ORIGINAL ARTICLE

# Spectrum and dosing of urate-lowering drugs in a large cohort of chronic kidney disease patients and their effect on serum urate levels: a cross-sectional analysis from the German Chronic Kidney Disease study

Jan T. Kielstein [1,2,*], Markus Heisterkamp[1,2,*], Jiaojiao Jing[3], Jennifer Nadal[4], Matthias Schmid[4], Florian Kronenberg[5], Martin Busch[6], Claudia Sommerer[7], Johan M. Lorenzen[1,2], Kai-Uwe Eckardt[8,9] and Anna Köttgen[3] for the GCKD Study Investigators

[1]Medical Clinic V: Nephrology | Rheumatology | Blood Purification, Academic Teaching Hospital Braunschweig, Braunschweig, Germany, [2]Department of Nephrology, Hannover Medical School, Hannover, Germany, [3]Institute of Genetic Epidemiology, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg, Germany, [4]Institute for Medical Informatics and Epidemiology, University Hospital Bonn, Bonn, Germany, [5]Institute of Genetic Epidemiology, Medical University of Innsbruck, Innsbruck, Austria, [6]Department of Internal Medicine III, University Hospital Jena, Friedrich Schiller University, Jena, Germany, [7]Department of Medicine, Division of Nephrology, University Hospital Heidelberg, Heidelberg, Germany, [8]Department of Nephrology and Medical Intensive Care, Charité - Universitätsmedizin Berlin, Berlin, Germany and [9]Department of Nephrology and Hypertension, Friedrich-Alexander Universität Erlangen Nürnberg, Erlangen, Germany

Correspondence to: Jan T. Kielstein; E-mail: kielstein@yahoo.com
*These authors contributed equally to this work and should be both considered first authors.

## ABSTRACT

**Background.** Despite a plethora of studies on the effect of urate-lowering therapy (ULT) in patients with chronic kidney disease (CKD), current guidelines on the treatment of hyperuricaemia and gout vary, especially concerning the need for dose adjustment of allopurinol, whose main metabolite is accumulating with declining renal function. Data on allopurinol dosing and its relationship to renal function, co-medication and sex and the resulting urate level in large cohorts are missing.

**Methods.** We studied a subgroup of 2378 patients of the German Chronic Kidney Disease (GCKD) study to determine prescription patterns of ULT among CKD patients under nephrological care and the relationship of ULT dose to urate levels. Prescription and dosing of ULT were manually abstracted from the patient's paper charts at the baseline visit, in which all currently used medications and their dosing were recorded.

**Results.** In this cohort, 39.6% were women, the mean estimated glomerular filtration rate (eGFR) was $51.3 \pm 19.3$ mL/min/ $1.73$ m$^2$ and the mean age was $59.0 \pm 12.4$ years. Of the 2378 examined patients, 666 (28.0%) received ULT. The dose of ULT was available for 572 patients. The main ULT agent was allopurinol (94.4%), followed by febuxostat (2.9%) and benzbromarone (2.6%). Of the 540 patients who used allopurinol with a reported daily dose, 480 had an eGFR $<60$ mL/min/ $1.73$ m$^2$ and 320 had an eGFR $<45$ mL/min/$1.73$ m$^2$, 31.5% of the latter ($n = 101$) received a dose $>150$ mg/day, the recommended maximal dose for this level of eGFR. The prescribed dose was not related to eGFR: the median eGFR for patients taking 100, 150 and 300 mg/day was 40 [interquartile range (IQR) 32–49], 43 (34–52) and 42 (35–54) mL/min/$1.73$ m$^2$, respectively. Patients with lower doses of allopurinol had higher serum urate levels than patients with higher (than recommended) allopurinol doses. Sex, alcohol intake, eGFR, use of diuretics and treatment with allopurinol were independent determinants of serum urate levels in multivariate regression analysis.

**Conclusions.** The most frequently used drug to lower serum urate levels in this CKD cohort was allopurinol. Even in patients regularly seen by nephrologists, the dose of allopurinol is often not adjusted to the current eGFR. Patients with higher ULT doses achieved better control of their serum urate levels. Lowering of serum urate in CKD patients requires balancing potential adverse effects of allopurinol with suboptimal control of serum urate levels.

## INTRODUCTION

In clinical practice, the proportion of chronic kidney disease (CKD) patients receiving urate-lowering therapy (ULT) is low. In the Chronic Kidney Disease–Renal Epidemiology and Information Network (CKD-REIN) cohort, 33.8% of the patients with an estimated glomerular filtration rate (eGFR) $<60$ mL/min/1.73 m$^2$ received anti-gout preparations [1]. We have previously shown in the German Chronic Kidney Disease (GCKD) study, an observational cohort study that enrolled 5217 patients under nephrological care, that both gout and hyperuricaemia are undertreated [2]. One reason for the reluctance to treat hyperuricaemia more aggressively might be the fact that the main metabolite of the classic xanthine oxidase inhibitor allopurinol, oxipurinol, accumulates in the setting of reduced glomerular filtration rate (GFR) [3]. Therefore a dose reduction that parallels the decline in GFR is recommended by the manufacturer as well as by current guidelines [4]. However, those guidelines vary dramatically concerning the need for dose adjustment of allopurinol. A recent systematic review of practice guidelines and consensus statements reported that the recommended renal function to initiate dose adjustment was a creatinine clearance ranging from 20 to 140 mL/min [5]. This might be one reason why, in a large US population, it has been shown that physicians fail to adapt the dose of allopurinol to the different stages of CKD [6]. As the efficacy of uricosuric drugs to lower serum urate diminishes with decreasing renal function, it is thought that these drugs are infrequently used in CKD. Aside from ULT, frequently used drugs in CKD, like thiazide diuretics, can promote hyperuricaemia, further challenging the control of serum urate levels.

Aside from a general overview of prescription patterns in the 3033 patients of the CKD-REIN cohort [1], there are currently no published data concerning practices of ULT prescription and dosing from Europe in patients with eGFR $<60$ mL/min/1.73 m$^2$, not to mention their relationship to urate levels. Hence the aim of our study was to analyse the prescription patterns, prescribed substances and dosing of urate-lowering drugs in relation to renal function as well as the resulting urate levels and determinants including co-medication patterns in a large sample of CKD patients.

## MATERIALS AND METHODS

### Study design

The GCKD study is an ongoing prospective observational national cohort study that enrolled 5217 patients 18–74 years of age with CKD of various aetiologies across nine centres in Germany. At the time of enrolment (2010–12), patients had an eGFR of 30–60 mL/min/1.73 m$^2$ or overt proteinuria, defined as albumin excretion $>300$ mg/g creatinine or protein excretion $>500$ mg/g creatinine or corresponding values of 24-h urinary excretion in the presence of a GFR $>60$ mL/min/1.73 m$^2$. Further information about inclusion and exclusion criteria of the GCKD study are provided elsewhere [7]. For this study, a subgroup of 2378 patients was examined, comprising all participating patients from five regional study centres (Hannover, Erlangen, Heidelberg, Freiburg and Jena). Of these, 1775/2378 patients (75%) had an eGFR $<60$ mL/min/1.73m$^2$.

Urate was measured from serum using an enzymatic colorimetric test (UA Plus, Roche/Hitachi Diagnostics, Mannheim, Germany). Medication intake at the time of baseline examination was assessed as a patient-reported item during structured interviews at the baseline visit. The reported medication intake was validated using the individual medical record. Information about the use of prescribed drugs as well as over-the-counter medication was obtained. Dosing of ULT was manually retrieved from the patients' paper charts. As the baseline examination was conducted just shortly after introduction of febuxostat to the German market and prior to the market authorization of lesinurad, the latter drug is not included in the analysis [8].

In accordance with numerous guidelines [5], including the European League Against Rheumatism and American College of Rheumatology recommendations for managing gout [9, 10], serum urate should be lowered to $<6$ mg/dL. We hence defined hyperuricaemia as a serum urate level $>6$ mg/dL.

For statistical analysis, SAS version 9.4 (SAS Institute, Cary, NC, USA) was used. The baseline characteristics are expressed as mean $\pm$ standard deviation for normally distributed variables or median (range; quartile 1, quartile 3) for non-normally distributed variables. Categorical variables were analysed using frequency tables. Binary logistic regression was used to relate ULT intake (yes/no) as the outcome of the baseline characteristics as predictors. Multivariable linear regression was used to test for determinants of serum urate levels, including the impact of ULT dose. A P-value $<0.05$ was considered statistically significant.

## RESULTS

Patient characteristics of the examined subcohort, overall and separately by ULT intake, are presented in Table 1. Briefly, 39.6%

Table 1. Patient characteristics of the entire cohort in patients with and without ULT

| Number of subjects | Total ($n = 2378$) | ULT ($n = 666$) | noULT ($n = 1712$) | P-value |
|---|---|---|---|---|
| Age (years), mean ± SD | 58.99 ± 12.42 | 62.55 ± 9.92 | 57.61 ± 13.01 | <0.0001 |
| Gender | | | | <0.0001 |
|   Male | 1437 (60.4) | 509 (76.4) | 928 (54.2) | |
|   Female | 941 (39.6) | 157 (23.6) | 784 (45.8) | |
| BMI (kg/m$^2$), mean ± SD | 29.44 ± 5.89 | 31.34 ± 5.87 | 28.70 ± 5.72 | <0.0001 |
|   <18.5 | 16 (0.7) | 3 (0.5) | 13 (0.8) | <0.0001 |
|   ≥18.5–<25 | 497 (21.1) | 61 (9.2) | 436 (25.8) | |
|   ≥25–<30 | 890 (37.8) | 241 (36.3) | 649 (38.4) | |
|   ≥30 | 952 (40.4) | 358 (54.0) | 594 (35.1) | |
| Smoking | | | | <0.0001 |
|   Non-smoker | 985 (41.6) | 250 (37.6) | 735 (43.2) | |
|   Current smoker | 1013 (42.8) | 338 (50.8) | 675 (39.6) | |
|   Smoker | 370 (15.6) | 77 (11.6) | 293 (17.2) | |
| Alcohol intake per week | | | | 0.0013 |
|   <3–6 times | 1912 (81.2) | 509 (77.0) | 1403 (82.8) | |
|   ≥3–6 times | 444 (18.8) | 152 (23.0) | 292 (17.3) | |
| Systolic blood pressure (mm/Hg), mean ± SD | 139.22 ± 20.77 | 139.43 ± 19.95 | 139.14 ± 21.10 | 0.7539 |
| Diastolic blood pressure (mm/Hg), mean ± SD | 79.85 ± 11.98 | 78.16 ± 11.86 | 80.51 ± 11.97 | 0.0001 |
| eGFR (CKD-EPI) (mL/min/1.73 m$^2$), mean ± SD | 51.34 ± 19.35 | 44.20 ± 14.86 | 54.11 ± 20.17 | <0.0001 |
|   ≥60 | 603 (25.4) | 76 (11.4) | 527 (30.8) | <0.0001 |
|   ≥45–<60 | 773 (32.6) | 205 (30.9) | 568 (33.2) | |
|   ≥30–<45 | 808 (34.1) | 298 (44.9) | 510 (29.8) | |
|   <30 | 189 (7.9) | 85 (12.8) | 104 (6.1) | |
| UACR (mg/g), median (Q1, Q3) | 60.6 (10.29, 445.83) | 78.64 (14.64, 532.76) | 55.10 (9.18, 405.33) | 0.6686 |
| Proteinuria (mg/L) | | | | 0.0042 |
|   <30 | 1077 (45.9) | 268 (41.0) | 809 (47.9) | |
|   30–300 | 699 (29.8) | 224 (34.3) | 475 (28.1) | |
|   >300 | 566 (24.2) | 162 (24.7) | 404 (23.9) | |
| Urate (mg/dL), mean ± SD | 7.18 ± 1.87 | 6.89 ± 1.78 | 7.30 ± 1.88 | <0.0001 |
| Hyperuricaemia | 1736 (73.0) | 457 (68.6) | 1279 (74.7) | 0.0027 |
| Gout | 561 (23.6) | 357 (53.6) | 204 (11.9) | <0.0001 |
| Diabetes | 811 (34.1) | 297 (44.6) | 514 (30.0) | <0.0001 |
| Hypertension | 2272 (95.6) | 663 (99.5) | 1609 (94.0) | <0.0001 |
| Chronic heart failure | 445 (18.7) | 178 (26.7) | 267 (15.6) | <0.0001 |
| Allopurinol (mg/day) | | | | NA |
|   <100 | 8 (1.5) | 8 (1.5) | NA | |
|   100 | 196 (36.3) | 196 (36.3) | NA | |
|   >100–<300 | 154 (28.5) | 154 (28.5) | NA | |
|   ≥300 | 182 (33.7) | 182 (33.7) | NA | |
| Azathioprine | 88 (3.7) | 21 (3.5) | 67 (3.9) | 0.3787 |
| Losartan | 76 (3.2) | 17 (2.6) | 59 (3.4) | 0.2678 |
| Diuretics | 1412 (59.4) | | 898 (52.5) | <0.0001 |
| Single RAAS inhibitors | 1719 (72.3) | 508 (76.3) | 1211 (70.8) | 0.0072 |
| Dual RAAS inhibition | 203 (8.5) | 76 (11.4) | 127 (7.4) | 0.0019 |

Values presented as *n* (%) unless stated otherwise. BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; RAAS, reninangiotensin-aldosterone system; UACR, urine albumin:creatinine ratio.

were women, mean eGFR was 51.3 ± 19.3 mL/min/1.73 m$^2$ and mean age was 59.0 ± 12.4 years. Of the 2378 patients examined, 666 (28%) received ULT (Table 1). The main ULT agent was allopurinol (94.4%), followed by febuxostat (2.9%) and benzbromarone (2.6%) (Figure 1). The dose of allopurinol at the time of the baseline examination was available for 540 of the 642 patients reporting allopurinol intake.

## Effect and dosing of allopurinol

Of the 540 patients who used allopurinol, 480 (89%) had an eGFR <60 mL/min/1.73 m$^2$ and 320 (59%) had an eGFR <45 mL/min/1.73 m$^2$. Of the latter, 31.5% (*n* = 101) received a dose >150 mg/

day, the recommended maximal dose for this level of eGFR. Patients with lower doses of allopurinol had higher serum urate levels than patients with higher allopurinol doses (Figure 2). The prescribed dose was not related to eGFR: the median eGFR levels for patients taking 100, 150 and 300 mg/day was 40 [interquartile range (IQR) 32–49], 43 (34–52) and 42 (35–54) mL/min/1.73 m$^2$, respectively. Almost one-third (30.6%) of all allopurinol users were prescribed ≤100 mg/day, 24.9% received 150 mg/day and 33.7% were prescribed a dose of 300 mg/day. Two patients were prescribed 600 mg/day. Patients receiving 300 mg/day were more likely to reach the treatment target of <6 mg/dL. The median urate level in patients receiving allopurinol 100 and 300 mg/day was 7.45 (IQR 6.48–8.49) and 6.1 (5.1–7.4) mg/dL,
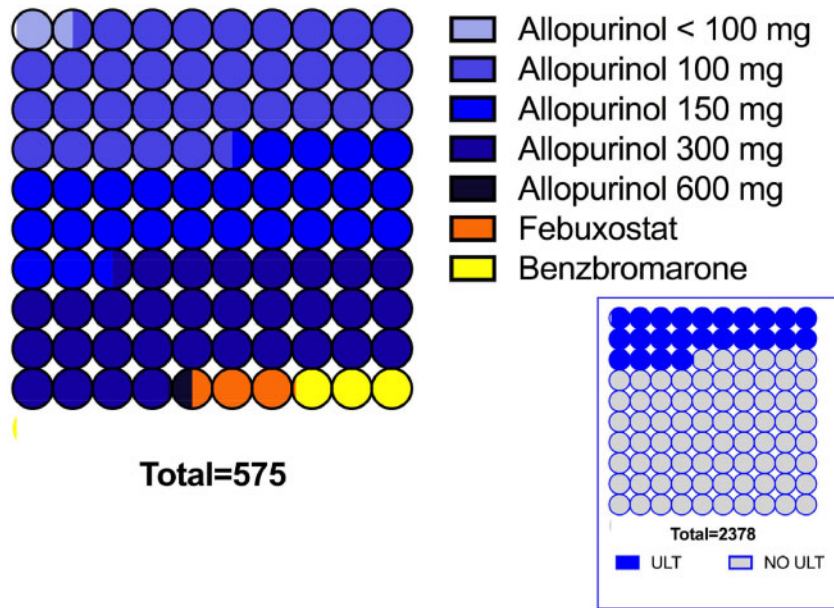
FIGURE 1: Chart on the use of ULT in the GCKD subcohort.

respectively (Figure 2). The lowest eGFR values among patients receiving 100, 150 and 300 mg/day were 13, 15 and 13 mL/min/1.73 m², respectively.

### Co-medication

Overall, 77.1% of patients receiving ULT were treated with any diuretic. Patients receiving diuretics had higher urate levels than patients taking no diuretics. However, this was only the case in patients without ULT, not in those receiving ULT (Figure 3). Within the group of patients receiving diuretics, the number of diuretic drugs and the prescribed compounds was also related to the serum urate level. The urate level of patients receiving diuretics was 0.39 mg/dL higher than in patients receiving no diuretics based on multivariable analyses that adjusted for renal function and other factors. Patients with a combination of a thiazide and a loop diuretic exhibited higher urate levels as compared with patients receiving diuretic therapy consisting of a loop diuretic in combination with a potassium-sparing diuretic or a mineralocorticoid receptor antagonist.

Overall, 69 patients were treated with azathioprine. None of them received a xanthine oxidase inhibitor, which in combination with azathioprine is known to cause bone marrow damage [11]. In multivariate analysis, male sex, use of any diuretics, lower eGFR and high alcohol intake were significantly associated with higher serum urate levels, whereas the use and higher dose of allopurinol was significantly associated with lower serum urate levels (Table 2). These results, obtained in the entire study sample, did not differ from the subgroup analysis of patients with eGFR <60 mL/min/1.73 m² (Table 3).

### Sex-specific aspects and alcohol intake

About 30% of all male patients reported suffering from gout, in contrast to 15% of all women (P < 0.001). One important predictor of gout was the amount of alcohol intake, which was higher in men than in women. While 63.2% of all male patients reported alcohol intake 1–7 times per week, only 20.5% of women reported drinking as frequently (P < 0.001). While 26.5%

of male gout patients reported alcohol intake 3–7 times per week, only 8.7% of women suffering from gout ingested alcohol that frequently (P < 0.001). On multivariate analysis, the degree of alcohol consumption showed borderline significant associations with serum urate levels (Table 2). Sex differences also occurred with respect to the treatment of gout. While only 50.5% of women with reported gout received ULT, this percentage was much higher in men (68.8%; P < 0.001). A more 'cautious' approach in treating gout in women could be deduced from the fact that not only the frequency of ULT was associated with sex, but also the prescribed dose. While only 25.3% of women received a dose of allopurinol of 300 mg/day, this percentage was 30.3% in men. In line with this pattern is the fact that more women than men (37.1% versus 31.2%) received a low dose of allopurinol (100 mg/day). This observation may be explained by serum urate levels, since the proportion of women having a serum urate level <6 mg/dL was higher than that of men (44.6% versus 31.2%; P < 0.0001). Overall, 28% of all treated gout patients achieved serum urate levels below the target threshold.

## DISCUSSION

This study confirms a high prevalence of hyperuricaemia in CKD patients as well as a relatively low prescription rate of ULT. The three main findings concerning the treatment with ULT are the dose of the predominantly used drug, allopurinol, was not always adjusted to the degree of renal function impairment; a treatment goal of uric acid <6.0 mg/dL was only reached in 31.9% of the patients on ULT and patients with an allopurinol dose currently considered too high for CKD patients had significantly lower urate levels and achieved the target range to a higher percentage than patients with an allopurinol dose currently considered being appropriate.

### Choice and dose of ULT

As febuxostat was introduced in Germany in the spring of 2010, patients at the time of the baseline examination of the GCKD cohort (2010–12) were mainly treated with allopurinol. Due to
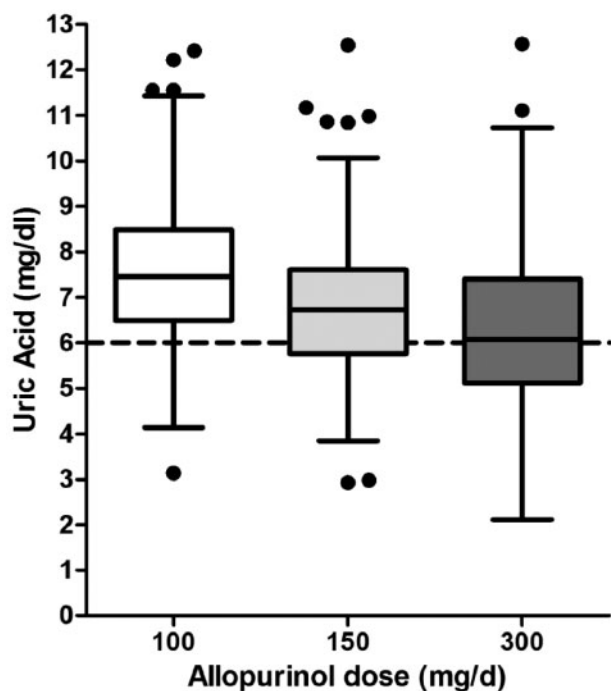
FIGURE 2: Comparison of the serum urate distribution for different doses of allopurinol intake. Urate levels were significantly different between groups (P < 0.0001). Only 31.9% of all patients using ULT achieved serum urate levels in the therapeutic target, i.e. <6 mg/dL.



FIGURE 3: Urate levels and the use of diuretics.

the accumulation of the main metabolite of allopurinol, oxipurinol, in patients suffering from CKD, dose reduction is recommended to avoid adverse effects. Hande et al. [3] suggested reducing the allopurinol dose to 200 mg/day in patients with a creatinine clearance <60 mL/min/1.73 m$^2$ and to 150 mg/day in patients with a creatinine clearance of 40 mL/min/1.73 m$^2$ [3]. Based on these recommendations, in a recent study examining patients >65 years of age with a creatinine clearance of 15–49 mL/min/1.73 m$^2$, allopurinol was one of the three drugs accounting for 76% of misprescribed medications with respect to kidney function [12]. However, it is known that tailoring allopurinol dosing to renal function leads to suboptimal control of uric acid levels [13], driving physicians to prescribe higher doses. Small studies seem to support this strategy, as they did not find that higher doses of allopurinol lead to more side effects in CKD patients [14].

In our cohort, the median dose of allopurinol was 150 mg/day and the average eGFR was 44.2 mL/min/1.73 m$^2$, suggesting that these recommendations were met in many patients. We did, however, see a wide variation of doses ranging from 100 to 600 mg/day, although the latter dose was only used in two patients. More than one-third of all allopurinol users were prescribed ≤100 mg/day, nearly a third received the recommended dose of 150 mg/day and more than one-quarter were prescribed a dose of 300 mg/day. Although our data are cross-sectional in nature, we observed that patients receiving 300 mg/day were more likely to reach a serum urate level of <6 mg/dL than those taking <300 mg/day. Despite the failure to adjust the dosing of allopurinol to renal function in all patients, our data show a much better adjustment than previously observed in a cohort treated by primary care physicians from the USA in which the median allopurinol dose at CKD Stage G3 was 300 mg/day [6]. Moreover, in that study only 22% of patients with CKD reached a target serum uric acid concentration of <6.0 mg/dL, compared with 31.9% of patients on ULT in this study.
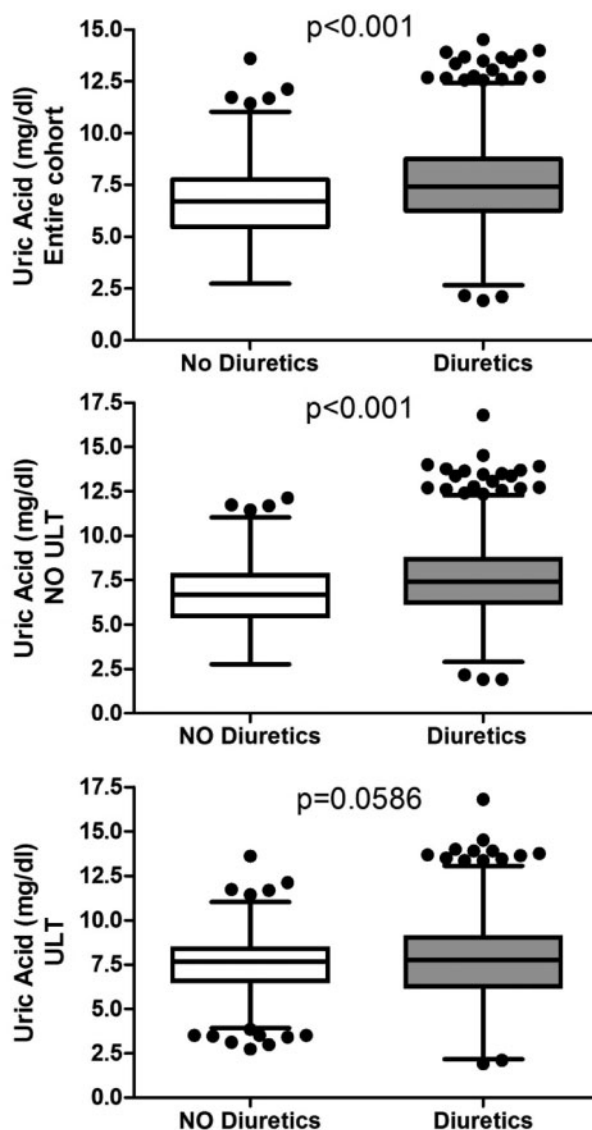
## Relationship of co-medication to uric acid levels as well as presence and intensity of ULT

It is well known that pharmacological therapy of diseases frequently accompanying hyperuricaemia, e.g. arterial hypertension, renal failure, heart failure and diabetes, can have a substantial effect on serum urate levels [15]. Our data support this observation, as patients with ULT and diuretic therapy were less likely to reach the current recommended target range of urate, i.e. a concentration <6 mg/dL, compared with those without diuretics.

This is in line with previous observations in the non-CKD population [16]. Our data add to the burgeoning body of evidence that potassium-sparing diuretics, including mineralocorticoid receptor antagonists, frequently chosen by nephrologists to optimize blood pressure and to enhance diuresis, do not increase urate levels even if used together with loop diuretics. In the light of our findings, it is unfortunate that fixed combinations of antihypertensive drugs with a diuretic nearly exclusively contain thiazides. One potential pitfall of this strategy is the fact that potassium-sparing diuretics

**Table 2.** Multivariable adjusted linear regression of the effect of different predictors on urate levels as outcome in the overall population ($n = 2378$)

| Variables | Effect on urate (mg/dL) | SE | P-value |
|---|---|---|---|
| Age (years) | −0.01 | 0.01 | 0.2262 |
| Gender | | | |
|   Male | 0.51 | 0.18 | 0.0050 |
|   Female | Reference | | |
| BMI (kg/m$^2$) | | | |
|   <18.5 | −0.13 | 0.98 | 0.2620 |
|   ≥18.5–<25 | Reference | | |
|   ≥25–<30 | 0.16 | 0.26 | |
|   ≥30 | 0.41 | 0.26 | |
| Alcohol intake per week | | | |
|   ≥3–6 times | 0.36 | 0.18 | 0.0459 |
|   <3–6 times | Reference | | |
| eGFR (CKD-EPI) (mL/min/1.73 m$^2$) | | | |
|   <30 | 0.88 | 0.31 | 0.0015 |
|   ≥30–<45 | 0.73 | 0.25 | |
|   ≥45–<60 | 0.25 | 0.26 | |
|   ≥60 | Reference | | |
| Diabetes, present versus absent | 0.22 | 0.16 | 0.1818 |
| Chronic heart failure, present versus absent | 0.14 | 0.17 | 0.4139 |
| Allopurinol (mg/day) | | | |
|   <100 | 0.51 | 0.60 | <0.0001 |
|   100 | Reference | | |
|   >100–<300 | −0.73 | 0.18 | |
|   ≥300 | −1.18 | 0.18 | |
| Diuretics | 0.39 | 0.19 | 0.0353 |
| Single RAAS blockers | −0.24 | 0.23 | 0.2809 |
| Dual RAAS blockade | −0.01 | 0.30 | 0.9851 |

BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; RAAS, renin–angiotensin–aldosterone system; SE, standard error.

**Table 3.** Multivariable adjusted linear regression analysis of the effect of different predictors on urate levels as the outcome in 1775 patients with an eGFR <60mL/min/1.73m$^2$

| Variables | Effect on urate (mg/dL) | SE | P-value |
|---|---|---|---|
| Age (years) | −0.01 | 0.01 | 0.2108 |
| Gender | | | |
|   Male | 0.52 | 0.18 | 0.0046 |
|   Female | Reference | | |
| BMI (kg/m$^2$) | | | |
|   <18.5 | −0.17 | 0.99 | 0.2880 |
|   ≥18.5–<25 | Reference | | |
|   ≥25–<30 | 0.17 | 0.27 | |
|   ≥30 | 0.41 | 0.26 | |
| Alcohol intake per week | | | |
|   ≥3–6 times | 0.36 | 0.19 | 0.0480 |
|   <3–6 times | Reference | | |
| eGFR (CKD-EPI) (mL/min/1.73 m$^2$) | | | |
|   <30 | 0.92 | 0.34 | 0.0028 |
|   ≥30–<45 | 0.78 | 0.29 | |
|   ≥45–<60 | 0.31 | 0.30 | |
|   ≥60 | Reference | | |
| Presence of diabetes | 0.18 | 0.17 | 0.2830 |
| Presence of chronic heart failure | 0.15 | 0.18 | 0.3932 |
| Allopurinol (mg/day) | | | |
|   <100 | 0.52 | 0.61 | <0.0001 |
|   100 | Reference | | |
|   >100–<300 | −0.71 | 0.19 | |
|   ≥300 | −1.20 | 0.18 | |
| Diuretics | 0.47 | 0.19 | 0.0160 |
| Single RAAS blockers | −0.26 | 0.23 | 0.2535 |
| Dual RAAS blockade | −0.06 | 0.31 | 0.8439 |

BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; RAAS, renin–angiotensin–aldosterone system; SE, standard error.

and mineralocorticoid receptor antagonists can increase the rate of hyperkalaemia, at least in patients with heart failure.

An additional finding evaluating the combination of pharmacotherapy is the fact that none of the patients had the dreaded combination of a xanthine oxidase inhibitor and azathioprine [11], even though 69 patients were on immunosuppression with azathioprine.

## Sex-specific aspects

The sex-specific aspects of gout have long been neglected. In the entire GCKD study cohort, it could be shown that male sex is a risk factor for self-reported gout [2]. This was also true for our subset of patients. The percentage of male patients reporting to suffer from gout was twice as high as in women. One important contributing factor may be the amount of alcohol intake. Alcohol intake of 1–7 times per week occurred in half of the male gout patients but only in a quarter of the female gout patients. This gender gap became even wider if an alcohol intake of 3–7 times per week was evaluated. These data are in line with reports indicating that alcohol consumption is a risk factor for gout [17] and hyperuricaemia [18]. Moreover, alcohol restriction is an important non-pharmacological way to lower elevated uric acid levels and to reduce gout attacks. The importance of alcohol consumption in the development of gout has also been emphasized in a recent review [19].

One of the bothersome findings of our study is the fact that sex also affected the frequency of treatment of patients with reported gout while 18% more men than women received such treatment. This is reminiscent of the management of other cardiovascular risk factors in which more intensive therapy has been shown in male patients [20]. The underlying reason for this sex difference is unclear. The very nature of our study does not allow us to elucidate the potential reasons. Potential explanations include a patient-inherent component like comorbidities, which were more prevalent in men as compared with women, personal views on medication, different frequency of gout episodes and their clinical severity and sex-biased prescription practices.

## Limitations of the study

We wish to point out important limitations of our study. We report cross-sectional, i.e. baseline data only that do not provide longitudinal analyses, especially regarding the potential occurrence and frequency of gout attacks, which might have influenced the prescription pattern of ULT. Yet this is the first study investigating treatment patterns of hyperuricaemia/gout and its pharmacological therapy in relation to renal function in a large cohort of CKD patients. Fuldeore *et al.* [6] reported on a larger number of patients in the general population ($n = 3929$ patients), yet only <10% were in CKD Stage G3. Interestingly, in their cohort, the majority (84%) was male and uric acid level was only available in 220 patients. In contrast to

their study, we did address sex aspects concerning dosing of ULT and comorbidities in patients being treated with ULT. The interesting relationship between the effect of different doses of allopurinol (100, 150 and 300 mg/day) on target attainment of serum urate level has to viewed with caution, as these are cross-sectional data.

In summary, we found inadequate control of serum urate in CKD patients if a serum urate level of <6 mg/dL was used as the target level. Our data suggest that higher than recommended doses of allopurinol are more effective in lowering urate levels. The potential side effects of this strategy have to be balanced against the risk of overdosing allopurinol. While febuxostat does not confer the risk of metabolite accumulation, its use in patients with heart failure is discouraged by a recent trial [21], although adverse effects were not confirmed by a new meta-analysis [22].

No matter what pharmaceutical intervention is used, lowering of serum urate in CKD patients requires balancing potential adverse effects of the specific drug with suboptimal control of serum urate levels and subsequent gout.

## FUNDING

## CONFLICT OF INTEREST STATEMENT

None declared.

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