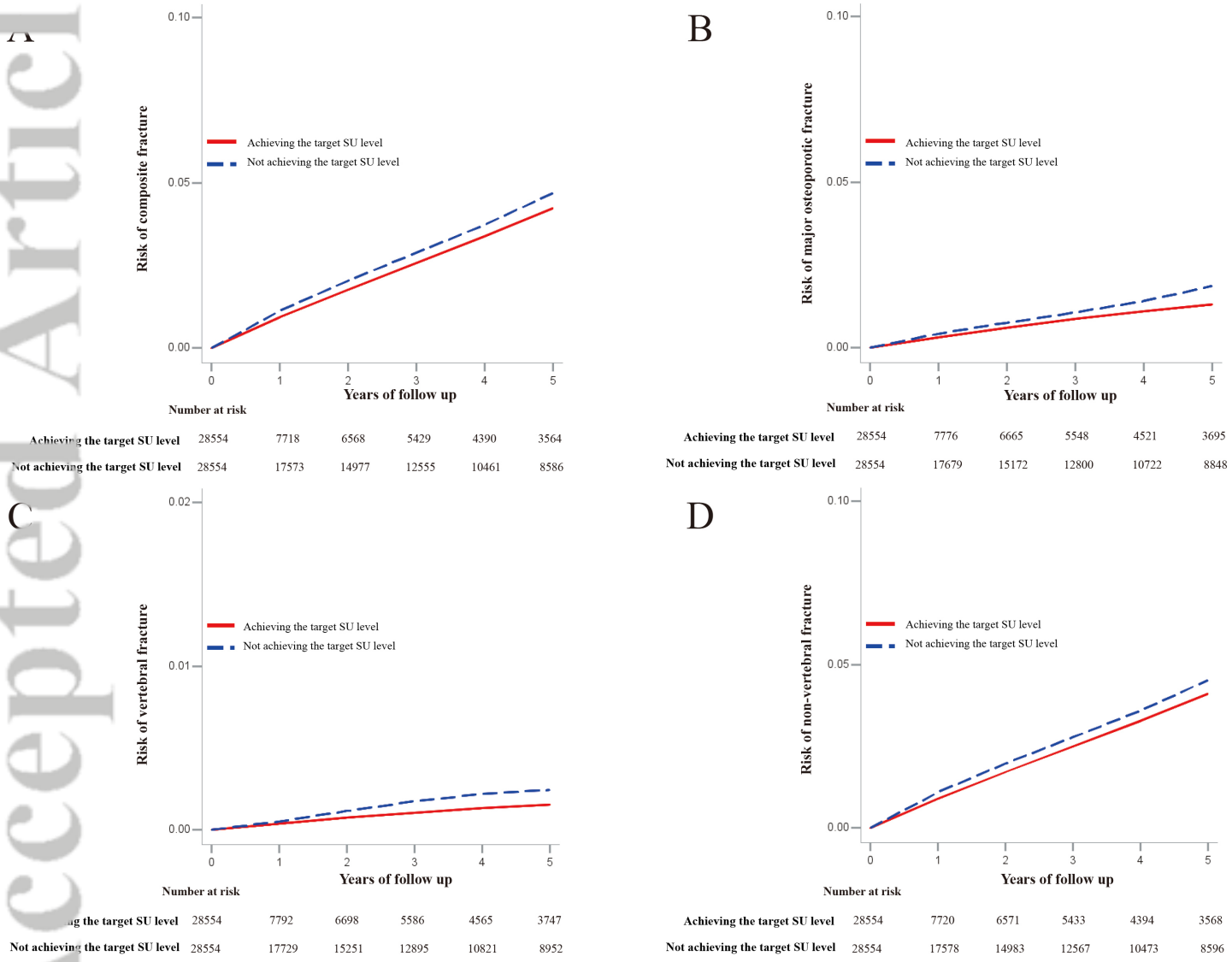


Number at risk

Achieving the target SU level	28554	7788	6690	5578	4558	3734
Not achieving the target SU level	28554	17713	15230	12878	10802	8927

ART_42504_Figure 2.tif



ART_42504_Figure 3.tif

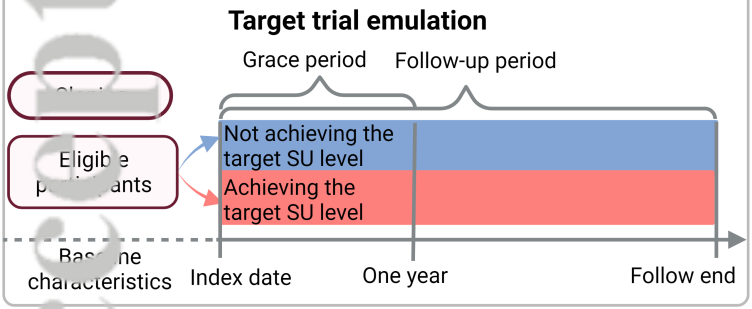
Lowering Serum Urate (SU) with Urate-Lowering Therapy to Target and Incident Fracture Among People With Gout

1 Study population

28,554 participants ages 40–89 years with gout and initiated urate-lowering therapy

- Sex: **23.7%** female
- Mean age: **65.3** years

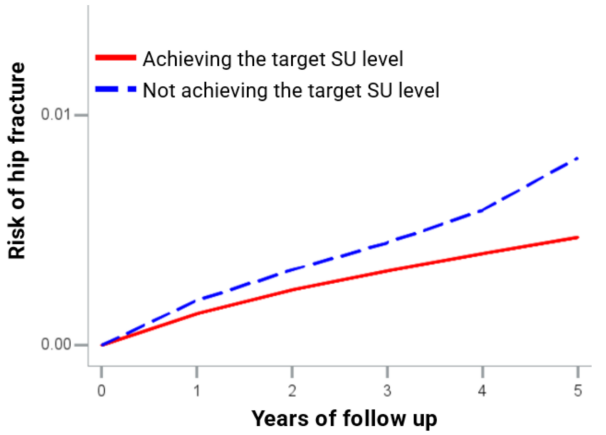
2 Study design



3 Results

Relationships of achieving the target SU level (<360 µmoles/liter) to hip fracture in people with gout initiating urate-lowering therapy

	Achieving the target SU level	Not achieving the target SU level
Weighted fracture (n)	105	152
Weighted Risk over 5 years (%)	0.5	0.8
Weighted risk difference (%, 95%CI)	-0.3 (-0.5, -0.1)	0.0 (reference)
Weighted hazard ratio (95%CI)	0.66 (0.46, 0.93)	1.00 (reference)



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