# Supplementary Online Content

Vargas-Santos AB, Peloquin CE, Zhang Y, Neogi T. Association of chronic kidney disease with allopurinol use in gout treatment. *JAMA Intern Med*. Published online October 08, 2018. doi:10.1001/jamainternmed.2018.4463



This supplementary material has been provided by the authors to give readers additional information about their work.

**Methods Supplement: Bias analysis**

**eMethods 1: Missing data**

Due to a high number of missing data on body mass index (BMI) and serum urate, respectively 11.6% and 36.6% of the 72,597 potentially eligible subjects after the blocking process, we performed multiple imputation. First, we imputed the high-dose allopurinol blocked dataset five times to impute missing BMI and serum urate values. Then, we created five propensity score- (PS)-matched datasets from the five imputed blocked datasets. For each of them, we calculated PS-matched hazards ratio (HR) with respective 95% confidence intervals (CI) and performed a second model additionally adjusting for the covariates included in the PS. Lastly, we calculated the mean HR and CI bounds from all five HR to create one summary HR for each model. The results from this multiple imputation analysis reinforced our primary findings, with a PS-matched HR of 0.89 (95% CI 0.82–0.97, p=0.007) and further adjusted for the PS variables, the HR was 0.92 (95% CI 0.84–1.00, p=0.05).

**eMethods 2: Covariate balance**

Covariate balance in the PS-matched dataset was assessed using the standardized mean difference (SMD), evaluated through SAS Macro %pmdiag. The closer the SMD is to 0, the better is the covariate balance. All SMD were lower than 0.1, ranging from <0.01 to 0.03, confirming a very good balance overall.

| | SMD prior to PS-matching | SMD post PS-matching |
|---|---|---|
| Age | 0.34 | 0 |
| Female | 0.20 | 0 |
| Body mass index | 0.21 | 0.01 |
| Gout duration | 0.97 | 0.02 |
| Hospitalization in year prior to index date | 0.05 | 0 |
| Visits to the general practitioners in year prior to index date | 0.06 | 0.01 |
| Baseline CKD stage 2 or eGFR 60-89 mL/min per 1.73m$^2$ | 0 | 0.01 |
| Hypertension | 0.04 | 0.01 |
| Diabetes mellitus | 0.10 | 0.01 |
| Cardiovascular disease | 0.01 | 0.01 |
| Heart failure | 0.07 | 0 |
| Diuretics (loop, thiazide, thiazide-like) | 0.24 | 0.01 |
| Angiotensin-converting-enzyme inhibitor | 0.01 | 0.01 |
| Losartan | 0.09 | 0.01 |
| Other angiotensin II receptor blockers | 0.03 | 0.01 |
| Colchicine | 0.32 | 0.01 |
| Nonsteroidal anti-inflammatory drugs | 0.64 | 0.02 |
| Low dose aspirin | 0.05 | 0 |
| Insulin | 0.02 | 0.01 |
| Other drugs for diabetes mellitus | 0.10 | 0.01 |
| Serum urate level | 0.93 | 0.03 |
| Albuminuria | 0.07 | 0 |

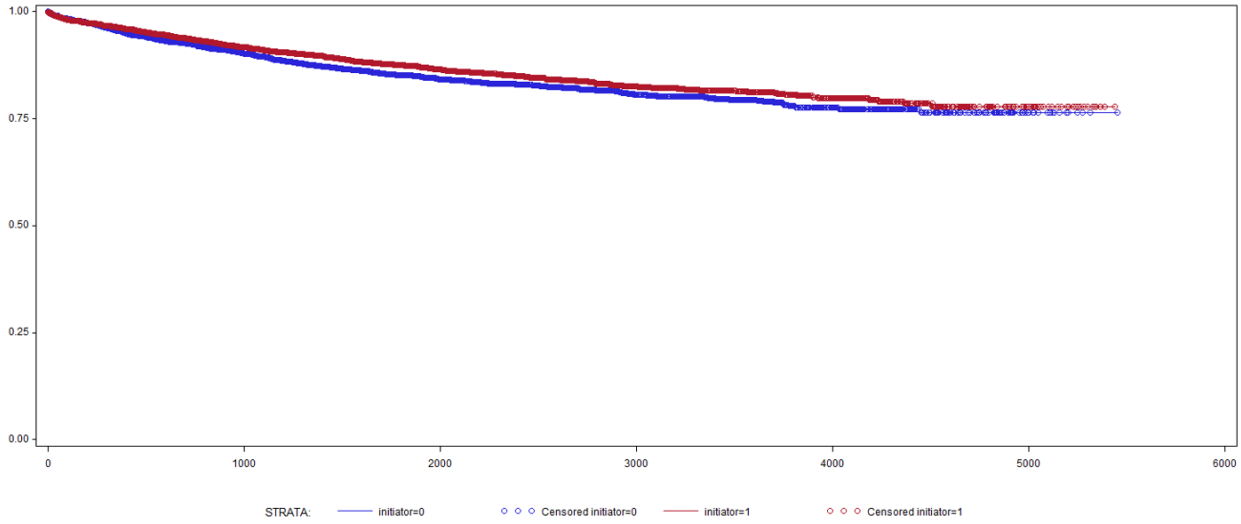
SMD: standardized mean difference; PS: propensity-score; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate.

**eMethods 3: Evaluation of the proportionality assumption**

To ensure that the methods used for our main analysis were appropriate, we assessed whether the major assumption of the Cox proportional hazards model was respected, which is that the effect of a given covariate does not change over time. To assess if there was any violation of the proportional hazards assumption, we performed three checks. First, we included an interaction term (log of time x initiator) in the proportional hazards regression model, obtaining a p-value of 0.7406, therefore rejecting the violation hypothesis. Second, we included an “ASSESS PH” statement in the regression

model,[1] and no violation was identified, with p=0.3680. Lastly, we created a Log-Negative Log plot, which showed both lines converging at the beginning of follow-up and persisting as roughly parallel lines throughout the graphic, confirming that the hazards were proportional over time (e**Figure**). Evaluation of the Schoenfeld residuals by visual inspection also indicated compatibility with proportional hazards assumption.

## eFigure. Log-Negative Log plot




**eReference**

1. Lin D, Wei LJ, Ying Z. Checking the Cox Model with Cumulative Sums of Martingale-Based Residuals. *Biometrika.* 1993;80(3):557–572.

## Supplementary tables

### eTable 1. Comparison of characteristics of excluded versus included subjects.

| Subjects | Excluded n = 41,009 | Eligible n = 31,588 | Matched n = 9,520 |
|---|---|---|---|
| **Demographics** | | | |
| Age, years, mean (SD) | 58.6 (14.8) | 59.2 (13.6) | 57.4 (13.6) |
| Male, n (%) | 33,196 (80.9) | 24,673 (78.1) | 7,946 (83.5) |
| Body mass index missing, n (%) | 8,440 (20.6) | 0 (0.0) | 0 (0.0) |
| Body mass index, kg/m$^2$, mean (SD) | 29.2 (5.4) | 29.2 (5.3) | 30.0 (5.5) |
| Gout duration, years, mean (SD) | 0.4 (0.4) | 1.1 (1.7) | 1.2 (1.9) |
| Hospitalization in year prior to index date, n (%) | 4,335 (10.6) | 3,343 (10.6) | 1,026 (10.8) |
| Visits to the GP in year prior to index date, n (%) | | | |
| 0 | 3,473 (8.5) | 1,433 (4.5) | 552 (5.8) |
| 1 | 6,106 (14.9) | 2,960 (9.4) | 968 (10.2) |
| 2 | 6,148 (15.0) | 4,026 (12.7) | 1,274 (13.4) |
| 3 | 5,190 (12.7) | 4,078 (12.9) | 1,159 (12.2) |
| 4 | 4,327 (10.6) | 3,693 (11.7) | 1,106 (11.6) |
| 5 | 3,334 (8.1) | 3,063 (9.7) | 872 (9.2) |
| 6-7 | 4,773 (11.6) | 4,638 (14.7) | 1,342 (14.1) |
| 8-10 | 3,903 (9.5) | 3,690 (11.7) | 1,068 (11.2) |
| ≥11 | 3,755 (9.2) | 4,007 (12.7) | 1,179 (12.4) |
| **Comorbid conditions, n (%)** | | | |
| CKD stage 2 or eGFR 60-89 mL/min per 1.73m$^2$ | 22,345 (54.5) | 21,826 (69.1) | 6,724 (70.6) |
| Hypertension | 16,308 (39.8) | 14,206 (45.0) | 4,466 (46.9) |
| Diabetes mellitus | 2,958 (7.2) | 2,749 (8.7) | 780 (8.2) |
| Cardiovascular disease | 4,986 (12.2) | 3,388 (10.7) | 1,091 (11.5) |
| Heart failure | 1,895 (4.6) | 979 (3.1) | 370 (3.9) |
| **Concomitant medication use, n (%)** | | | |
| Diuretics (loop, thiazide, thiazide-like) | 11,523 (28.1) | 8,676 (27.5) | 2,960 (31.1) |
| Angiotensin-converting-enzyme inhibitor | 9,294 (22.7) | 7,733 (24.5) | 2,510 (26.4) |
| Losartan | 761 (1.9) | 769 (2.4) | 194 (2.0) |
| Other angiotensin II receptor blockers | 2,224 (5.4) | 1,980 (6.3) | 726 (7.6) |
| Colchicine | 5,952 (14.5) | 4,351 (13.8) | 1,601 (16.8) |
| Nonsteroidal anti-inflammatory drugs | 27,652 (67.4) | 21,084 (66.7) | 6,960 (73.1) |
| Low dose aspirin | 7,317 (17.8) | 5,582 (17.7) | 1,644 (17.3) |
| Insulin | 317 (0.8) | 259 (0.8) | 61 (0.6) |
| Other drugs for diabetes mellitus | 1,790 (4.4) | 1,677 (5.3) | 444 (4.7) |
| **Laboratory data** | | | |
| Serum urate level missing, n (%) | 26,572 (64.8) | 0 (0.0) | 0 (0.0) |
| Serum urate level, mg/dL, mean (SD) | 8.2 (1.5) | 7.3 (1.6) | 8.2 (1.4) |
| Albuminuria, n (%) Missing | 37,905 (92.4) | 28,464 (90.1) | 8,732 (91.7) |
| Normal (<3mg/mmol) | 2,193 (5.3) | 2,227 (7.1) | 563 (5.9) |
| Moderately increased (3-30mg/mmol) | 769 (1.9) | 788 (2.5) | 181 (1.9) |
| Severely increased (>30mg/mmol) | 142 (0.3) | 109 (0.3) | 44 (0.5) |

SD: Standard deviation; GP: general practitioner; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate.

**eTable 2: Post-baseline characteristics of allopurinol initiators at ≥300mg/day versus non-initiators.**

| | n (%) |
|---|---|
| **Allopurinol initiators:** | |
| Decreased dose then stopped allopurinol | 296 (6.2) |
| Stable dose then stopped allopurinol | 2,471 (51.9) |
| Increased dose then stopped allopurinol | 73 (1.5) |
| Remained on allopurinol at a decreased dose | 95 (2) |
| Remained on allopurinol at the same dose | 1,757 (36.9) |
| Remained on allopurinol at an increased dose | 68 (1.4) |
| Allopurinol use duration: | |
| <6 months | 1,990 (41.8) |
| 6 months - <1 year | 536 (11.3) |
| 1 - <2 years | 592 (12.4) |
| 2 - <4 years | 618 (13.0) |
| ≥4 years | 1,024 (21.5) |
| Use of nonsteroidal anti-inflammatory drugs | 3,589 (75.4) |
| Use of colchicine | 1,166 (24.5) |
| Allopurinol hypersensitivity syndrome | 6 (0.13) |
| | |
| **Non-initiator (comparator) group:** | |
| Started allopurinol | 396 (8.3) |
| Use of nonsteroidal anti-inflammatory drugs | 3,002 (63.1) |
| Use of colchicine | 707 (14.9) |
| Allopurinol hypersensitivity syndrome | 2 (0.04) |
| | |

**eTable 3. Sensitivity analysis: Baseline characteristics of allopurinol initiators at <300mg/day versus non-initiators.**

| | Allopurinol initiators at <300mg/day | Non-initiators |
|---|---|---|
| | n = 10,179 | n = 10,179 |
| **Demographics** | | |
| Age, years, mean (SD) | 58.6 (13.4) | 58.4 (13.9) |
| Male, n (%) | 8,429 (82.8) | 8,431 (82.8) |
| Body mass index, kg/m$^2$, mean (SD) | 30.0 (5.4) | 30.0 (5.4) |
| Gout duration, years, mean (SD) | 1.5 (2.5) | 1.4 (1.8) |
| Hospitalization in year prior to index date, n (%) | 1,319 (13.0) | 1,330 (13.1) |
| Visits to the general practitioners in year prior to index date, n (%) | | |
| 0 | 451 (4.4) | 428 (4.2) |
| 1 | 910 (8.9) | 872 (8.6) |
| 2 | 1,235 (12.1) | 1,288 (12.7) |
| 3 | 1,256 (12.3) | 1,313 (12.9) |
| 4 | 1,122 (11.0) | 1,103 (10.8) |
| 5 | 981 (9.6) | 975 (9.6) |
| 6-7 | 1,465 (14.4) | 1,438 (14.1) |
| 8-10 | 1,337 (13.1) | 1,328 (13.0) |
| ≥11 | 1,422 (14.0) | 1,434 (14.1) |
| **Comorbid conditions, n (%)** | | |
| Chronic kidney disease stage 2 or eGFR 60-89 mL/min per 1.73m$^2$ | 7,137 (70.1) | 7,181 (70.5) |
| Hypertension | 4,781 (47.0) | 4,786 (47.0) |
| Diabetes mellitus | 912 (9.0) | 873 (8.6) |
| Cardiovascular disease | 1,280 (12.6) | 1,283 (12.6) |
| Heart failure | 443 (4.4) | 438 (4.3) |
| **Concomitant medication use, n (%)** | | |
| Diuretics (loop, thiazide, thiazide-like) | 3,011 (29.6) | 2,968 (29.2) |
| Angiotensin-converting-enzyme inhibitor | 2,825 (27.8) | 2,821 (27.7) |
| Losartan | 228 (2.2) | 222 (2.2) |
| Other angiotensin II receptor blockers | 757 (7.4) | 718 (7.1) |
| Colchicine | 2,397 (23.5) | 2,279 (22.4) |
| Nonsteroidal anti-inflammatory drugs | 7,129 (70.0) | 7,299 (71.7) |
| Low dose aspirin | 1,891 (18.6) | 1,877 (18.4) |
| Insulin | 74 (0.7) | 67 (0.7) |
| Other drugs for diabetes mellitus | 541 (5.3) | 516 (5.1) |
| **Laboratory data** | | |
| Serum urate level, mg/dL, mean (SD) | 8.2 (1.3) | 8.2 (1.3) |
| Albuminuria, n (%)<br>Missing | 8,963 (88.1) | 9,007 (88.5) |
| Normal (<3mg/mmol) | 864 (8.5) | 812 (8.0) |
| Moderately increased (3-30mg/mmol) | 304 (3.0) | 309 (3.0) |
| Severely increased (>30mg/mmol) | 48 (0.5) | 51 (0.5) |

SD: standard deviation; eGFR: estimated glomerular filtration rate.

**eTable 4. Sensitivity analysis: Risk of developing CKD ≥3 among subjects with incident gout and incident allopurinol use of <300mg/day.**

| Main results | Incident allopurinol user (n = 10,179) | Non-allopurinol user (n = 10,179) |
|---|---|---|
| Incident CKD stage ≥3, n (%) | 986 (9.7) | 970 (9.5) |
| Death, n (%) | 404 (4) | 454 (4.5) |
| Mean follow-up time, years | 3.6 | 3.5 |
| Crude incidence rate (CKD stage ≥3) per 1000 person-years | 26.7 | 27.1 |
| Propensity score-matched hazards ratio (95% CI) | 1.00 (0.91–1.09) | |
| Adjusted* hazards ratio (95% CI) | 1.02 (0.93–1.12) | |

* Variables included in the propensity-score model and included in the adjusted hazards ratio model: 1) gout duration; 2) baseline serum urate; 3) baseline kidney function and albuminuria; 4) general (age, gender, body mass index); 5) comorbidities (cardiovascular disease, diabetes mellitus, heart failure, hypertension); 6) hospitalization; 7) number of visits to the general practitioner; 8) medication use (angiotensin-converting-enzyme inhibitor, aspirin, colchicine, diuretics, insulin, other drugs for diabetes mellitus, losartan, other angiotensin II receptor blockers, nonsteroidal anti-inflammatory drugs).
CKD: chronic kidney disease; CI: confidence interval.

**eTable 5. Comparisons of baseline characteristics of participants for allopurinol initiators at ≥300mg/day versus <300mg/day.**

| | Allopurinol initiators at <300mg/day | Allopurinol initiators at ≥300mg/day |
|---|---|---|
| | **n = 10,179** | **n = 4,760** |
| **Demographics** | | |
| Age, years, mean (SD) | 58.6 (13.4) | 57.4 (13.3) |
| Male, n (%) | 8,429 (82.8) | 3,975 (83.5) |
| Body mass index, kg/m$^2$, mean (SD) | 30.0 (5.4) | 30.0 (5.4) |
| Gout duration, years, mean (SD) | 1.5 (2.5) | 1.2 (2.1) |
| Hospitalization in year prior to index date, n (%) | 1,319 (13.0) | 516 (10.8) |
| Visits to the general practitioners in year prior to index date, n (%) | | |
| 0 | 451 (4.4) | 269 (5.7) |
| 1 | 910 (8.9) | 474 (10.0) |
| 2 | 1,235 (12.1) | 636 (13.4) |
| 3 | 1,256 (12.3) | 601 (12.6) |
| 4 | 1,122 (11.0) | 547 (11.5) |
| 5 | 981 (9.6) | 442 (9.3) |
| 6-7 | 1,465 (14.4) | 675 (14.2) |
| 8-10 | 1,337 (13.1) | 536 (11.3) |
| ≥11 | 1,422 (14.0) | 580 (12.2) |
| **Comorbid conditions, n (%)** | | |
| Chronic kidney disease stage 2 or eGFR 60-89 mL/min per 1.73m$^2$ | 7,137 (70.1) | 3,354 (70.5) |
| Hypertension | 4,781 (47.0) | 2,223 (46.7) |
| Diabetes mellitus | 912 (9.0) | 396 (8.3) |
| Cardiovascular disease | 1,280 (12.6) | 538 (11.3) |
| Heart failure | 443 (4.4) | 187 (3.9) |
| **Concomitant medication use, n (%)** | | |
| Diuretics (loop, thiazide, thiazide-like) | 3,011 (29.6) | 1,472 (30.9) |
| Angiotensin-converting-enzyme inhibitor | 2,825 (27.8) | 1,246 (26.2) |
| Losartan | 228 (2.2) | 93 (2.0) |
| Other angiotensin II receptor blockers | 757 (7.4) | 359 (7.5) |
| Colchicine | 2,397 (23.5) | 791 (16.6) |
| Nonsteroidal anti-inflammatory drugs | 7,129 (70.0) | 3,461 (72.7) |
| Low dose aspirin | 1,891 (18.6) | 819 (17.2) |
| Insulin | 74 (0.7) | 33 (0.7) |
| Other drugs for diabetes mellitus | 541 (5.3) | 227 (4.8) |
| **Laboratory data** | | |
| Serum urate level, mg/dL, mean (SD) | 8.2 (1.3) | 8.2 (1.4) |
| Albuminuria, n (%)<br>Missing | 8,963 (88.1) | 4,367 (91.7) |
| Normal (<3mg/mmol) | 864 (8.5) | 276 (5.8) |
| Moderately increased (3-30mg/mmol) | 304 (3.0) | 98 (2.1) |
| Severely increased (>30mg/mmol) | 48 (0.5) | 19 (0.4) |

SD: standard deviation; eGFR: estimated glomerular filtration rate.