One-year Urate-Lowering Therapy Adherence and Risk of Major Osteoporotic Fracture: A Target Trial Emulation Study

Abstract

Background: Urate-lowering therapy (ULT) is central to gout management, yet long-term adherence is often suboptimal. Evidence regarding whether higher real-world adherence to ULT reduces fracture risk remains limited and may be affected by time-related biases.

Objective: To evaluate the association between one-year adherence to ULT and subsequent risk of major osteoporotic fracture (MOF) using a target trial emulation framework.

Methods: Using nationwide Korean claims data (NHIS-NSC), we emulated a target trial of ULT adherence among adults with gout who newly initiated ULT. Adherence during the first year after initiation was quantified using proportion of days covered (PDC) and fixed at a one-year landmark to define exposure groups. The primary outcome was incident MOF requiring hospitalization after the landmark. We estimated hazard ratios (HRs) using propensity score matching and Cox proportional hazards models. Sensitivity analyses included a stricter adherence threshold (PDC ≥90%), hip fracture as an outcome, competing risk modeling, and a per-protocol analysis using clone–censor–weighting (CCW).

Results: Among 5,987 eligible patients, 722 high-adherence and 722 low-adherence patients were matched at the landmark. In landmark-based analyses, high adherence was not associated with a statistically significant difference in MOF risk compared with low adherence. Results were consistent across sensitivity analyses. In per-protocol CCW analyses accounting for non-random treatment discontinuation, sustained ULT use was associated with a modest reduction in fracture risk, although estimates were sensitive to adherence definitions.

Conclusions: Higher adherence to ULT was not associated with increased fracture risk in landmark-based analyses. Per-protocol analyses suggested potential benefit under sustained use, highlighting both the fracture safety of ULT and challenges of maintaining long-term adherence in real-world gout care.

Introduction

Gout is a common inflammatory arthritis characterized by hyperuricemia and recurrent flares. Urate-lowering therapy (ULT) is recommended for long-term management to reduce serum urate levels and prevent disease progression. Despite its established efficacy,

adherence to ULT in routine clinical practice is frequently suboptimal, with many patients discontinuing therapy within the first year of treatment.

Beyond gout-related outcomes, interest has emerged regarding the potential effects of ULT on bone health. Chronic inflammation, comorbidities, and medication use among patients with gout may influence fracture risk. However, longitudinal observational studies evaluating ULT adherence and fracture outcomes are scarce and often vulnerable to time-related biases, including immortal time bias and exposure misclassification due to treatment changes over follow-up.

To address these limitations, we applied a target trial emulation framework. By explicitly defining eligibility, treatment strategies, follow-up, and outcomes, and by fixing adherence status at a pre-specified landmark, we aimed to estimate the association between ULT adherence and fracture risk while mitigating common biases in observational research.

Methods

Data Source

We used the Korean National Health Insurance Service–National Sample Cohort (NHIS-NSC), a nationwide claims database containing demographic information, diagnoses, procedures, and prescription records.

Target Trial Specification and Emulation

We specified a hypothetical target trial comparing high versus low adherence to ULT over the first year after initiation, followed by assessment of fracture risk. This trial was emulated using observational data through the following components.

Eligibility Criteria

Adults aged 18 years or older with confirmed gout who newly initiated ULT were eligible. Gout was defined by ICD-10 code M10 recorded in at least one inpatient claim or two outpatient claims. To identify new users, patients with any ULT prescription in the 24 months prior to initiation were excluded. We further excluded patients with Paget's disease, prior major osteoporotic fracture within 24 months before initiation, or fractures occurring during the one-year adherence assessment window.

Time Zero and Landmark

The index date (time zero) was defined as the first ULT prescription after gout confirmation. Adherence was assessed during the first 365 days after initiation. A one-year landmark (index + 365 days) was used to fix exposure status and initiate fracture follow-up, thereby avoiding time-related biases.

Exposure: ULT Adherence

Adherence was quantified using proportion of days covered (PDC) during the first year. High adherence was defined as PDC ≥80% in the primary analysis, with a stricter threshold of PDC ≥90% examined in sensitivity analyses.

Outcome

The primary outcome was incident major osteoporotic fracture (MOF), defined as hospitalization with qualifying ICD-10 codes for hip, vertebral, wrist, or humerus fractures occurring after the landmark. Hip fracture was examined as a secondary outcome.

Follow-up

Patients were followed from the landmark date until the first occurrence of fracture, death, or end of study period (31 December 2019), whichever came first.

Confounding Control

Baseline covariates assessed prior to ULT initiation included age, sex, insurance type, comorbidities, and concomitant medications. Propensity scores were estimated using logistic regression and used for 1:1 matching between high- and low-adherence groups. Covariate balance was assessed using absolute standardized mean differences.

Statistical Analysis

We estimated hazard ratios (HRs) using Cox proportional hazards models in the matched cohort. Sensitivity analyses included (1) stricter adherence definition (PDC ≥90%), (2) competing risk analysis treating death as a competing event using Fine–Gray models, and (3) subgroup analyses by age.

Per-protocol Analysis Using CCW

To estimate per-protocol effects, we applied clone–censor–weighting (CCW). Patients were cloned into sustained and usual-care strategies. Clones deviating from the sustained strategy (defined by a prescription gap ≥90 days or lack of ULT prescription within each 6-month interval) were censored. Inverse probability of censoring weights (IPCW) were used to account for informative censoring, with weight truncation applied to improve stability.

Results

Study Population

A total of 30,546 patients met gout confirmation criteria, of whom 5,987 comprised the final landmark cohort. After propensity score matching, 722 patients were included in each adherence group.

Primary Analysis

In landmark-based analyses, high adherence to ULT was not associated with a statistically significant difference in MOF risk compared with low adherence (HR 0.93; 95% CI 0.67-1.29). Incidence rates were similar between groups, and adjusted hazard ratios indicated no increased fracture risk associated with higher adherence (14.10 vs 15.24 per 1,000 person-years).

Sensitivity and Subgroup Analyses

Results were consistent when applying a stricter adherence threshold (PDC ≥90%), restricting outcomes to hip fracture, and accounting for competing risk of death. No clear effect modification was observed across age subgroups, although confidence intervals were wide due to limited events.

Per-protocol CCW Analysis

Approximately one-third of patients deviated from the sustained adherence strategy during follow-up, primarily due to prescription gaps. CCW analyses accounting for this non-random discontinuation suggested a modest reduction in fracture risk under sustained ULT use (HR 0.82; 95% CI 0.70-0.96). However, estimates varied depending on adherence definitions, underscoring sensitivity to strategy specification.

Discussion

In this nationwide target trial emulation, higher one-year adherence to ULT was not associated with increased risk of major osteoporotic fractures. These findings were robust across multiple sensitivity analyses and outcome definitions. Per-protocol analyses using CCW suggested potential benefit under sustained therapy, but results were sensitive to how adherence strategies were defined, reflecting challenges of maintaining long-term treatment in real-world practice.

Our study highlights the importance of explicitly addressing time-related biases when evaluating medication adherence and long-term outcomes. By fixing adherence at a landmark and applying CCW for per-protocol estimation, we aimed to provide complementary perspectives on the association between ULT adherence and fracture risk.

Limitations

This study is subject to limitations inherent to claims data, including potential misclassification and residual confounding. Sustained adherence was difficult to maintain, leading to informative censoring and reduced precision in per-protocol estimates.

Conclusion

Higher adherence to urate-lowering therapy was not associated with increased fracture risk in landmark-based analyses. Per-protocol analyses suggested possible benefit under sustained use, emphasizing both the fracture safety of ULT and the need to improve long-term adherence in gout management.

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