The effect of trajectory of serum uric acid on patients and renal outcomes in patients with stage-3 chronic kidney disease

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Abstract

Background  Uric acid (UA) is associated with renal and patient survivals but the causal association in nature remains unclear. Also, no finding is yet available regarding longitudinal UA control (trajectory). Methods  We enrolled 808 subjects diagnosed with stage 3 chronic kidney disease from 2007 to 2017. We plotted the mean UA over a period of 6 months with a minimum of three samples of UA was required. From the sampled points, we generated for each patient an interpolated line by joining mean values of the UA levels over time. And from the lines from all patients, we classified them into three groups of trajectories (low, medium and high) through group-based trajectory modeling, and then we further separated into either a treatment or no-treatment subgroups. Due to multiple comparisons, we performed post hoc analysis by Bonferroni adjustment. Using the univariate competing-risks regression, we calculated the competing risk analysis with subdistribution hazard ratio of possible confounders. Results  All of the 6 trajectories appeared as gradually falling functions with time without any of the curves crossed over one another. For all-cause mortality risk, none of the variables (including age, gender, coronary arterial disease, cerebrovascular disease, diabetes mellitus, renin-angiotensin-aldosterone system inhibitors, trajectories of UA, and treatment of UA) was statistically significant. All 6 trajectories appeared as steady curve without crossovers among them over the entire period of follow-up. Patients with DM were statistically more likely to undergo dialysis. There was only a trend that the on-treatment trajectories, compared to their no-treatment trajectories, had lower risks for dialysis. There was no effect of UA control on patients’ survival. Conclusions  Initial treatment of UA is utterly important for UA control. However, the long-term effects on patients and renal survivals maybe minor without statistical significance. Keyword: uric acid, patient survival, renal survival, long-term effect, trajectory, competing risk analysis

Background

Uric acid (UA) is no doubt associated with gout, and hyperuricemia is the major risk factor for the development of gout[1]. The prevalence of gout is around 1% in the general population but the prevalence of hyperuricemia is way higher, up to 70.2% (i.e., serum uric acid >6.0 mg/dl) (NAHSIT_Taiwanese). Therefore, having the condition of hyperuricemia does not mean gout attack.
That is why all guidelines worldwide (except Japan) do not recommend treatment for asymptomatic hyperuricemia. Recently, UA is shown to be an inflammatory factor to increase oxidative stress in the renin angiotensin aldosterone system [2]. However, it remains unclear regarding the associations between hyperuricemia and all-cause mortality, cardiovascular mortality (CV) or renal survivals, especially in patients with chronic kidney disease (CKD). In the general population, hyperuricemia usually implies high mortality [3,4], while other investigators disagree on any causal association. In this context, the association between hyperuricemia and mortality in patients with CKD is not yet determined [5]. As for the association with renal survival, no consensus is found [6-9]. Due to the absence of strong evidence on any causal relationship between hyperuricemia and renal and patient survivals, all meta-analyses failed to prove the causal effect[10] and to recommend the treatment for asymptomatic hyperuricemia in guidelines. In addition, some factors compete in renal survival. Patients who died with functional kidneys were usually recorded as both patient death and renal death. Thus competing risk analyses with subdistribution hazard need to be performed accordingly[11].

Another important issue in UA control is the variation or long-term control over time. The role of the trajectory (trend) of UA on patient outcome, CV outcome and renal outcome remains unexplored. Currently, only Ceriello et al have reported a study [12] that high variability in UA (hazard ratio = 1.54) conferred the highest risk of decline in estimated glomerular filtration rate (eGFR). In that study, they evaluated the role of interaction between the variability of UA and the increased risk of CKD. They separated the variability of UA into 4 groups according to quartiles. However, there was no long-term evaluation of tendency for UA control and the outcome to patients and renal survivals. In the present study, we aimed to investigate the long-term tendency (trajectory) of UA, and the effect on patients and renal survivals (competing risk analysis for renal survival) on the risk of mortality. The study enrolled outpatients with stage 3-CKD who were separated into subgroups based on their trajectories of UA recorded over 7 years.

Methods

Study population
We conducted this retrospective study in a medical center in central Taiwan. A flow chart of patients’ inclusion and exclusion is summarized in Figure S1 (supplementary data). From 2007 to 2017, outpatients with stage 3-CKD aged >20 years old were enrolled. Patients who had died within two years after the enrollment were excluded. We calculated that every mean UA level from UA samples measured within 6 months. We required at least three samples to generate the mean UA used for our analysis. Finally, 808 subjects were successfully enrolled for this study. This study was approved by Ethics Committee of Taichung Veterans General Hospital (the number of institutional review board CE16235A). All methods were carried out in accordance with relevant guidelines and regulations and all participants signed informed consents.

**Data collection and outcome assessment**
All data were retrospectively collected from medical records of patients. Tests of renal function were serum creatinine (SCr) level (mg/dl) and eGFR (ml/min/1.732m²) (The eGFR was calculated by the equation of modification of diet of renal disease)[13]. Other demographic and laboratory data were also collected from medical records, including systolic blood pressure (SBP), DBP, glycated hemoglobin (HbA1c), total cholesterol, triglyceride, UA, hematocrit, and alanine transaminase (ALT).

The primary outcome is all-cause mortality. The CVD, coronary arterial disease (CAD), and congestive heart failure (CHF) were defined as previous CV outcome trial in type 2 diabetes mellitus (DM)[14]. The renal death was defined if patients should undergo regular course of dialysis for 30 or more days[15]. Medication of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), and medications used for gout were collected if the duration of prescriptions was longer than three months.

**Statistical methods**
Continuous variables were reported as means ± SDs and categorical data were as numbers (percentages). Statistical significances across trajectories were determined using the Chi-square test for categorical variables, or one-way analysis of variance for continuous variables. To evaluate the UA trajectory, we used group-based trajectory modeling analysis, which is a statistical methodology to analyze developmental trajectories - the evolution of an outcome over time[16]. This analysis is
typically used to describe the data with a time-based dimension to provide the empirical foundation for analyzing developmental trajectories. It can be used to identify unique subgroups within a cohort with participants following the same temporal trajectory[17]. It can be also used to analyze developmental trajectories of distinct but related behaviors (group-based method)[17]. It is the alternative method for analyzing the longitudinal data to evaluate outcomes[18]. We used this method to identify optimal groups of UA trajectory over time (Supplementary data, S2. detailed methods of model building process).

Cox’s proportional hazards model was used to compare the differences of all-cause mortality, dialysis, and either one of them among different UA trajectories. As for dialysis, due to competing risk of death and dialysis, we used competing risk analysis as a sensitivity test for dialysis[19]. Competing risk analysis with subdistribution hazard ratio (SHR) and 95% confidence interval (95% CI) of the SHR of possible confounders were calculated by using competing-risks regression[11]. This model was used to determine factors confounding patient death to renal death.

All statistical analyses were performed using the SAS software, version 9.4 (SAS Institute, Inc., Cary, NC, USA). Regarding statistical significance, p value <0.05 was significant in the initial analysis for three trajectories of UA. Due to multiple comparisons, we perform post hoc analysis by Bonferroni adjustment (total 6 analyses). Therefore, after Bonferroni correction, the significance for this study would be 0.008 (0.05/6) if 6 comparisons, and it would be 0.017 (0.05/3) if 3 comparisons.

Results

**Longitudinal data of long-term UA treatment**

A total of 5742 patients of stage 3-CKD were enrolled, and among them, 808 patients were analyzed in this study (figure S1). Each subject was then grouped into one of the three trajectories based on the mean UA curve calculated over 6 months. Initially, three distinct trajectories (low (UA=6.21±1.76 mg/dl), medium (UA=7.78±1.85 mg/dl) and high UA (UA=8.83±1.44 mg/dl)) were identified (table1). We further separated each trajectory into two subgroups according to whether or not treatment. Finally, we obtained 6 trajectories as presented in table 2 and figure 1. All 6 trajectories appeared as steady curve without crossovers among them over the entire period of follow-up (figure 1). As shown
in table 1, patients with low level of UA were older (p=0.036), more females (p=0.021), better renal function (lower SCr) (p=0.001), lower SBP (p=0.028), lower UA (p<0.0001), and lower ALT (p=0.040), less mortality (p=0.032) and received fewer dialyses (p=0.019). On the other hand, no significant differences were found in the rates of DM, CAD, cerebrovascular attack (CVA), CHF, malignancy, liver disease, smoking or receiving ACEIs or ARBs. As shown in table 2, male patients received more UA-lowering treatments in all three UA trajectories (p=0.0281, 0.0126, and 0.040 for low, medium and high UA trajectory, respectively). Among patients in the low UA trajectory, those treated for UA showed significantly higher SCr levels as compared to those not treated for UA.

**Longitudinal data of the three UA trajectories on mortality and dialysis**

Regarding all-cause mortality risk (figure 2A), no variables (age, gender, CAD, CVA, DM, ACEI, ARB, trajectories of UA, and treatment of UA) were found to be significant. However, compared with the “low UA-no treatment” trajectory, we observed no events on “low UA-on treatment” trajectory. As for the renal outcome, patients with DM had significantly more chances in receiving dialysis (Log HR=0.771 (95% CI=0.0278-1.265 ) in figure 2B and Log HR=0.72 (95% CI=0.149-1.292) in figure 2D). Even without statistical significances, there was a trend that “on-treatment” trajectory across all 3 UA trajectories had lower risks for dialysis, when compared to all 3 “no-treatment” trajectory counterparts (figure 2D).

**Discussion**

In the general population, serum UA level is associated with CVD [3,4], and UA is considered an independent risk factor of CV mortality[20]. UA may be involved in the pathogenesis of CVD, but the causal relationship between UA and CVD remains unclear[21]. The situation is similar to the relationship between UA and renal injury [10,22]. Besides, the association between CVD and renal injury in patients with CKD is further rare [5] and the exact relationship has no consensus. In addition to UA level, the association between UA variability and patient survival or renal survival is further not well-studied [12]. In other words, the long-term effect and longitudinal tendency of UA is not known. The strength of our present study is that we have clarified the relationship between long-term effect of UA and patient or renal survival in the CKD groups. Currently, our study is the first one to research
the trajectory of UA to patients and renal survivals.

The treatment response rates of allopurinol and febuxostat are around 40% and 70%, respectively [23]. In our study, the controlled levels of all three “on-treatment” trajectories were as follows: 9.6% in the low UA group (7.03±2.25 mg/dl), 76.2% in the medium UA group (8.14±2.1 mg/dl), and 14.2% in the high UA group (9.2±1.58 mg/dl). Most “on-treatment” patients (85.8%) were maintained at UA levels ≤8.14 mg/dl.

As shown in figure 1, 6 trajectories of UA did not cross one another during the entire period of follow-up, which indicated that the treatment response was very rapid to achieve the stable level. As a result, there was no crossing over the curves. This finding is compatible with the studies on the pharmacodynamics of allopurinol, febuxosate and uricosuric agents [24]. According to the prescription guideline of allopurinol, the drop in serum UA level begins on day 2 before reaching the peak on day 7. The normal serum UA levels can be achieved typically within 1 to 3 weeks. Similarly, the peak UA-lowering effect of febuxostat also appears during the first 5 to 7 days of treatment. Therefore, the long-term effect of UA control is based on the treatment decision (treat or not treat) during the first few weeks.

In the group of low UA trajectory, participants had better renal function (lower SCr) (p=0.001), lower SBP (p=0.028), less UA (p<0.0001), less ALT (p=0.040), fewer deaths (p=0.032) and fewer receiving dialysis (p=0.019). These findings suggested that patients in this group had the lowest risk for metabolic syndrome and oxidative stress. Moreover, we chose low UA-no treatment trajectory as the reference group for analysis instead of low UA-on treatment trajectory. This is because the trajectory of low UA-on treatment must have hyperuricemia before UA-lowering agents. Those patients had already experienced higher risk of metabolic syndrome and oxidative stress before the treatment. The risk of metabolic disease for “on-treatment” trajectory should be higher than for “no-treatment” trajectory. In summary, choosing low UA-no treatment trajectory as reference group is reasonable.

The pleotropic effect of UA-lowering agents is still under debate. In animal models, xanthine oxidase may cause kidney fibrosis through inflammation, endothelial dysfunction, oxidative stress, and activation of the renin-angiotensin system [25]. In some studies, both allopurinol [26-29] and
Febuxosate[30-34] show renal protections independent from their UA lowering effect. Our present results did not support renal protection of the UA-lowering agents with statistical significance. There was only a trend that “on-treatment” trajectory across all 3 UA trajectories had lower risks for dialysis, when compared to all 3 “no-treatment” trajectory counterparts (figure 2D). However, the same trend was not observed regarding the all-cause mortality. Our study is the first one to indicate the long-term effect of UA control on patients and renal survivals. The long-term benefit of UA control maybe much minor than the control of BP, hyperlipidemia and DM.

There are some limitations of this study. First, detailed medication data were not available. However, regarding the therapy for our patients with stage 3-CKD, xanthine oxidase inhibitor therapy is the consensus first-line treatment in line with previous studies [35] and guidelines in Taiwan[36]. The effect of this limitation may be not large. Second, only patients surviving ≥ 2 years from the time of enrolment were included in this study. This could imply minor bias toward good adherence to medical follow-ups. Third, this is a retrospective cohort study on a heterogeneous population. It still needs more prospective studies to confirm the long-term effect of UA variability on patients and renal outcome.

Conclusion

Earlier treatment for hyperuricemia is important for UA control due to rapid response of medications. However, the benefit on patients and renal outcomes of UA control maybe minor in the long-term follow-up without confounded by patient death.

Declarations

Ethics approval and consent to participate: This study was approved by Ethics Committee of Taichung Veterans General Hospital, IRB number[CE16235A. All methods were carried out in accordance with relevant guidelines and regulations and all participants signed informed consents.

Consent to publish: Not applicable

Availability of data and materials: The individual patient-level data was not made publically available due to containing potentially identifying patient data; however, the study data may be made available from the authors upon reasonable request.
**Competing interests:** The author declare they have no competing interests.

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**Authors' contributions:** SFT, CHC, MJW, and CLL for the design of the work; SFT and CLL for the acquisition, and analysis. SFT and CLL for the interpretation of data; SFT has drafted the work; SFT and CLL substantively revised this article; SFT, CHC, MJW, and CLL approved the submitted version; SFT, CHC, MJW, and CLL read and approved the final manuscript.

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**Table 1 Baseline characteristics of study subjects by trajectory of serum uric acid (UA)**

| Variable                        | overall | Low UA | Medium UA | High UA | P value |
|---------------------------------|---------|--------|-----------|---------|---------|
| Patients, n                     | 808     | 124    | 555       | 129     |         |
| Age, years                      | 71.08±14.53 | 73.07±14.65 | 71.25±14 | 68.44±16.27 | 0.0356 |
| Female, n (%)                   | 230 (28.47) | 43(34.68) | 162(29.19) | 25(19.38)** | 0.021 |
| Serum creatinine, mg/dl         | 1.72±0.3 | 1.66±0.3 | 1.72±0.3 | 1.8±0.29 | 0.0015 |
| eGFR, ml/min.1.732m²            | 40.31±6.72 | 41.26±7.26 | 40.22±6.55 | 39.75±6.83 | 0.2021 |
| Systolic BP, mmHg               | 133.16±17.24 | 129.66±16.07 | 133.05±16.49 | 137.03±20.2 | 0.0283 |
| Diastolic BP, mmHg              | 74.53±10.3 | 72.56±10.47 | 74.89±10.09 | 75.17±10.79 | 0.1782 |
| HbA1C, %                        | 7.18±1.45 | 7.18±1.24 | 7.25±1.54 | 6.88±1.23 | 0.3796 |
| Total cholesterol, mg/dl        | 189.2±42.34 | 187.5±42.75 | 190.22±42.63 | 186.53±40.92 | 0.6666 |
| Triglyceride, mg/dl             | 154.54±92.68 | 160.05±102.97 | 154.69±92.13 | 148.42±84.35 | 0.6713 |
| Uric acid, mg/dl                | 7.7±1.92 | 6.21±1.76 | 7.78±1.85** | 8.83±1.44** | <.0001 |
| Hematocrit                      | 37.07±5.17 | 37.5±4.91 | 37.06±5.19 | 36.62±5.37 | 0.478 |
| ALT, U/L                        | 22.5±15.58 | 19.57±11.41 | 21.54±13.21 | 31.44±26.31 | 0.0399 |
| Diabetes mellitus, n (%)        | 255(31.56) | 42(33.87) | 168(30.27) | 45(34.88) | 0.4981 |
| CAD, n (%)                      | 29(3.59) | 6(4.84) | 17(3.06) | 6(4.65) | 0.4907 |
| CVA, n (%)                      | 32(3.96) | 5(4.03) | 20(3.6) | 7(5.43) | 0.6325 |
| CHF, n (%)                      | 11(1.36) | 2(1.61) | 6(1.08) | 3(2.33) | 0.5283 |
| Malignancy, n (%)               | 57(7.05) | 8(6.45) | 37(6.67) | 12(9.3) | 0.5515 |
| Liver disease, n (%)            | 42(5.2) | 5(4.03) | 26(4.68) | 11(8.53) | 0.1703 |
| ACEIs or ARBs, n (%)            | 444(54.95) | 67(54.03) | 301(54.23) | 76(58.91) | 0.6138 |
| Treatment for gout              | 260(32.18) | 25(20.16) | 198(35.68)** | 37(28.68) | 0.0024 |
| Death                           | 18(2.23) | 1(0.81) | 13(2.34) | 4(3.1) | 0.0324 |
| Dialysis                        | 17(2.1) | 1(0.81) | 11(1.98) | 5(3.88) | 0.0188 |

*Fisher's exact test, p<0.05
** Bonferroni adjustment, p<0.05/3.

Values are means ± SD or n (%); BP: blood pressure; HbA1c: glycated hemoglobin; eGFR: estimated glomerular filtration rate; ALT: alanine transaminase; CAD: coronary arterial disease; CVD: cerebral
vascular disease; CHF: congestive heart failure; ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin II receptor blockers

Table 2 Baseline characteristics of study subjects by trajectory of serum uric acid (UA) with or without treatments

| Variable                      | Low UA No Treatment | Low UA On Treatment | P value (between no/on treatment) | Medium UA No Treatment | Medium UA On Treatment | P value (between no/on treatment) | High UA No Treatment | High UA On Treatment | P value (between no/on treatment) | P value (all 6 variables) |
|-------------------------------|---------------------|---------------------|------------------------------------|------------------------|------------------------|------------------------------------|----------------------|----------------------|------------------------------------|--------------------------|
| Patients, n                   | 99                  | 25                  |                                    | 357                    | 198                    |                                    | 92                   | 37                   |                                    |                          |
| Age, years                    | 72.34±1.51          | 75.96±12.43         | 0.2                                | 71.18±13.86            | 71.37±14.29            | 0.8                                | 67.76±15.78          | 70.14±17.56          | 0.4                                | 0.1 (0.03)               |
| Female, n (%)                 | 39(39.39)           | 4(16)               | 0.0                                | 171(32.77)             | 452.23±17.77           | 0.0                                | 22.39±1              | 3(3.11)              | 0.0                                | 0.0 (0.00)              |
| Serum creatinine, mg/dl       | 1.63±0.29           | 1.78±0.34           | 0.0                                | 1.70±0.01              | 1.75±0.02              | 0.0                                | 1.80±0.29            | 1.80±0.3              | 0.9                                | 0.8 (0.04)              |
| eGFR, ml/min.1.73 m²          | 41.6±7.09           | 39.7±7.44           | 0.2                                | 40.4±6.72              | 40.3±6.66              | 0.8                                | 39.2±7.02            | 41.1±6.91            | 0.1                                | 0.3 (0.05)              |
| Systolic BP, mmHg             | 129.8±15.28         | 128.7±19.59         | 0.8                                | 131.96±16.19           | 135.15±16.95           | 0.1                                | 138.69±21.22         | 133.89±18.11         | 0.3                                | 0.0 (0.00)              |
| Diastolic BP, mmHg            | 72.47±0.7           | 72.93±9.79          | 0.8                                | 74.33±9.9              | 75.96±16.02            | 0.2                                | 74.41±10.57          | 76.59±11.25          | 0.3                                | 0.3 (0.03)              |
| HbA1C, %                      | 7.28±1.35           | 6.88±0.74           | 0.4                                | 7.34±1.01              | 7.06±1.39              | 0.2                                | 7.05±1.72            | 6.48±1.48            | 0.4                                | 0.4 (0.04)              |
| Total cholesterol, mg/dl      | 189.18±44.99        | 181.4±33.03         | 0.4                                | 191.2±44.43            | 188.58±39.66           | 0.5                                | 191.3±43.43          | 176.2±33.22          | 0.0                                | 0.0 (0.04)              |
| Triglyceride, mg/dl           | 156.62±108.54       | 172.36±80.84        | 0.5                                | 152.15±86.09           | 158.99±101.66          | 0.4                                | 153.68±87.79         | 176.4±76.48          | 0.3                                | 0.7 (0.07)              |
| Uric acid, mg/dl              | 5.98±1.54           | 7.03±2.53           | 0.0                                | 7.56±1.64              | 8.14±1.39              | 0.0                                | 8.67±1.58            | 9.2±1.35             | 0.0                                | <0.0 (0.01)             |
| Hematocrit                    | 37.15±5.02          | 38.91±4.27          | 0.1                                | 36.52±5.08             | 38.08±5.26             | 0.0                                | 35.95±5.73           | 38.06±5.5             | 0.0                                | 0.0 (0.00)              |
| ALT, U/L                      | 18.79±1.92          | 23.25±8.92          | 0.4                                | 20.44±12.45            | 23.26±4.36             | 0.3                                | 33.67±13.05          | 28.57±16.05          | 0.7                                | 0.1 (0.02)              |
| Diabetes mellitus, n (%)      | 35(35.35)           | 7(28)               | 0.4                                | 117(32.77)             | 51(25.76)              | 0.0                                | 33(35.87)            | 12(32.43)            | 0.7                                | 0.4 (0.04)              |
| CAD, n (%)                    | 4(4.04)             | 2(8)                | 0.2                                | 11(3.08)               | 6(3.03)                | 0.9                                | 2(2.17)              | 4(10.81)             | 0.0                                | <0.0 (0.001)            |
| CVA, n (%)                    | 5(5.05)             | 0(0)                | 0.3                                | 12(3.36)               | 8(4.04)                | 0.6                                | 4(4.35)              | 3(8.11)              | 0.2                                | 0.0 (0.003)             |
| Condition                  | CHF, n (%) | Malignancy, n (%) | Liver disease, n (%) | Smoking | ACEIs or ARBs, n (%) | Treatment for gout | Death | Dialysis |
|----------------------------|------------|-------------------|----------------------|---------|----------------------|-------------------|-------|----------|
| n (%)                      | 2(2.02)    | 8(8.08)           | 4(4.04)              | 32(32.32) | 55(55.56)           | 0(0)              | 1(1.01)| 1(1.01)  |
| (%)                        | 0(0)       | 0(0)              | 1(4)                 | 14(56)  | 12(48)               | 25(100)**         | 0(0)  | 0(0)     |
| *                          | 0.6 361    | 0.1 555           | 0.4 180              | 0.0 285 | 0.4 982              | <.0 001           | 0.7 984| 0.7 984  |
| **                         | 4(1.12)    | 27(7.56)          | 16(4.48)             | 132(36.97) | 185(51.82)           | 0(0)              | 8(2.24)| 9(2.52)  |
|                           | 2(1.01)    | 10(5.05)          | 10(5.05)             | 83(41.92) | 116(58.59)           | 198(100)**        | 5(2.53)| 2(1.01)  |
|                           | 0.3 285    | 0.2 557           | 0.7 613              | 0.2 520 | 0.1 254              | <.0 001           | 0.2 206| 0.1 311  |
|                           | 1(1.09)    | 7(7.61)           | 11(11.9)             | 39(42.39) | 54(58.79)           | 0(0)              | 5(2.17)| 5(5.43)  |
|                           | 2(5.41)    | 5(13.51)          | 0(0)                 | 21(56.76) | 22(59.46)           | 37(100)**         | 2(5.41)| 0(0)     |
|                           | 0.1 753    | 0.1 460           | 0.0 202              | 0.1 39  | 0.9 36               | <.0 001           | 0.2 532| 0.1 787  |
|                           | 0.0 17     | 0.3 25            | <.0 001              | 0.4 59  | 0.5 78               | <.0 001           | 0.0 014| 0.0 004  |

*Fisher's exact test, p<0.05

** Bonferroni adjustment, p<0.05/3.

Values are means ± SD or n (%); BP: blood pressure; HbA1c: glycated hemoglobin; eGFR: estimated glomerular filtration rate; ALT: alanine transaminase; CAD: coronary arterial disease; CVD: cerebral vascular disease; CHF: congestive heart failure; ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin II receptor blockers

Figures
Figure 1

Trajectories of mean serum uric acid (UA) with or without treatments

A

All Cause Mortality
Log Hazard ratio and 95% CI

|                          | LogHR | LCI   | UCI   |
|--------------------------|-------|-------|-------|
| Age                      | 0.011 | -0.006| 0.028 |
| Female vs. Male          | -0.41 | -1.367| 0.549 |
| CAD or CVA vs. non CAD or CVA | 0.49  | -0.077| 1.057 |
| Smoke vs. non Smoke      | 0.373 | -0.123| 0.869 |
| DM vs. non DM            | 0.134 | -0.3   | 0.568 |
| Use ACEI or ARB vs. non use | 0.344 | -0.194| 0.682 |
| Low UA -No Treatment     | REF   |       |       |
| Low UA -On Treatment     | No event |     |       |
| Medium UA -No Treatment  | 0.415 | -0.485| 1.336 |
| Medium UA -On Treatment  | 0.367 | -0.58  | 1.314 |
| High UA -No Treatment    | 0.367 | -0.693| 1.426 |
| High UA -On Treatment    | 0.895 | -0.308| 1.327 |

B

Dialysis
Log Hazard ratio and 95% CI

|                          | LogHR | LCI   | UCI   |
|--------------------------|-------|-------|-------|
| Age                      | -0.015| -0.031| 0.002 |
| Female vs. Male          | 0.442 | -0.097| 0.981 |
| CAD or CVA vs. non CAD or CVA | 0    |       |       |
| Smoke vs. non Smoke      | -0.003| -0.587| 0.579 |
| DM vs. non DM            | 0.771 | 0.278 | 1.265 |
| Use ACEI or ARB vs. non use | 0.554 | -0.007| 1.115 |
| Low UA -No Treatment     | REF   |       |       |
| Low UA -On Treatment     | No event |     |       |
| Medium UA -No Treatment  | 0.425 | -0.479| 1.328 |
| Medium UA -On Treatment  | 0.053 | -1.604| 1.11  |
| High UA -No Treatment    | 0.78  | -0.176| 1.736 |
| High UA -On Treatment    | No event |     |       |

C

All Cause Mortality or Dialysis
Log Hazard ratio and 95% CI

|                          | LogHR | LCI   | UCI   |
|--------------------------|-------|-------|-------|
| Age                      |       |       |       |
| Female vs. Male          |       |       |       |
| CAD or CVA vs. non CAD or CVA |       |       |       |
| Smoke vs. non Smoke      |       |       |       |
| DM vs. non DM            |       |       |       |
| Use ACEI or ARB vs. non use |       |       |       |
| Low UA -No Treatment     |       |       |       |
| Low UA -On Treatment     |       |       |       |
| Medium UA -No Treatment  |       |       |       |
| Medium UA -On Treatment  |       |       |       |
| High UA -No Treatment    |       |       |       |
| High UA -On Treatment    |       |       |       |
Figure 2

Adjusted hazard ratios (HRs) for all-cause mortality (A), renal death (B), renal death or patient death (C), and competing risk for dialysis (D).

Supplementary Files
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