One-yar urate-lowering therapy adherence and major osteoporotic fracture risk among patients with gout: a landmark propensity-score matched analysis and per-protocol emulation

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Background & Objective

Background
- Urate-lowering therapy (ULT) is a cornerstone of gout management, but adherence is often suboptimal.
- Evidence on whether higher real-world ULT adherence reduces fracture risk remains limited

Gap in evidence
- Existing longitudinal evidence is scarce and often affected by time-related biases and treatment changes during follow-up.

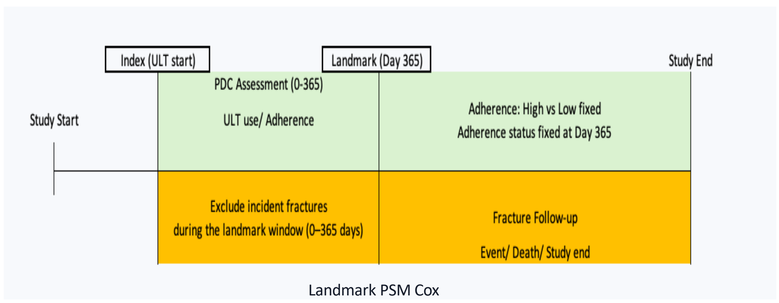
Objective
- To evaluate the association between 1-year ULT adherence and subsequent risk of major osteoporotic fracture (MOF) using a landmark propensity-score matched design.
- To explore per-protocol effects using clone-censor-weight (CCW).

Target trial emulation

Component (Target Trial)	Clinical definition	Operational definition (emulation)
Eligibility	Adults with confirmed gout eligible for ULT initiation	Age ≥18 at index; gout: ICD-10 M10 with ≥1 inpatient OR ≥2 outpatient visits
Time zero (Index)	Start of urate-lowering therapy	First ULT prescription date after gout confirmation
New-user	Incident initiators to avoid prevalent user bias	24-month washout: no ULT prescriptions in prior 730 days
Run-in (Adherence Assessment)	Assess adherence before outcome follow-up	0–365 days after index used to compute PDC
Landmark	Fix exposure status before follow-up to avoid time-related bias	Landmark at Day 365; follow-up begins at landmark; exposure fixed at landmark
Exclusion	Remove patients with prior outcome or strong alternative bone pathology	Paget's disease (ICD-10 M88); prior MOF within 24 months; MOF during 0–365 days landmark window
Treatment Strategies	High vs low adherence during first year of ULT	High: PDC ≥80% vs Low: <80% (sensitivity: ≥90%)
Treatment Strategies	Sustained ULT use vs usual care	Strategy A: no gap ≥90 days AND ≥1 ULT Rx per 6 months; Srrategy B: no restrictions
Outcome	Incident major osteoporotic fracture after exposure definition	MOF defined by inpatient claims with pre-specified ICD-10 prefixes; event date = first qualifying admission after landmark
Follow-up	From start of follow-up until outcome, death, or study end	Landmark → MOF / death / 31 Dec 2019
Caual contrast (estimand)	ITT effect of high vs low adherence; per-protocol effect of sustained use	ITT: HR from landmark PS-matched cohort; Per-protocol: CCW + IPCW weighted Cox
Confounding control	Balance baseline risk factors	PS model using demographics, comorbidities, and baseline meds; 1:1 PSM; balance assessed by aSMD <0.1
Sensitivity analyses	Check robustness to alternative definitions and competing events	PDC≥90; Hip fracture; Fine–Gray (death competing); age subgroups

Study Design (Timeline)

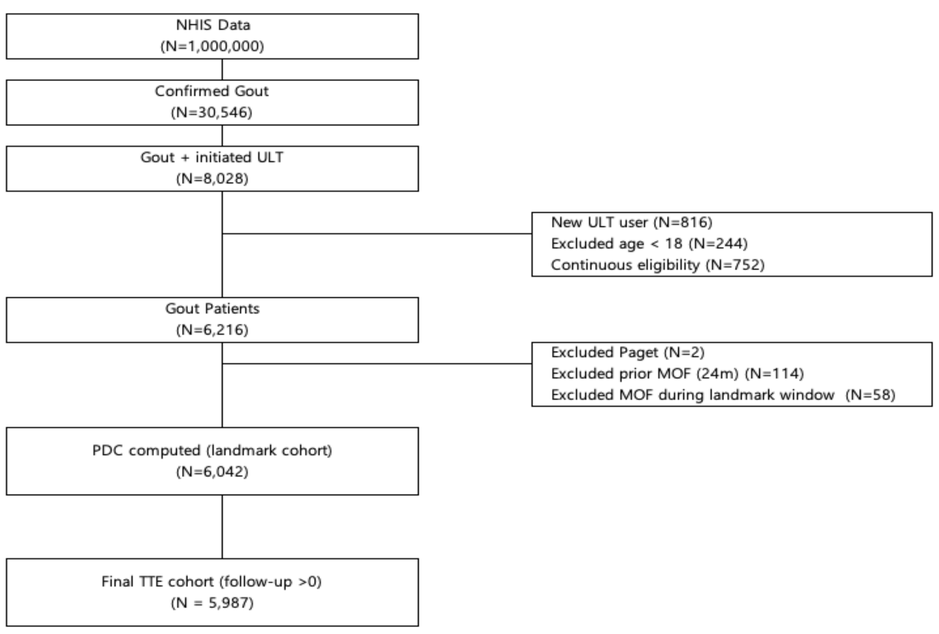
Index: ULT initiation
0-365 days: PDC measurement (**High adherence;** PDC ≥80% vs **Low adherence;** PDC <80%)
Landmark: Day 365 (exposure fixed)
Follow-up started at **day 365 (landmark)** after ULT initiation; until MOF/hip fracture event , death, or 31 Dec 2019



Landmark PSM Cox

Statistical Analysis
Primary analysis: 1:1 propensity-score matching (PSM) at the landmark, followed by a stratified Cox model by matched pair to estimate hazard ratios (HRs).
Sensitivity analyses: PDC ≥90%, Fine–Gray competing risk model (death as competing event), and age subgroup analyses (≥40, ≥60 years).

Cohort Flow



Baseline Balance (Table 1)

Key Covariate	Pre-match High	Pre-match Low	Post-match High	Post-match Low	aSMD (Post)
Age, mean ± SD	62.97 ± 14.61	52.56 ± 16.18	62.99 ± 14.61	63.52 ± 14.53	**0.041**
HTN, n (%)	2207	627	608	595	**0.048**
AF, n (%)	165	66	63	61	**0.01**
Stroke, n (%)	239	85	79	83	**0.018**
CKD, n (%)	453	262	233	249	**0.047**
DM, n (%)	1122	396	366	374	**0.022**
HF, n (%)	289	142	135	135	**0**
Dyslipidemia, n (%)	1784	528	499	500	**0.003**
COPD, n (%)	512	112	114	106	**0.031**
Cancer, n (%)	319	75	71	70	**0.005**

Main Results (Table 2)

Across multiple analytic approaches, including landmark ITT and per-protocol CCW analyses, higher ULT adherence was not associated with a statistically significant increase in fracture risk, with per-protocol estimates suggesting a modest risk reduction under sustained use.

N(per group)	Events (Low/High)	PY (Low/High)	IR/1000 PY (Low/High)	Effects (HR)	95% CI
722/ 722	53 / 47	3476.8 / 3334.5	15.24 / 14.10	0.93	**0.67 – 1.29**

Sensitivity Analyses
Results were robust across multiple sensitivity analyses, including a stricter adherence definition, competing risk modeling, and per-protocol estimation using CCW.

Analysis	Definition	Effects (HR/ sHR)	95% CI
Primary (reference)	PDC ≥80%, landmark PSM Cox	0.93	0.67 – 1.29
Stricter adherence	PDC ≥90%	0.84	0.57 – 1.24
Competing risk	Fine–Gray model (death as competing event)	0.95 (sHR)	0.68 – 1.33
CCW (per-protocol)	Sustained use vs usual care (IPCW, p99 truncation)	0.82	0.70 – 0.96

Subgroup Analyses
No clear effect modification was observed across age subgroups or when restricting the outcome to hip fractures, although estimates were imprecise due to limited events.

Subgroup	Effects (HR)	95% CI
Age ≥40 years	0.89	0.63 – 1.24
Age ≥60 years	1.02	0.71 – 1.47
Hip fracture only	1.32	0.73 – 2.38

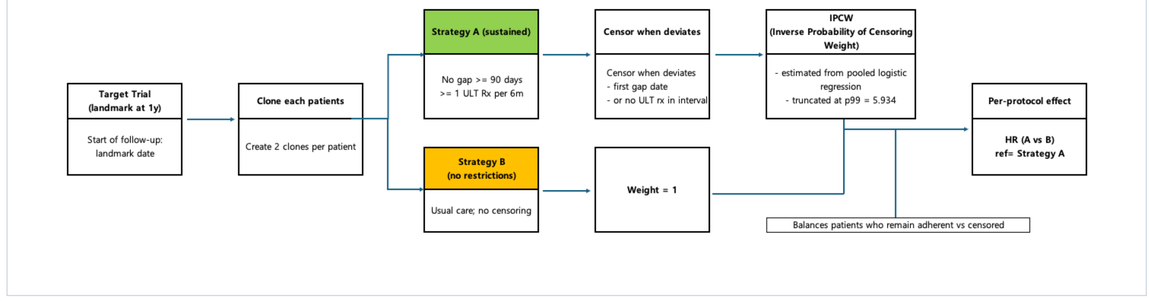
Per-protocol (CCW) Diagram + Diagnostics

Per-protocol CCW analysis suggested a modest reduction in fracture risk under sustained ULT use. However, estimates were sensitive to adherence definitions, reflecting substantial real-world discontinuation.

Metric	Value	Interpretation
Protocol deviation rate	36.6% (2,193 / 5,987)	Substantial non-random deviation from sustained strategy
Primary deviation reason	Gap ≥90 days (100%)	Reflects real-world discontinuation
IPCW weights (Strategy A)	Median 1.15, Max 5.93	No extreme weights after truncation
ESS (Strategy A)	≈23,800	Adequate effective sample size
Strategy persistence	6m: 87.7%	Rapid decline in sustained adherence
	12m: 63.1%	
	24m: 34.5%	

🔹 *Weights truncated at p99 = 5.93*

- CCW was used to estimate a per-protocol effect accounting for non-random discontinuation of ULT.
- Inverse probability of censoring weights were applied to rebalance patients who remained adherent and those censored due to protocol deviation.



Conclusion

• High ULT adherence was not associated with increased fracture risk in landmark-based analyses.
• CCW per-protocol estimates suggested potential benefit under sustained use but were sensitive to strategy definitions.
• Results should be interpreted in the context of substantial real-world treatment discontinuation.

Research conducted at DreamCIS Inc.