Supplementary Material*

Wei J, Choi HK, Neogi T, et al. Allopurinol initiation and all-cause mortality among patients with gout and concurrent chronic kidney disease. A population-based cohort study. Ann Intern Med. 25 January 2022. [Epub ahead of print]. doi:10.7326/M21-2347

Item	Page
1. Method	2
1.1 Time-stratified propensity score matching	2
1.2 Target trial emulation	5
References	9
2. SAS code for the PS matching analysis and target trial emulation	16

* This supplementary material was provided by the authors to give readers further details on their article. The material was reviewed but not copyedited.

1. Method

1.1 Time-stratified propensity score matching

We conducted a time-stratified propensity score (PS) matched cohort study to examine the relation of allopurinol initiation to the risk of all-cause mortality. PS was estimated for the eligible participants based on the covariates preceding their index dates and were used to match each allopurinol initiator to a contemporaneous non-initiator. To adjust for potential secular trends in allopurinol use and mortality, we divided the study period (1 January 2000–1 January 2018) into 18 1-year cohort accrual blocks. Within each annual cohort accrual block, allopurinol initiators were defined as participants who started allopurinol during that year, while participants who did not start allopurinol during the same annual accrual block served as potential comparators. The date of the first allopurinol prescription was assigned as the index date for allopurinol initiators, and a random date within that time block was assigned as the index date for non-initiators. Within each cohort accrual block, we calculated PS for initial prescription of allopurinol using logistic regression. The variables included in the model were sociodemographic factors (i.e., age, sex, socioeconomic deprivation index score, and region), body mass index (BMI), lifestyle factors (i.e., smoking status and alcohol consumption), CKD severity, SU, eGFR, comorbidities (i.e., 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) prior to the index date, medication use (i.e., antihypertensive drug, statin, antidiabetic drug, diuretics, aspirin, systemic corticosteroid, topical corticosteroid, non-steroidal anti-inflammatory drugs [NSAIDs], nitrates, and colchicine) and healthcare utilization during the one year prior to the index date. Within each time block, each eligible

allopurinol initiator was matched to a contemporaneous non-initiator within a 0.1 caliper of propensity without replacement (40). The PS greedy matching method attempted to achieve the comparability of the potential confounders at baseline between allopurinol initiators and non-initiators. A previous study suggested that optimal matching may not result in improved balance in measured baseline covariates when comparing with greedy match (75). In addition, using Monte Carlo simulations, increasing the number of untreated subjects matched to each treated subject, on average, increased the bias of the estimated treatment effect; conversely, it tended to result in increased precision (76). To minimize potential bias, we only matched one non-initiator to each allopurinol initiator with the greedy matching method in the primary analysis. To avoid duplicated subjects in the PS-matched cohorts, subjects who were PS-matched in the early annual accrual block were excluded from the later annual accrual block (i.e., sampling without replacement). Subjects who were not PS-matched to the initiators in the early annual accrual block were still eligible to serve as the potential comparators in the late annual accrual block if they remained non allopurinol initiators. Thereby, there were replicates in the pre-matched comparison cohort and we used "records" to describe the number of the comparison cohort before PS matching. Participants in each cohort were followed until the first of the following events: death, disenrollment from a GP practice participating in THIN, five years follow-up, or the end of the study (30 April 2019).

Rate difference calculation

We estimated the absolute rate difference (RD) and its 95% confidence intervals [CI]) in mortality between the two comparison groups using the following formula:

$$RD = \text{rate (initiators)} - \text{rate (non-initiators)}$$

$$SE_{RD}=\sqrt{\frac{a}{PT_a^2}+\frac{b}{PT_b^2}}$$

Where a and b refer to the number of events in each cohort, PT_a and PT_b refer to the total person-time accumulated in each cohort, and 95% CI: RD ± 1.96*SE_{RD}.

Cumulative mortality curve

The cumulative mortality curve over 5 years of follow-up plots the inverses of Kaplan-Meier estimates, which is a non-parametric statistic used to estimate the survival function from lifetime data.

Hazard ratio calculation

We obtained the hazard ratio (HR) of mortality for the allopurinol initiators vs. non-initiators using the Cox proportional hazard model. The Cox model is expressed by the hazard function denoted by h(t). Briefly, the hazard function can be interpreted as the risk of dying at time t. It can be estimated as follows:

$$h(t) = h_0(t) \times exp\left(b_1x_1 + b_2x_2 + \cdots + b_px_p\right)$$

where:

- t represents the survival time;
- h(t) is the hazard function determined by a set of p covariates (x_1, x_2,…x_p); the coefficients (b_1, b_2,…b_p) measure the impact (i.e., the effect size) of covariates;
- the term h_0 is measures the baseline hazard. It corresponds to the value of the hazard if all the x_i are equal to zero (the quantity exp(0) equals 1).

The exponentiate of b_i, i.e., exp(b_i), is a HR. In the PS-matched cohort study, we only included the indicator of the allopurinol initiator (i.e., allopurinol initiator vs. non-initiator) in the model because the baseline characteristics were well-balanced after PS matching. To obtain appropriate standard error (SE) and confidence interval

of HR in PS-matched study design, we performed a “sandwich estimation” in the Cox proportional hazards model, accomplished in SAS PROC PHREG.

1.2 Target trial emulation

To assess the effect of achieving target SU level with allopurinol (or allopurinol dose escalation) on the risk of mortality, we emulated a hypothetical target trial comparing mortality in participants who achieved target SU level (or who escalated their allopurinol dose) within one year after the initiation of allopurinol with that in participants who did not achieve target SU level (or who did not escalate allopurinol dose) within one year after initiation of allopurinol. Because the exposure of interest (i.e., time to “achieving target SU level” or “allopurinol dose escalation”) was “duration to reach an exposure level”, we adopted a “cloning, censoring, and weighting” approach that emulated an RCT to test the hypotheses using observational data (41-43). This approach aims to eliminate immortal time bias in the estimates of absolute and relative risk (42).

Cloning: assign patients to a treatment strategy at time zero

We assigned each person to two treatment strategies (i.e., “achieving target SU level vs. “not achieving target SU level” or “allopurinol dose escalation” vs. “no allopurinol dose escalation” within one year after initiation of allopurinol). Assigning a person to two treatment strategies simultaneously is equivalent to having two copies (or clones) of the person in the dataset, with each copy assigned to a different strategy. For example, when assessing the effect of “achieving target SU level” during one year after the index date on the risk of mortality, we assigned one clone to the “achieving target SU level” arm (i.e., achieving the target SU during one year after the index

date, A=1) and the other clone to the "not achieving target SU level" arm (i.e., not achieving the target SU during one year after the index date, A=0). "Cloning" makes two comparison groups compatible with their observed data at time zero.

Censoring: ensure that people follow their assigned strategy during the first year follow up

We allowed for a grace period of one year measured from baseline for individuals to achieve the target SU level or to escalate the allopurinol dose (14, 44). 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 target SU level" arm (or "allopurinol dose escalation") (A=1) 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 target SU level" (or no allopurinol dose escalation) arm (A=0) were censored if they achieved the target SU (or increased allopurinol dose) at during the first year of follow-up. During the grace period, if an individual died before achieving the target SU or escalating allopurinol dose, that person was considered consistent with his/her assignment in both arms (or clones) and contributed the death outcome to each of the assigned arms.

Weighting: adjust for selection bias

To eliminate the selection bias due to artificial censoring, we used inverse probability weighting (42). Specifically, we used the baseline covariates to estimate the probability of being artificially censored at the end of the first year of follow-up and build the inverse-probability weight as below:

$$f(A_t|A_{t-1}, L_0, D_{t-1} = 0) = \theta_0 + \theta_1 L_0$$

$$W = \frac{1}{f(A_t|A_{t-1}, L_0, D_{t-1} = 0)}$$

where A is an indicator for treatment arm, L_0 is a vector of baseline covariates, D is an indicator for death. The denominator of the IPW was the probability that a replicate adhered to his/her assigned intervention arm using the logistic regression model which consisted of the baseline covariates (see **Assessment of covariates**). Since we gave clones one year to achieve the target SU (or to escalate allopurinol dose), clones assigned to A=1 are not artificially censored if they died during the first year, because they adhered to their strategy. That is, the probability of being uncensored is 1 for clones who assigned to A=1 and died during the first year. The inverse probability weighting allowed us to create a pseudo-population in which no one is censored, and everybody follows their assigned treatment strategy.

Estimating weighted hazard ratio:

We used a pooled logistic regression model to estimate the hazard as below:

$$logit[Pr\ (Y_{t+1} = 1|Y_t = 0, A, L_0)] = \alpha_{0,t} + \alpha_1 A + \alpha_2 L_0$$

where Y_{t+1} is an indicator (1: yes, 0: no) for death at year $t + 1$, A is an indicator for treatment arm. The pooled logistic regression model included an indicator for the treatment strategies (A), the baseline covariates (L0), and the year of follow-up (linear and quadratic term) (52, 53).

Estimating absolute risk difference:

We fitted a pooled logistic model that included a product term between the treatment arm indicator and time, and estimated the predicted survival probability at time *t* for individual *i* under regime a, $\hat{S}_{i,t}^{a}$, conditional on the individual's baseline values of

confounders L_0:

$$logit[Pr(Y_t = 1|\bar{Y}_{t-1} = 0\ , A, L_0)] = \alpha_{0,t} + \alpha_1 A + \alpha_2 A * t\ + {\alpha_3}^T L_0$$

$$\hat{S}^a_{i,t} = \prod_{k=1}^{t}[1 - \frac{exp(\alpha_{0,k} + \alpha_1 A + \ \alpha_2 A * k\ + {\alpha_3}^T L_0)}{1 + exp(\alpha_{0,k} + \alpha_1 A + \ \alpha_2 A * k\ + {\alpha_3}^T L_0)}]$$

We then used the empirical distribution of the baseline confounders in the entire study population to calculate standardized survival probabilities at each time-point:

$$\hat{S}^a_t = \frac{1}{n}\sum_{i=1}^{n} \hat{S}^a_{i,t}$$

where *n* is the total number of individuals. Risks were calculated by subtracting the survival probabilities from 1 at time *t.* We estimated the confidence interval of the risk differences at 5 years of follow-up using nonparametric bootstrapping with 100 samples (54).

References

1. **Dehlin M, Jacobsson L, Roddy E.** Global epidemiology of gout: prevalence, incidence, treatment patterns and risk factors. Nat Rev Rheumatol. 2020;16:380-390. [PMID: 32541923] doi:10.1038/s41584-020-0441-1

2. **Kuo CF, Grainge MJ, Mallen C, et al.** Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. Ann Rheum Dis. 2015;74:661-7. [PMID: 24431399] doi:10.1136/annrheumdis-2013-204463

3. **Rai SK, Aviña-Zubieta JA, McCormick N, et al.** The rising prevalence and incidence of gout in British Columbia, Canada: population-based trends from 2000 to 2012. Semin Arthritis Rheum. 2017;46:451-456. [PMID: 28040245] doi:10.1016/j.semarthrit.2016.08.006

4. **Zobbe K, Prieto-Alhambra D, Cordtz R, et al.** Secular trends in the incidence and prevalence of gout in Denmark from 1995 to 2015: a nationwide register-based study. Rheumatology (Oxford). 2019;58:836-839. [PMID: 30590724] doi:10.1093/rheumatology/key390

5. **Kim JW, Kwak SG, Lee H, et al.** Prevalence and incidence of gout in Korea: data from the national health claims database 2007-2015. Rheumatol Int. 2017;37:1499-1506. [PMID: 28676911] doi:10.1007/s00296-017-3768-4

6. **Dehlin M, Drivelegka P, Sigurdardottir V, et al.** Incidence and prevalence of gout in Western Sweden. Arthritis Res Ther. 2016;18:164. [PMID: 27412614] doi:10.1186/s13075-016-1062-6

7. **Safiri S, Kolahi AA, Cross M, et al.** Prevalence, incidence, and years lived with disability due to gout and its attributable risk factors for 195 countries and territories 1990-2017: a systematic analysis of the global burden of disease study 2017. Arthritis Rheumatol. 2020;72:1916-1927. [PMID: 32755051] doi:10.1002/art.41404

8. **Xia Y, Wu Q, Wang H, et al.** Global, regional and national burden of gout, 1990-2017: a systematic analysis of the Global Burden of Disease Study. Rheumatology (Oxford). 2020;59:1529-1538. [PMID: 31624843] doi:10.1093/rheumatology/kez476

9. **FitzGerald JD, Dalbeth N, Mikuls T, et al.** 2020 American College of Rheumatology guideline for the management of gout. Arthritis Care Res (Hoboken). 2020;72:744-760. [PMID: 32391934] doi:10.1002/acr.24180

10. **Hui M, Carr A, Cameron S, et al; British Society for Rheumatology Standards, Audit and Guidelines Working Group.** The British Society for Rheumatology guideline for the management of gout. Rheumatology (Oxford). 2017;56:e1-e20. [PMID: 28549177] doi:10.1093/rheumatology/kex156

11. **Richette P, Doherty M, Pascual E, et al.** 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis. 2017;76:29-42.

[PMID: 27457514] doi:10.1136/annrheumdis-2016-209707

12. **Sivera F, Andrés M, Carmona L, et al.** Multinational evidence-based recommendations for the diagnosis and management of gout: integrating systematic literature review and expert opinion of a broad panel of rheumatologists in the 3e initiative. Ann Rheum Dis. 2014;73:328-35. [PMID: 23868909] doi:10.1136/annrheumdis-2013-203325

13. **Kim SC, Neogi T, Kim E, et al.** Trends in utilization of urate-lowering therapies following the US Food and Drug Administration's boxed warning on febuxostat. Arthritis Rheumatol. 2021;73:542-543. [PMID: 33029931] doi:10.1002/art.41550

14. **Stamp LK, Chapman PT, Barclay ML, et al.** A randomised controlled trial of the efficacy and safety of allopurinol dose escalation to achieve target serum urate in people with gout. Ann Rheum Dis. 2017;76:1522-1528. [PMID: 28314755] doi:10.1136/annrheumdis-2016-210872

15. **Luk AJ, Levin GP, Moore EE, et al.** Allopurinol and mortality in hyperuricaemic patients. Rheumatology (Oxford). 2009;48:804-6. [PMID: 19447769] doi:10.1093/rheumatology/kep069

16. **Larsen KS, Pottegård A, Lindegaard HM, et al.** Effect of allopurinol on cardiovascular outcomes in hyperuricemic patients: a cohort study. Am J Med. 2016;129:299-306.e2. [PMID: 26589484] doi:10.1016/j.amjmed.2015.11.003

17. **Dubreuil M, Zhu Y, Zhang Y, et al.** Allopurinol initiation and all-cause mortality in the general population. Ann Rheum Dis. 2015;74:1368-72. [PMID: 24665118] doi:10.1136/annrheumdis-2014-205269

18. **Chen JH, Lan JL, Cheng CF, et al.** Effect of urate-lowering therapy on the risk of cardiovascular disease and all-cause mortality in patients with gout: a case-matched cohort study. J Rheumatol. 2015;42:1694-701. [PMID: 26077411] doi:10.3899/jrheum.141542

19. **Kuo CF, Grainge MJ, Mallen C, et al.** Effect of allopurinol on all-cause mortality in adults with incident gout: propensity score-matched landmark analysis. Rheumatology (Oxford). 2015;54:2145-50. [PMID: 26170376] doi:10.1093/rheumatology/kev246

20. **Ju C, Lai RWC, Li KHC, et al.** Comparative cardiovascular risk in users versus non-users of xanthine oxidase inhibitors and febuxostat versus allopurinol users. Rheumatology (Oxford). 2020;59:2340-2349. [PMID: 31873735] doi:10.1093/rheumatology/kez576

21. **Suissa S, Suissa K, Hudson M.** Effectiveness of allopurinol in reducing mortality: time-related biases in observational studies. Arthritis Rheumatol. 2021;73:1749-1757. [PMID: 33645906] doi:10.1002/art.41710

22. **Hay CA, Prior JA, Belcher J, et al.** Mortality in patients with gout treated with allopurinol: a systematic review and meta-analysis. Arthritis Care Res

(Hoboken). 2021;73:1049-1054. [PMID: 32286732] doi:10.1002/acr.24205

23. **Coburn BW, Michaud K, Bergman DA, et al.** Allopurinol dose escalation and mortality among patients with gout: a national propensity-matched cohort study. Arthritis Rheumatol. 2018;70:1298-1307. [PMID: 29513934] doi:10.1002/art.40486

24. **Bevis M, Blagojevic-Bucknall M, Mallen C, et al.** Comorbidity clusters in people with gout: an observational cohort study with linked medical record review. Rheumatology (Oxford). 2018;57:1358-1363. [PMID: 29672754] doi:10.1093/rheumatology/key096

25. **Zhu Y, Pandya BJ, Choi HK.** Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007-2008. Am J Med. 2012;125:679-687.e1. [PMID: 22626509] doi:10.1016/j.amjmed.2011.09.033

26. **Weiner DE, Tighiouart H, Elsayed EF, et al.** Uric acid and incident kidney disease in the community. J Am Soc Nephrol. 2008;19:1204-11. [PMID: 18337481] doi:10.1681/ASN.2007101075

27. **Obermayr RP, Temml C, Gutjahr G, et al.** Elevated uric acid increases the risk for kidney disease. J Am Soc Nephrol. 2008;19:2407-13. [PMID: 18799720] doi:10.1681/ASN.2008010080

28. **Hsu CY, Iribarren C, McCulloch CE, et al.** Risk factors for end-stage renal disease: 25-year follow-up. Arch Intern Med. 2009;169:342-50. [PMID: 19237717] doi:10.1001/archinternmed.2008.605

29. **Badve SV, Pascoe EM, Tiku A, et al; CKD-FIX Study Investigators.** Effects of allopurinol on the progression of chronic kidney disease. N Engl J Med. 2020;382:2504-2513. [PMID: 32579811] doi:10.1056/NEJMoa1915833

30. **Doria A, Galecki AT, Spino C, et al; PERL Study Group.** Serum urate lowering with allopurinol and kidney function in type 1 diabetes. N Engl J Med. 2020;382:2493-2503. [PMID: 32579810] doi:10.1056/NEJMoa1916624

31. **Conway R.** Allopurinol and chronic kidney disease [Letter]. N Engl J Med. 2020;383:1689. [PMID: 33085873] doi:10.1056/NEJMc2026125

32. **McCormick N, Zhang Y, Choi HK.** Allopurinol and chronic kidney disease [Letter]. N Engl J Med. 2020;383:1689-1690. [PMID: 33085874] doi:10.1056/NEJMc2026125

33. **Chisholm J.** The read clinical classification [Editorial]. BMJ. 1990;300:1092. [PMID: 2344534]

34. **First Databank.** FDB Multilex. Accessed at www.fdbhealth.co.uk/solutions/multilex-clinical-decision-support on 8 March 2021.

35. **Lewis JD, Schinnar R, Bilker WB, et al.** Validation studies of the Health Improvement Network (THIN) database for pharmacoepidemiology research.

Pharmacoepidemiol Drug Saf. 2007;16:393-401. [PMID: 17066486]

36. **Langan SM, Schmidt SA, Wing K, et al.** The reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE). BMJ. 2018;363:k3532. [PMID: 30429167] doi:10.1136/bmj.k3532

37. **Zhang Y, Peloquin CE, Dubreuil M, et al.** Sleep apnea and the risk of incident gout: a population-based, body mass index-matched cohort study. Arthritis Rheumatol. 2015;67:3298-302. [PMID: 26477891] doi:10.1002/art.39330

38. **Schlesinger N, Lu N, Choi HK.** Gout and the risk of incident erectile dysfunction: a body mass index-matched population-based study. J Rheumatol. 2018;45:1192-1197. [PMID: 30008453] doi:10.3899/jrheum.170444

39. **Vargas-Santos AB, Peloquin CE, Zhang Y, et al.** Association of chronic kidney disease with allopurinol use in gout treatment. JAMA Intern Med. 2018;178:1526-1533. [PMID: 30304329] doi:10.1001/jamainternmed.2018.4463

40. **Seeger JD, Williams PL, Walker AM.** An application of propensity score matching using claims data. Pharmacoepidemiol Drug Saf. 2005;14:465-76. [PMID: 15651087]

41. **Lyu H, Yoshida K, Zhao SS, et al.** Delayed denosumab injections and fracture risk among patients with osteoporosis: a population-based cohort study. Ann Intern Med. 2020;173:516-526. [PMID: 32716706] doi:10.7326/M20-0882

42. **Hernán MA.** How to estimate the effect of treatment duration on survival outcomes using observational data. BMJ. 2018;360:k182. [PMID: 29419381] doi:10.1136/bmj.k182

43. **Hernán MA, Robins JM.** Using big data to emulate a target trial when a randomized trial is not available. Am J Epidemiol. 2016;183:758-64. [PMID: 26994063] doi:10.1093/aje/kwv254

44. **Mikuls TR, Cheetham TC, Levy GD, et al.** Adherence and outcomes with urate-lowering therapy: a site-randomized trial. Am J Med. 2019;132:354-361. [PMID: 30503879] doi:10.1016/j.amjmed.2018.11.011

45. **Levey AS, Bosch JP, Lewis JB, et al.** A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999;130:461-70. [PMID: 10075613]

46. **Webster-Clark M, Stürmer T, Wang T, et al.** Using propensity scores to estimate effects of treatment initiation decisions: state of the science. Stat Med. 2021;40:1718-1735. [PMID: 33377193] doi:10.1002/sim.8866

47. **Lin DY, Wei LJ, Ying Z.** Checking the Cox model with cumulative sums of Martingale-based residuals. Biometrika. 1993;80:557-72. doi:10.2307/2337177

48. **Dunkler D, Ploner M, Schemper M, et al.** Weighted Cox regression using the R

package coxphw. J Stat Softw. 2018;84:1-26. doi:10.18637/jss.v084.i02

49. **Rubin DB.** Multiple Imputation for Nonresponse in Surveys. J Wiley; 2004.

50. **Meier CR, Jick H.** Omeprazole, other antiulcer drugs and newly diagnosed gout. Br J Clin Pharmacol. 1997;44:175-8. [PMID: 9278205]

51. **VanderWeele TJ, Ding P.** Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med. 2017;167:268-274. [PMID: 28693043] doi:10.7326/M16-2607

52. **Emilsson L, García-Albéniz X, Logan RW, et al.** Examining bias in studies of statin treatment and survival in patients with cancer. JAMA Oncol. 2018;4:63-70. [PMID: 28822996] doi:10.1001/jamaoncol.2017.2752

53. **Hernán MA, Brumback B, Robins JM.** Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. Epidemiology. 2000;11:561-70. [PMID: 10955409]

54. **Danaei G, García Rodríguez LA, Cantero OF, et al.** Electronic medical records can be used to emulate target trials of sustained treatment strategies. J Clin Epidemiol. 2018;96:12-22. [PMID: 29203418] doi:10.1016/j.jclinepi.2017.11.021

55. **Domrongkitchaiporn S, Sritara P, Kitiyakara C, et al.** Risk factors for development of decreased kidney function in a southeast Asian population: a 12-year cohort study. J Am Soc Nephrol. 2005;16:791-9. [PMID: 15677313]

56. **Kuo CF, Luo SF, See LC, et al.** Hyperuricaemia and accelerated reduction in renal function. Scand J Rheumatol. 2011;40:116-21. [PMID: 20868309] doi:10.3109/03009742.2010.507218

57. **Hughes K, Flynn T, de Zoysa J, et al.** Mendelian randomization analysis associates increased serum urate, due to genetic variation in uric acid transporters, with improved renal function. Kidney Int. 2014;85:344-51. [PMID: 24048376] doi:10.1038/ki.2013.353

58. **Ahola AJ, Sandholm N, Forsblom C, et al; FinnDiane Study Group.** The serum uric acid concentration is not causally linked to diabetic nephropathy in type 1 diabetes. Kidney Int. 2017;91:1178-1185. [PMID: 28238338] doi:10.1016/j.kint.2016.11.025

59. **Jordan DM, Choi HK, Verbanck M, et al.** No causal effects of serum urate levels on the risk of chronic kidney disease: a Mendelian randomization study. PLoS Med. 2019;16:e1002725. [PMID: 30645594] doi:10.1371/journal.pmed.1002725

60. **Kanbay M, Ozkara A, Selcoki Y, et al.** Effect of treatment of hyperuricemia with allopurinol on blood pressure, creatinine clearance, and proteinuria in patients with normal renal functions. Int Urol Nephrol. 2007;39:1227-33. [PMID: 17701281]

61. **Pai BH, Swarnalatha G, Ram R, et al.** Allopurinol for prevention of progression

of kidney disease with hyperuricemia. Indian J Nephrol. 2013;23:280-6. [PMID: 23960345] doi:10.4103/0971-4065.114499

62. **Levy GD, Rashid N, Niu F, et al.** Effect of urate-lowering therapies on renal disease progression in patients with hyperuricemia. J Rheumatol. 2014;41:955-62. [PMID: 24692523] doi:10.3899/jrheum.131159

63. **Krishnamurthy A, Lazaro D, Stefanov DG, et al.** The effect of allopurinol on renal function. J Clin Rheumatol. 2017;23:1-5. [PMID: 28002149] doi:10.1097/RHU.0000000000000480

64. **Singh JA, Yu S.** Are allopurinol dose and duration of use nephroprotective in the elderly? A Medicare claims study of allopurinol use and incident renal failure. Ann Rheum Dis. 2017;76:133-139. [PMID: 27296322] doi:10.1136/annrheumdis-2015-209046

65. **Goicoechea M, Garcia de Vinuesa S, Verdalles U, et al.** Allopurinol and progression of CKD and cardiovascular events: long-term follow-up of a randomized clinical trial. Am J Kidney Dis. 2015;65:543-9. [PMID: 25595565] doi:10.1053/j.ajkd.2014.11.016

66. **Siu YP, Leung KT, Tong MK, et al.** Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. Am J Kidney Dis. 2006;47:51-9. [PMID: 16377385]

67. **Liu P, Chen Y, Wang B, et al.** Allopurinol treatment improves renal function in patients with type 2 diabetes and asymptomatic hyperuricemia: 3-year randomized parallel-controlled study. Clin Endocrinol (Oxf). 2015;83:475-82. [PMID: 25400252] doi:10.1111/cen.12673

68. **Goicoechea M, de Vinuesa SG, Verdalles U, et al.** Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. Clin J Am Soc Nephrol. 2010;5:1388-93. [PMID: 20538833] doi:10.2215/CJN.01580210

69. **Kao MP, Ang DS, Gandy SJ, et al.** Allopurinol benefits left ventricular mass and endothelial dysfunction in chronic kidney disease. J Am Soc Nephrol. 2011;22:1382-9. [PMID: 21719783] doi:10.1681/ASN.2010111185

70. **MacIsaac RL, Salatzki J, Higgins P, et al.** Allopurinol and cardiovascular outcomes in adults with hypertension. Hypertension. 2016;67:535-40. [PMID: 26865199] doi:10.1161/HYPERTENSIONAHA.115.06344

71. **Kim SC, Neogi T, Kang EH, et al.** Cardiovascular risks of Probenecid versus allopurinol in older patients with gout. J Am Coll Cardiol. 2018;71:994-1004. [PMID: 29496000] doi:10.1016/j.jacc.2017.12.052

72. **Shoji A, Yamanaka H, Kamatani N.** A retrospective study of the relationship between serum urate level and recurrent attacks of gouty arthritis: evidence for reduction of recurrent gouty arthritis with antihyperuricemic therapy. Arthritis Rheum. 2004;51:321-5. [PMID: 15188314]

73. **Dalbeth N, Billington K, Doyle A, et al.** Effects of allopurinol dose escalation on

bone erosion and urate volume in gout: a dual-energy computed tomography imaging study within a randomized, controlled trial. Arthritis Rheumatol. 2019;71:1739-1746. [PMID: 31081595] doi:10.1002/art.40929

74. **Doherty M, Jenkins W, Richardson H, et al.** Efficacy and cost-effectiveness of nurse-led care involving education and engagement of patients and a treat-to-target urate-lowering strategy versus usual care for gout: a randomised controlled trial. Lancet. 2018;392:1403-1412. [PMID: 30343856] doi:10.1016/S0140-6736(18)32158-5

75. **Austin PC.** A comparison of 12 algorithms for matching on the propensity score. Stat Med. 2014;33:1057-69.

76. **Austin PC.** Statistical criteria for selecting the optimal number of untreated subjects matched to each treated subject when using many-to-one matching on the propensity score. Am J Epidemiol. 2010;172:1092-7.

2. SAS code for the PS matching analysis and target trial emulation analysis

```
/*greedy PS matching*/
/*Choosing subjects from the first time-block*/
%let maxblock=18;
data pat;
       set allo;
       if block=1;
    run;

/*Calculating PS*/
PROC LOGISTIC DATA=pat Descend noprint;
class treat(ref="0") drink_status (ref="0")
smoking_status_ordinal(ref="0") sex(ref="2") sdin(ref="1") country
(ref="E")/param=ref;
MODEL treat= bmi diabete drink_status hypertension mi stroke angina
varicose pneu_infl hyperlipid depression tia chf COPD ihd
smoking_status_ordinal gfr ua hospitalization visit_n refer sdin sex
age country ckd_stage lupus colchicine ACE antico asp antidiab BETA
CCBs cortico_syst cortico_topical loop nitrate nsaids potsparing
statin thiazides;
OUTPUT OUT= Propen1 prob=prob; run;

/*PS Greedy Matching*/
proc psmatch data=Propen1 region=cs;
class treat country;
psdata ps=prob treatvar=treat(treated='1');
match method=greedy (k=1 order=random(seed=123)) distance=lps
caliper=0.1 exact=country;
output out(obs=match)=psmatched1 lps=_Lps matchid=_MatchID;
run;

data ps_match;
set psmatched1;
run;

/*Starting the loop from the second time-block to the last time-
block*/
%macro runps;
%do iloop=2 %to &maxblock;

/*Removing the PS-matched subjects in early accrual time blocks from
```

```
the later accrual time blocks*/
proc sql; create table allo1_1 as
    select * from allo where subjid not in (select subjid from
ps_match);
    quit;
    data pat&iloop;
        set allo1_1;
        if block=&iloop;
    run;
PROC LOGISTIC DATA=pat&iloop Descend noprint;
class treat(ref="0") drink_status (ref="0")
smoking_status_ordinal(ref="0") sex(ref="2") sdin(ref="1") country
(ref="E")/param=ref;
MODEL treat= bmi diabete drink_status hypertension mi stroke angina
varicose pneu_infl hyperlipid depression tia chf COPD ihd
smoking_status_ordinal gfr ua hospitalization visit_n refer sdin sex
age country ckd_stage lupus colchicine ACE antico asp antidiab BETA
CCBs cortico_syst cortico_topical loop nitrate nsaids potsparing
statin thiazides;
OUTPUT OUT= Propen&iloop prob=prob; run;

proc psmatch data=Propen&iloop region=cs;
class treat country;
psdata ps=prob treatvar=treat(treated='1');
match method=greedy (k=1 order=random(seed=123)) distance=lps
caliper=0.1 exact=country;
output out(obs=match)=psmatched&iloop lps=_Lps matchid=_MatchID;
run;

/*Combining all PS matched dataset*/
data ps_match;
set Psmatched1-psmatched&iloop;
run;

%end;
%mend;
%runps;


data ps_match_greedy;
set ps_match;
run;

/*Cox proportional model*/
```

```
/*Sandwich estimation*/
proc phreg data=ps_match_greedy COVSANDWICH;
class treat(ref='0')_matchid/param=ref;
model followy*death(0)=treat/risklimits;
id _matchid;
run;
```

```
/*Target trial emulation */
/*data d_all represents the person-year format data of
allopurinol initiators*/
/*A=1 represents that individual actually achieve the target
SU during the first year after the index date*/
/*A=0 represents that individual actually does not achieve the
target SU during the first year after the index date*/

/* STEP 1: Create replicates (clones) for each individual */
data pooled_TTE3;
set d_all;
treat=0; output;
treat=1; output;
run;

/* STEP 2: Censor replicates when they deviate from their assigned
strategy */
proc sort data=pooled_TTE3; by subjid treat time_b; run;
data pooled_TTE3;
set pooled_TTE3;
by subjid treat time_b;
retain c;
if first.treat then c=0;
if treat=0 and A=1 then c=1;
if treat=1 and A=0 then c=1;

if c=0 then adhr=1;
if c=1 then adhr=0;
run;

data nocensor censor;
set pooled_TTE3;
if c=0 then output nocensor;
if c=1 then output censor;
run;

proc sort data=censor; by subjid treat time_b; run;
data censor;
set censor;
by subjid treat time_b;
if first.treat;
run;

data pooled_TTE4;
```

```
set nocensor censor;
run;

/*STEP 3: Estimate probabilities for denominator of the IP weights */
proc logistic data =pooled_TTE4 descending;
class adhr(ref="0") drink_status (ref="0")
smoking_status_ordinal(ref="0") sex(ref="2") sdin(ref="1") country
(ref="E")/param=ref;
MODEL adhr=bmi diabetes drink_status hypertension mi stroke angina
varicose pneu_infl hyperlipid depression tia chf COPD ihd
smoking_status_ordinal gfr first_ua hospitalization visit_n refer
sdin sex age country ckd_stage colchicine ACE antico asp antidiab
BETA CCBs cortico_syst cortico_topical loop nitrate nsaids potsparing
statin thiazides;
output out = _modelAd_1 (keep = subjid pdenom_1 time_b) p=pdenom_1;
where time_b=0 and treat=1;
run;

proc logistic data =pooled_TTE4 descending;
class adhr(ref="0") drink_status (ref="0")
smoking_status_ordinal(ref="0") sex(ref="2") sdin(ref="1") country
(ref="E")/param=ref;
MODEL adhr= bmi diabetes drink_status hypertension mi stroke angina
varicose pneu_infl hyperlipid depression tia chf COPD ihd
smoking_status_ordinal gfr first_ua hospitalization visit_n refer
sdin sex age country ckd_stage colchicine ACE antico asp antidiab
BETA CCBs cortico_syst cortico_topical  loop nitrate nsaids
potsparing statin thiazides;
output out = _modelAd_0 (keep = subjid pdenom_0 time_b) p=pdenom_0;
where time_b=0 and treat=0;
run;

/*  STEP 4: Build the unstabilized IP weights */
data pooled_TTE4_1 pooled_TTE4_0;
set pooled_TTE4;
if treat=1 then output pooled_TTE4_1;
if treat=0 then output pooled_TTE4_0;
run;

/*  STEP 4_1 Build the weights  for subjects who were assigned to
achieving the target SU during the first year */
proc sql;
create table pooled_TTE4_11 as
select a.*, b.pdenom_1 from pooled_TTE4_1 a left join _modelAd_1 b
```

```
on a.subjid=b.subjid;
quit;

data pooled_TTE4_11;
set pooled_TTE4_11;
unsw = 1.0/pdenom_1;
run;

/* weight set to 1 for subjects who were assigned to achieving the
target SU during the first year */
/* subjects were censored if they did not achieve the target SU level
at the end of the first year*/
data pooled_TTE4_11;
set pooled_TTE4_11;
if time_b=0 then unsw=1;
else if c=1 then unsw=0; run;

/* STEP 4_2 Build the weights for subjects who were assigned to not
achieving the target SU during the first year */
proc sql;
create table pooled_TTE4_00 as
select a.*, b.pdenom_0 from pooled_TTE4_0 a left join _modelAd_0 b
on a.subjid=b.subjid;
quit;

data pooled_TTE4_00;
set pooled_TTE4_00;
unsw = 1.0/pdenom_0;
run;

/* subjects were censored if they achieved the target SU level*/

data pooled_TTE4_00;
set pooled_TTE4_00;
if c=1 then unsw=0; run;

data pooled_TTE5;
set pooled_TTE4_11 pooled_TTE4_00;
run;

data pooled_TTE5;
set pooled_TTE5;
if unsw=0 then delete;
run;
```

```
/* STEP 5: Truncate the weights at the 99th percentile*/

proc means data = pooled_TTE5 p99 noprint;
var unsw;
output out=pctl (keep=p99) p99=p99;
run;
data temp;
set pctl;
call symput ('cutoff', p99);
run;
data pooled_TTE6;
set pooled_TTE5;
unsw_t = unsw;
if unsw>%sysevalf(&cutoff) then do;
    unsw_t = %sysevalf(&cutoff);
end;
run;

proc univariate data=pooled_TTE6; var unsw unsw_t; run;

/*STEP 6: Estimate weighted hazard ratio*/
/*Y refers to death*/

proc genmod data=pooled_TTE6 descending;
class subjid Y(ref="0") treat(ref="0") drink_status (ref="0")
smoking_status_ordinal(ref="0") sex(ref="2") sdin(ref="1") country
(ref="E")/param=ref;
MODEL Y=treat time_b time_b*time_b bmi diabete drink_status
hypertension mi stroke depression tia chf COPD ihd angina varicose
pneu_infl hyperlipid smoking_status_ordinal gfr first_ua
hospitalization visit_n refer sdin sex age country ckd_stage
colchicine ACE antico asp antidiab BETA CCBs cortico_syst
cortico_topical loop nitrate nsaids potsparing statin thiazides;
scwgt unsw_t;
repeated subject=subjid/type=ind;
estimate "Achieving target SU" treat 1/exp;
run;

/*Calculating the five-year risk difference and plotting the weighted
survival curves*/

data pooled_TTE6;
set pooled_TTE6;
```

```
time_b2=time_b*time_b;
randtime_b=treat*time_b;
randtime_b2=treat*time_b2;
run;

proc genmod data=pooled_TTE6 descending;
class subjid treat(ref="0")/param=ref;
model Y=treat time_b time_b2 randtime_b randtime_b2/link=logit
dist=bin;
weight unsw_t;
ods output ParameterEstimates = plrFit_ix_SWT;
run;

data plrFit_ix_SWT;
set plrFit_ix_SWT;
    if PARAMETER = "Scale" then delete;
run;

proc sql noprint;
    select ESTIMATE FORMAT =16.12 INTO: IBC_ESTIMATE separated by ' '
from plrFit_ix_SWT;
quit;

proc sql noprint;
    select PARAMETER INTO: MODEL separated by ' ' from plrFit_ix_SWT;
quit;
proc means sum noprint data = plrFit_ix_SWT;
    var DF;
    output out = nobs (drop = _type_ _freq_ where=(_stat_ ="N"));
run;

proc sql noprint;
    select DF into:NVAR separated by ' ' from nobs;  quit;

data untreated (keep = s ci treat time_b);
set pooled_TTE6;
where time_b = 0;
    array var{&nvar} &model;
    array coef{&nvar} (&ibc_estimate);
    intercept = 1;
    s=1;
    treat = 0;
    do time_b = 0 to 4;
        time_b2 = time_b*time_b;
```

```
        xbeta = 0;
        randtime_b=treat*time_b;
        randtime_b2=treat*time_b2;

        do i = 1 to dim(var);
            xbeta = xbeta + coef[i] *var[i];
        end;
    p = 1/(1+exp(-xbeta));
        s = s*(1-p);
        ci = 1-s;
        output;
    end;
run;

data treated (keep = s ci treat time_b);
set pooled_TTE6;
where time_b = 0;
    array var{&nvar} &model;
    array coef{&nvar} (&ibc_estimate);
    intercept = 1;
    s=1;
    treat = 1 ;
    do time_b = 0 to 4;
        time_b2 = time_b*time_b;
        xbeta = 0;
        randtime_b=treat*time_b;
        randtime_b2=treat*time_b2;

        do i = 1 to dim(var);
            xbeta = xbeta + coef[i] *var[i];
        end;
    p = 1/(1+exp(-xbeta));
        s = s*(1-p);
        ci = 1-s;
        output;
    end;
run;

data both;
set untreated treated;
by treat;
run;

/* Calculate the mean survival at each year within each treatment
```

```
arm*/
proc means data = both mean;
    class time_b treat;
    types treat*time_b;
    var s;
    output out = means (drop = _type_ _freq_) mean(s) = s;
run;

proc transpose data=means out = wideres prefix = Surv_;
var s;
id treat;
by time_b;
run;

data wideres;
set wideres;
    time_b = time_b+1;
    merge_id = 1;
    rd = (1-Surv_1) -(1- Surv_0);
run;

data wideres;
set wideres;
total + ratio;
drop total ratio;
run;

data zero;
    time_b = 0;
    merge_id = 1;
    surv_0 = 1;
    surv_1 = 1;
    rd = 0;
run;

data results_1;
merge wideres zero;
by time_b;
drop merge_id _NAME_;
run;

/*Plot the results*/
data results_1;
set results_1;
```

```
mortality_1=1-surv_1;
mortality_0=1-surv_0;
run;

goptions reset=all;
axis1 length=5.9in label=(angle=90 height=2 "Risk of Death") width=1
order=(0 to 0.3 by .1)
    major=(height=2 width=2) minor=none value=(height=1.5)
offset=(2,2);
axis2 length=5.9in label=(height=2 justify=center "Years of follow
up")
    width=1 order=(0 to 5 by 1) major=(height=1 width=2)
    minor=none value=(height=1.5) offset=(2,2);
symbol1 c=red h=12 l=1 w=2 v=none i=line mode=include;
symbol2 c=blue h=12 l=4 w=2 v=none i=line mode=include;
legend1 label=none value=(color=black h=1.5 "Achieving target SU
level" "Not achieving target SU level")
    down=4 position=(MIDDLE  left inside) FWIDTH=1
    shape=symbol(6,3) offset=(0,1) mode=protect;

proc gplot data=results_1; plot (mortality_1
mortality_0)*time_b/overlay vaxis=axis1 haxis=axis2
    legend=legend1 noframe;
run;
quit;

/* Print risk difference*/
proc print data = results_1;
var time_b mortality_1 mortality_0 rd;
run;
```