Research Square

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Efficacy And Renal Safety of Febuxostat In Management of Gout And Chronic Kidney Disease: A Retrospective Study

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Abstract

Background: Elevated serum urate levels are associated with renal deterioration of chronic kidney disease (CKD). Whether urate-lowering treatment with febuxostat can improve renal function or attenuate the decline of the estimated glomerular filtration rate (eGFR) is controversial. The current study sought to explore efficacy and renal safety of febuxostat in gout patients with CKD and explore factors correlated with target serum urate (sUA).

Methods: The current study was a single-center retrospective study comprising male gout patients with CKD. sUA, the rate of sUA < 360 μmol/L and renal safety were analyzed in subjects who had been treated with febuxostat for more than 44 weeks. Factors correlated with target sUA were explored by logistic regression analysis.

Results: A total of 87 patients who had been diagnosed with gout and CKD met the inclusion criteria for the study. Twenty-five (28.73%) patients presented with stage 2 CKD, 58 (66.67%) were diagnosed with stage 3 CKD and 4 (4.60%) were diagnosed with stage 4 CKD. Analysis of sUA level showed a significant reduction at week 44~ (598.22 ± 95.11 μmol/L vs. 429.76 ± 123.45 μmol/L; $P < 0.05$), and the RAT increased to 34.50%. eGFR level of all patients was 52.37 ± 11.74 ml/min/1.73cm^2 at baseline and 56.51 ± 15.01 ml/min/1.73cm^2 at week 44~ ($P < 0.05$). The findings showed improvement of eGFR level in different stages of CKD, mainly in stage 3 CKD patients ($P < 0.05$). After stratification based on risk factors of hypertension, diabetic mellitus, hyperlipidemia and the usage of Non-Steroidal Anti-inflammatory Drugs (NSAIDs), the findings showed that eGFR levels of patients with ≤ 1 risk factors showed significant improvement ($P < 0.05$). Logistic regression analysis indicated that baseline sUA level and acute arthritis were correlated with the RAT in gout and CKD patients treated with febuxostat.

Conclusions: In this retrospective study, febuxostat demonstrated effective and renal safety in gout patients with CKD. Baseline sUA level and acute arthritis may affect achieving of target sUA.

Introduction

Gout is an inflammatory joint disease caused by chronic deposition of monosodium urate (MSU) crystals in joints[1]. Hyperuricemia is a primary stage of gout. Elevated serum urate (sUA) level can cause structure and function damage of kidney, resulting in nephrolithiasis or kidney injuries[2]. Notably, renal impairment is an important risk factor for hyperuricemia and it can exacerbate severity of gout by decreasing excretion of sUA[3].

Studies report that patients with moderate-to-severe chronic kidney disease (CKD) or sUA concentratio[1]n >9 mg/dL have a higher risk of gout progression[4-7].[3,43-5] Urate-lowering treatment (ULT) is recommended at early stages of patients with gout and CKD, which comprises regular management patients and maintaining sUA level less than 360 μmol/L[8]. Xanthine Oxidase Inhibitors (XOIs) and uricosurics are the main urate-lowering drugs used in China[9, 10]. Allopurinol is associated with severe hypersensitivity reaction whereas benzbromarone is contraindicated in patients with a history of nephrolithiasis, thus febuxostat is commonly used in hospitals. Previous studies report that febuxostat is effective in treatment of gout patients with CKD, however, the effects on renal function are controversial, mainly under complex clinical conditions[11-14].

Therefore, a retrospective study was conducted to explore efficacy and the effect of febuxostat on renal function in gout patients with CKD in clinical practice. The study further explored the clinical factors that affect the rate of

achieving target sUA (RAT).

Methods

Study Design

The current study was a single-center retrospective study conducted in Rheumatology Department of the Second Affiliated Hospital of Zhejiang University School of medicine, in Southern China. Patient data were retrieved from the Electronic Medical Records System (EMRS). The study was approved by the ethics Committee of the Second Affiliated Hospital of Zhejiang University School of medicine (the ethics approval number: 2021-0027). The requirement for written informed consent was waived owing to the retrospective nature of the study.

Participants

The study comprised patients who were diagnosed with gout and kidney disease in the Rheumatology Department of the Second Affiliated Hospital of Zhejiang University School of medicine. Patients who met the following criteria were included in the study.

The inclusion criteria included: (i) Male patients, age ≥ 18 and ≤ 80 years old, diagnosed with primary gout and CKD. (ii) Patients treated with febuxostat continuously for at least 44 weeks. (iii) Baseline sUA ≥ 420 μmol/L and sCr ≥ 106 μmol/L. The exclusion criteria included: (i) Patients with severe liver injury, with alanine aminotransferase (ALT)/aspartate aminotransferase (AST) level > 3 times the upper limit of the normal range. (ii) Patients receiving two kinds of urate-lowering drugs. (iii) Patients without laboratory test results at baseline and at 44~ weeks. (iv) Patients with acute kidney injury. (v) Cancer patients, patients undergoing renal transplantation or patients on dialysis prior to the index date.

The index date was defined as the date of the first febuxostat prescription at the beginning of regular follow-up. Diagnosis of gout was performed following 2015 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Gout Classification Criteria and the target of sUA for ULT was defined as less than 360 μmol/L[15]. Patients with CKD diagnosis and classification of CKD stage was done using the 2012 KDIGO guidelines[16]. eGFR was determined to assess renal function by Modification of Diet in Renal Disease (MDRD) Study Equation as shown below:

Male: $eGFR\ (ml/min/1.73m^2) = 186 \times (sCr/88.402)^{-1.154} \times Age^{-0.203}$

sCr: serum creatinine (μmol/L).

Data Source

EMRS comprises patients' general information, diagnosis, prescription, laboratory data and information on hospital admissions. Data on clinical information, prescription and laboratory results, including age, history of gout, comorbidities, tophus, concomitant medications as well as sUA, sCr, acute gouty arthritis at baseline and during the follow-up were retrieved from EMRS.

Statistical analysis

Statistical analysis was performed using SPSS, version 22.0, software for Windows. All analyses were two sided and a $P < 0.05$ was considered statistically significant. Single-sample Kolmogorov-Smirnov (K-S) test or Shapiro-Wilk (S-W) test was used to determine normality of data. Continuous variables were presented as mean ± standard deviation (SD), and discrete variables were expressed as median and quartile intervals. Qualitative variables were expressed as frequencies (%). One-way ANOVA-Scheffe test was used to compare continuous variables recorded at both baseline and follow-up examinations. T-test was used for comparison between two groups. Univariate logistic regression analysis was used to identify any possible associated factors for target sUA and significantly correlated variables were further analyzed using a multivariate logistic regression model. All figures were generated using GraphPad Prism 8.

Results

Participant Characteristics

A total of 644 patients were diagnosed with gout and kidney disease between January 2017 and December 2019. Eighty-seven eligible individuals were included in the final analysis after screening based on clinical information, prescription and laboratory data. A flow chart of inclusion and exclusion of subjects in the current study is shown in Fig. 1. Main characteristics of patients are presented in Table 1. Out of the 87 subjects, 25 (28.73%) were diagnosed with stage 2 CKD, 58 (66.67%) with stage 3 CKD and 4 (4.60%) with stage 4 CKD. The sUA level of stage 4 CKD patients was higher compared with that of stage 2 CKD and stage 3 CKD ($P < 0.05$).

Level of mean sUA, sCr, eGFR and RAT after ULT with febuxostat

Mean overall sUA levels or at different stages of CKD were significantly decreased after initiation of regular treatment with febuxostat ($P < 0.05$; Fig. 2A and D). The findings showed that no patient had sUA < 180 μmol/L. RAT level of overall patients increased up to 34.50%. After classification of CKD by eGFR, the RAT level significantly fluctuated over time with final value of 24.00%, 37.90% and 50.00% for stage 2 CKD, stage 3 CKD, and stage 4 CKD patients, respectively (Fig. 3A). Number of patients who achieved sUA level < 300 μmol/L were lower compared with that of patients who achieved RAT (Fig.3.B and Table S2 in additional file 1).

The mean sCr level was decreased and eGFR level was slightly increased for all subjects after treatment for 44~ weeks (sCr: 138.42 ± 42.77 μmol/L vs. 131.54±44.91 μmol/L, eGFR: 52.37 ± 11.73 ml/min/1.73cm^2 vs. 56.51 ± 15.01 ml/min/1.73cm^2; $P < 0.05$) (Fig. 2B and C). sCr and eGFR levels in stage 2 CKD patients were relatively stable (sCr: 111.72 ± 3.67 μmol/L vs. 110.24 ± 19.43 μmol/L, eGFR: 64.34 ± 3.54 ml/min/1.73cm^2 vs. 67.34 ± 12.40 ml/min/1.73cm^2; $P > 0.05$). sCr and eGFR levels in stage 3 CKD were significantly improved within 40 weeks (sCr: 139.51 ± 24.64 μmol/L vs. 122.97 ± 25.05 μmol/L, eGFR: 49.30 ± 8.01 ml/min/1.73cm^2 vs. 57.81 ± 11.88 ml/min/1.73cm^2; $P < 0.05$), but were slightly reversed after 44 weeks (sCr: 131.53 ± 28.17 μmol/L, eGFR: 53.84 ± 12.21 ml/min/1.73cm^2; $P < 0.05$). The findings showed that renal function in stage 4 CKD patients was improved but not significantly (sCr: 289.50 ± 66.28 μmol/L vs. 264.75 ± 110.85 μmol/L, eGFR: 22.04 ± 4.79 ml/min/1.73cm^2 vs. 27.50 ± 12.66 ml/min/1.73cm^2; $P > 0.05$) (Fig. 2E and F). Details on the data are presented in additional file 1 (Table S2).

Stratification analysis of level of mean sUA, sCr and eGFR based on hypertension, diabetic mellitus, hyperlipidemia and use of NSAIDs

Hypertension, diabetic mellitus, hyperlipidemia and the use of Non-Steroidal Anti-inflammatory Drugs (NSAIDs) affect renal outcomes, thus a stratification analysis was performed based on the four risk factors. All subjects were assigned to four group as follows: group a, subjects without risk factors; group b, subjects with one risk factor; group c, subjects presenting with two risk factors and group d, subjects presenting with three risk factors. Analysis showed that there was no subject in the current study with four risk factors. A total of 27 (31.03%), 30 (34.48%), 25 (28.74%) and 5 (5.75%) subjects were assigned to group a, b, c, and d, respectively. Mean sUA, sCr and eGFR levels for each group are presented in Table 2. sUA levels were significantly reduced in all groups ($P < 0.05$). eGFR level were improved in all groups, whereas, statistically significant improvement of eGFR level was only showed in group a and group b ($P < 0.05$). Effect of different risk factors in group b are presented in additional file 1 (Table S1). Hypertension was the primary comorbidity in group b.

Baseline sUA and acute arthritis were correlated with target sUA as shown by multivariate logistic regression analysis

Univariate logistic regression analysis of the characteristics was performed to explore key variables which may affect the target sUA. The findings showed that baseline acute arthritis was correlated with target sUA (Table S3 in additional file 1; $P < 0.05$). Baseline sUA, eGFR, acute arthritis and body weight were used for the multivariate logistic regression analysis based on the results from univariate logistic regression analysis. The findings showed that acute arthritis was correlated with target sUA for febuxostat users in the current study, even after adjusting for confounding factors (Table 3; $P < 0.05$). Furthermore, baseline sUA was showed to be correlated with target sUA in multivariate logistic regression model.

Discussion

This study is one of few that conducted to explore the efficacy and renal safety of febuxostat in gout and CKD patients. The findings showed that febuxostat was effective on sUA reduction for CKD patients and it appeared to improve renal function in these patients. Moreover, analysis showed that baseline sUA and acute arthritis were correlated with target sUA in these patients.

Febuxostat is the first-line ULT drug for gout patients recommended by Chinese gout clinical guidelines[9, 10]. The drug is metabolized in the liver and excreted through the urinary system and intestinal tract[17]. Notably, the dosage for patients with mild to moderate renal insufficiency does not require adjustment (eGFR $\geq$ 30mL/min/1.73m^2). However, the dosage should be carefully chosen for patients with severe renal insufficiency (eGFR < 30mL/min/1.73m^2)[10, 18, 19]. Randomized controlled trials (RCTs) or cohort studies report that the uric acid-lowering effect of febuxostat is similar to that of allopurinol or benzbromarone in CKD with hyperuricemia[20-23]. In addition, it could improve endothelial function and slow eGFR decline[24-27]. The findings of the current study showed a significant effect of febuxostat on sUA reduction and renal function improvement in gout patients with CKD.

A “treat to target (sUA < 360 μmol/L) management strategy” is strongly recommended for all gout patients receiving ULT[28]. However, urate-lowering effect of febuxostat in gout and CKD patients undergoing the treat-to-target approach has not been fully explored. In the current study, a flexible dose of febuxostat reduced sUA by approximately 170 μmol/L and the overall RAT showed an increase during follow-up with maximum of 34.50% at the end of the study. This level was lower compared with the value reported in previous RCTs whereby the

dosage of febuxostat was fixed[14, 19]. However, it was similar to values reported in Chinese cohort studies on treatment of gout using febuxostat 20~80mg/day, whereby RAT varied from 22.5% to 70%[29-32]. Furthermore, the findings from stratification analysis based on baseline stage of CKD indicate that sUA level in patients with different CKD stages reduced by approximately 140~350 μmol/L, and the RAT level was 24%~50%. RAT level for patients with stage 3 and 4 CKD was higher compared with that of stage 2 CKD. These findings are important for management of gout patients with CKD.

Previous studies report that several factors can affect achieving target sUA in gout patients[33, 34]. Sheer et al conducted a retrospective cohort study for 365 days and reported that adherence to febuxostat and low baseline sUA level were significant predictors of achieving target sUA in gout patients treated with febuxostat[34]. A Chinese primary gout cohort study reported that baseline sUA level and renal function predict outcomes of ULT in patients receiving low dose of febuxostat (20mg/day)[31]. These studies were performed with gout patients presenting with normal renal function, and the dosage of febuxostat was low and fixed. Therefore, the findings should be considered carefully in clinical practice. The current study compensated for lack of evidence in gout and CKD patients on the treat-to-target approach and the finding showed that baseline sUA and acute arthritis were correlated with achieving target sUA in gout and CKD patients in clinical practice in multivariate logistic regression analysis.

Furthermore, a kidney improvement effect of febuxostat was observed in all patients, with significant effects observed in stage 3 CKD patients. In stratification analysis, eGFR level in group a and b was significant improved. Previous studies on gout and CKD patients with febuxostat are few and the findings are controversial. A placebo-controlled study was conducted on gout patients with moderate-to-severe renal impairment for 12 months and reported no significant changes in renal function[14]. Similar findings were reported by a retrospective study conducted on stage 4/5 CKD patients (eGFR: 21.6 ml/min/1.73m^2 vs. 20.5 ml/min/1.73m^2)[13]. A study by Kim reported renal improvement in eGFR <30 ml/min/1.73m^2, however, the difference was not significant (eGFR: 19.84 ml/min/1.73m^2 vs. 23.49 ml/min/1.73m^2)[11]. Only a previous study reported that XOIs could help conserve and improve renal function in patients with gout and stage 3 CKD, but the study did not explore the renal safety of febuxostat separately[12]. Most studies on renal protective effects of febuxostat have focused on patients with hyperuricemia and CKD or renal transplant recipients[35, 36]. In addition, a meta-analysis conducted by Sharma et al. reported that significantly higher improvement in eGFR and sCr was observed in patients treated with febuxostat use for ≥ 1 year, compared with the level observed for <1 year, and compared with the level for the control group[37]. The current study evaluated eGFR level in gout and CKD patients under clinical aspects, and conducted a stratified analysis of CKD and comorbidities. Although, the follow-up time of our study was less than 1 year, a significant improvement in renal function was observed. Improvement of renal function can be attributed to decrease in uric acid level, inhibition of oxidative stress and reduced signal transduction of renal fibrosis induced by febuxostat[38-40].

These findings provide clinicians with information for the treatment and guidance of gout patients with CKD. However, the current study had some limitations. Firstly, the study was a retrospective study thus there is a potential misjudgment of febuxostat status because febuxostat use was based on prescription data and clinical information, and actual adherence in these data was not evaluated. Previous evidence showed that gout patients have the worst drug adherence of all patients with chronic illnesses[41]. This may also be the reason for the relatively low RAT of this study. Secondly, the study was a single-center study with small population, the number

of patients in different groups were unequal, and female patients were excluded which may lead to case selection bias thus affecting the findings. Thirdly, there may be insufficient power as a result of small size, the OR of sUA was close to 1 and contrary to *P* value in univariate logistic regression model, thus the findings should be interpreted with caution. Fourthly, our data cannot represent the effect of long-term febuxostat exposure on the renal function of CKD, because the follow-up time was short and eGFR remained fairly constant over 12 weeks. Fifthly, the use of a serum creatinine-based equation for the calculation of eGFR was less accurate than that of creatinine- and cystatin C- based equations[42]. Lastly, the study did not include a control group, thus the effects of other variables, such as the cause of CKD and concomitant medication were not factored in. In spite of these, the current study was a clinical study and comprised a representative of the population with gout and CKD. Further studies with a larger population, including multiple centers, longer follow up duration and effective control of confounding factors should be conducted to further explore the renal effects of ULT after treatment with febuxostat and the sustained maintenance of target sUA patients with gout and CKD.

Conclusions

In summary, the findings of the current study showed that febuxostat was effective in reducing sUA level and could improve renal function to some extent in gout patients with CKD. Patients with stage 3 CKD, without hypertension, diabetic mellitus, hyperlipidemia and usage of NSAIDs showed significant improvement of eGFR level. Baseline sUA and acute arthritis are associated factors for achieving target sUA. To the best of our knowledge, this is the first study to explore the risk factors of ULT in patients with gout and CKD. The findings of the current study provide information for clinicians to guide gout and CKD patients to achieve target sUA level with febuxostat treatment.

Abbreviations

CKD, chronic kidney disease. eGFR, estimated glomerular filtration rate. sUA, serum urate. NSAIDs, Non-Steroidal Anti-inflammatory Drugs. RAT, achieving target sUA. MSU, monosodium urate.

ULT, urate-lowering treatment. XOIs, Xanthine Oxidase Inhibitors. EMRS, Electronic Medical Records System.

ALT, alanine aminotransferase. AST, aspartate aminotransferase. ACR/EULAR, American College of Rheumatology / European League Against Rheumatism. MDRD, modification of Diet in Renal Disease.

Declarations

Ethics approval and consent to participate:

The study was approved by the ethics Committee of the Second Affiliated Hospital of Zhejiang University School of medicine and written informed consent was waived (the ethics approval number: 2021-0027).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions

PYZ was responsible for the study design, conducting of the study, statistical analyses and drafting and revising of the manuscript. MC, JDW and SJH participated in conducting the study and helped in data curation, statistical analyses and drafting the manuscript. XYL and HXW were responsible for the study design, conducting of the study and helped in the drafting and revising the manuscript. All authors read and approved the final manuscript.

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Supplemental material

Supplemental material for this article is available online.

References

1. Dalbeth N, Gosling AL, Gaffo A, Abhishek A: **Gout**. *Lancet* 2021, **397**(10287):1843-1855.

2. Ponticelli C, Podesta MA, Moroni G: **Hyperuricemia as a trigger of immune response in hypertension and chronic kidney disease**. *Kidney Int* 2020, **98**(5):1149-1159.

3. Krishnan E: **Reduced glomerular function and prevalence of gout: NHANES 2009-10**. *PLoS One* 2012, **7**(11):e50046.

4. Campion EW, Glynn RJ, DeLabry LO: **Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study**. *Am J Med* 1987, **82**(3):421-426.

5. 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**(3):321-325.

6. Dalbeth N, House ME, Horne A, Taylor WJ: **Reduced creatinine clearance is associated with early development of subcutaneous tophi in people with gout**. *BMC Musculoskelet Disord* 2013, **14**:363.

7. Lu CC, Wu SK, Chen HY, Chung WS, Lee MC, Yeh CJ: **Clinical characteristics of and relationship between metabolic components and renal function among patients with early-onset juvenile tophaceous gout**. *J Rheumatol* 2014, **41**(9):1878-1883.

8. Chinese consensus expert group on the diagnosis and treatment of chronic kidney disease patients with hyperuricemia: [**Chinese experts consensus on the management of chronic kidney disease with hyperuricemia**]. *Chin J Nephrol* 2017, **33**(6):463-469.

9. Chinese Rheumatology Association: [**2016 Guidelines for the Diagnosis and Treatment of Gout in China**]. *Zhong Hua Nei Ke Za Zhi* 2016, **55**(11):892-899.

10. Xu Dong, Zhu Xiaoxia, Zeng Xuejun, Zou Hejian, Gu Jieruo, Zhou Jingguo, Zeng Xiaofeng, Zhao Yan: [**Recommendations of diagnosis and treatment of gout**]. *Zhong Hua Nei Ke Za Zhi* 2020, **59**(6):421-426.

11. Kim SH, Lee SY, Kim JM, Son CN: **Renal safety and urate-lowering efficacy of febuxostat in gout patients with stage 4-5 chronic kidney disease not yet on dialysis**. *Korean J Intern Med* 2020, **35**(4):998-1003.

12. Novella-Navarro M, Cabrera-Alarcon JL, Diaz-Torne C, Aramburu-Munoz F, Janta I, de la O MCO, Prada-Ojeda A, Sala-Icardo L, Urruticoechea-Arana A, Lefebvre PGD *et al*: **A treat-to-target approach for gout confers renoprotective effect in patients with chronic kidney disease stage 3**. *Rheumatol Int* 2020, **40**(7):1081-1087.

13. Juge PA, Truchetet ME, Pillebout E, Ottaviani S, Vigneau C, Loustau C, Cornec D, Pascart T, Snanoudj R, Bailly F *et al*: **Efficacy and safety of febuxostat in 73 gouty patients with stage 4/5 chronic kidney disease: A retrospective study of 10 centers**. *Joint Bone Spine* 2017, **84**(5):595-598.

14. Saag KG, Whelton A, Becker MA, MacDonald P, Hunt B, Gunawardhana L: **Impact of Febuxostat on Renal Function in Gout Patients With Moderate-to-Severe Renal Impairment**. *Arthritis Rheumatol* 2016, **68**(8):2035-

2043.

15. Neogi T, Jansen TLTA, Dalbeth N, Fransen J, Schumacher HR, Berendsen D, Brown M, Choi H, Edwards NL, Janssens HJEM *et al*: **2015 Gout Classification Criteria An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative**. *Arthritis Rheumatol* 2015, **67**(10):2557-2568.

16. Group KDIGOKCW: **KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease**. *Kidney Int Suppl* 2013, **3**:1-150.

17. Kamel B, Graham GG, Williams KM, Pile KD, Day RO: **Clinical Pharmacokinetics and Pharmacodynamics of Febuxostat**. *Clin Pharmacokinet* 2017, **56**(5):459-475.

18. Gunawardhana L, Becker MA, Whelton A, Hunt B, Castillo M, Saag K: **Efficacy and safety of febuxostat extended release and immediate release in patients with gout and moderate renal impairment: phase II placebo-controlled study**. *Arthritis Res Ther* 2018, **20**.

19. Becker MA, Schumacher HR, Espinoza LR, Wells AF, MacDonald P, Lloyd E, Lademacher C: **The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial**. *Arthritis Res Ther* 2010, **12**(2).

20. Liu XM, Wang HF, Ma RX, Shao LP, Zhang W, Jiang W, Luo CJ, Zhai TT, Xu Y: **The urate-lowering efficacy and safety of febuxostat versus allopurinol in Chinese patients with asymptomatic hyperuricemia and with chronic kidney disease stages 3-5**. *Clinical and Experimental Nephrology* 2019, **23**(3):362-370.

21. Sezai A, Soma M, Nakata K, Osaka S, Ishii Y, Yaoita H, Hata H, Shiono M: **Comparison of febuxostat and allopurinol for hyperuricemia in cardiac surgery patients with chronic kidney disease (NU-FLASH trial for CKD)**. *J Cardiol* 2015, **66**(4):298-303.

22. Tanaka K, Nakayama M, Kanno M, Kimura H, Watanabe K, Tani Y, Hayashi Y, Asahi K, Terawaki H, Watanabe T: **Renoprotective effects of febuxostat in hyperuricemic patients with chronic kidney disease: a parallel-group, randomized, controlled trial**. *Clin Exp Nephrol* 2015, **19**(6):1044-1053.

23. Yu H, Liu X, Song Y, Cheng J, Bao H, Qin L, Zhou X, Wang L, Peng A: **Safety and Efficacy of Benzbromarone and Febuxostat in Hyperuricemia Patients with Chronic Kidney Disease: A Prospective Pilot Study**. *Clin Exp Nephrol* 2018, **22**(6):1324-1330.

24. Sircar D, Chatterjee S, Waikhom R, Golay V, Raychaudhury A, Chatterjee S, Pandey R: **Efficacy of Febuxostat for Slowing the GFR Decline in Patients With CKD and Asymptomatic Hyperuricemia: A 6-Month, Double-Blind, Randomized, Placebo-Controlled Trial**. *Am J Kidney Dis* 2015, **66**(6):945-950.

25. Mukri MNA, Kong WY, Mustafar R, Shaharir SS, Shah SA, Abdul Gafor AH, Mohd R, Abdul Cader R, Kamaruzaman L: **Role of febuxostat in retarding progression of diabetic kidney disease with asymptomatic hyperuricemia: A 6-months open-label, randomized controlled trial**. *EXCLI J* 2018, **17**:563-575.

26. Tsuruta Y, Kikuchi K, Tsuruta Y, Sasaki Y, Moriyama T, Itabashi M, Takei T, Uchida K, Akiba T, Tsuchiya K *et al*: **Febuxostat improves endothelial function in hemodialysis patients with hyperuricemia: A randomized controlled study**. *Hemodial Int* 2015, **19**(4):514-520.

27. Alshahawey M, Shahin SM, Elsaid TW, Sabri NA: **Effect of Febuxostat on the Endothelial Dysfunction in Hemodialysis Patients: A Randomized, Placebo-Controlled, Double-Blinded Study**. *Am J Nephrol* 2017, **45**(5):452-459.

28. FitzGerald JD, Dalbeth N, Mikuls T, Brignardello-Petersen R, Guyatt G, Abeles AM, Gelber AC, Harrold LR, Khanna D, King C *et al*: **2020 American College of Rheumatology Guideline for the Management of Gout**. *Arthritis Rheumatol* 2020, **72**(6):879-895.

29. Huang XF, Du H, Gu JR, Zhao DB, Jiang LD, Li XF, Zuo XX, Liu Y, Li ZG, Li XP *et al*: **An allopurinol-controlled, multicenter, randomized, double-blind, parallel between-group, comparative study of febuxostat in Chinese patients with gout and hyperuricemia**. *Int J Rheum Dis* 2014, **17**(6):679-686.

30. Xu SY, Liu XY, Ming J, Chen SR, Wang YG, Liu XM, Liu H, Peng YD, Wang JQ, Lin JY *et al*: **A phase 3, multicenter, randomized, allopurinol-controlled study assessing the safety and efficacy of oral febuxostat in Chinese gout patients with hyperuricemia**. *Int J Rheum Dis* 2015, **18**(6):669-678.

31. Liang N, Sun MS, Sun RX, Xu T, Cui LL, Wang C, Ma LD, Cheng XY, Xue XM, Sun WY *et al*: **Baseline urate level and renal function predict outcomes of urate-lowering therapy using low doses of febuxostat and benzbromarone: a prospective, randomized controlled study in a Chinese primary gout cohort**. *Arthritis Res Ther* 2019, **21**(1).

32. Zhang FC, Liu ZC, Jiang LD, Zhang H, Zhao DB, Li Y, Zou HJ, Wang XY, Li XP, Shi BY *et al*: **A Randomized, Double-Blind, Non-Inferiority Study of Febuxostat Versus Allopurinol in Hyperuricemic Chinese Subjects With or Without Gout**. *Rheumatol Ther* 2019, **6**(4):543-557.

33. Mu Z, Wang W, Wang J, Lv W, Chen Y, Wang F, Yu X, Wang Y, Cheng B, Wang Z: **Predictors of poor response to urate-lowering therapy in patients with gout and hyperuricemia: a post-hoc analysis of a multicenter randomized trial**. *Clin Rheumatol* 2019, **38**(12):3511-3519.

34. Sheer R, Null KD, Szymanski KA, Sudharshan L, Banovic J, Pasquale MK: **Predictors of reaching a serum uric acid goal in patients with gout and treated with febuxostat**. *Clinicoecon Outcomes Res* 2017, **9**:629-639.

35. Lin TC, Hung LY, Chen YC, Lo WC, Lin CH, Tam KW, Wu MY: **Effects of febuxostat on renal function in patients with chronic kidney disease A systematic review and meta-analysis**. *Medicine* 2019, **98**(29).

36. Liu X, Liu K, Sun Q, Wang Y, Meng J, Xu Z, Shi Z: **Efficacy and safety of febuxostat for treating hyperuricemia in patients with chronic kidney disease and in renal transplant recipients: A systematic review and meta-analysis**. *Exp Ther Med* 2018, **16**(3):1859-1865.

37. Sharma G, Dubey A, Nolkha N, Singh JA: **Hyperuricemia, urate-lowering therapy, and kidney outcomes: a systematic review and meta-analysis**. *Ther Adv Musculoskelet Dis* 2021, **13**:1759720X211016661.

38. Liu L, You L, Sun K, Li F, Qi Y, Chen C, Wang C, Lao G, Xue S, Tang J *et al*: **Association between uric acid lowering and renal function progression: a longitudinal study**. *PeerJ* 2021, **9**:e11073.

39. Tsuda H, Kawada N, Kaimori JY, Kitamura H, Moriyama T, Rakugi H, Takahara S, Isaka Y: **Febuxostat suppressed renal ischemia-reperfusion injury via reduced oxidative stress**. *Biochem Biophys Res Commun* 2012,

427(2):266-272.

40. Omori H, Kawada N, Inoue K, Ueda Y, Yamamoto R, Matsui I, Kaimori J, Takabatake Y, Moriyama T, Isaka Y *et al*: **Use of xanthine oxidase inhibitor febuxostat inhibits renal interstitial inflammation and fibrosis in unilateral ureteral obstructive nephropathy**. *Clin Exp Nephrol* 2012, **16**(4):549-556.

41. Doherty M, Jansen TL, Nuki G, Pascual E, Perez-Ruiz F, Punzi L, So AK, Bardin T: **Gout: why is this curable disease so seldom cured?** *Ann Rheum Dis* 2012, **71**(11):1765-1770.

42. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, Crews DC, Doria A, Estrella MM, Froissart M *et al*: **New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race**. *N Engl J Med* 2021, **385**(19):1737-1749.

Tables

Table 1. Baseline characteristics of the subjects

	All	CKD2	CKD3	CKD4
Total, No. (%)	87	25 (28.73%)	58 (66.67%)	4 (4.60%)
Follow-up time, weeks	51.70 ± 6.02	51.23 ± 4.93	51.80 ± 6.10	53.29 ± 11.58
Age, years	58.30 ± 12.92	51.28 ± 12.69	61.50 ± 11.54#	55.75 ± 18.78
Gout duration, years	8.74 ± 7.81	6.48 ± 5.72	9.46 ± 8.12	11.75 ± 12.61
Family history of gout, No. (%)	6 (6.90%)	0 (0.00%)	4 (6.90%)	2 (50.00%)
Acute arthritis（baseline, %）	48 (55.20%)	11 (44.00%)	35 (60.30%)	2 (50.00%)
Body Weight, kg	71.22 ± 9.86	75.06 ± 11.52	69.61 ± 8.31#	70.13 ± 15.07
BMI, kg/m^2	24.85 ± 3.24	25.74 ± 3.94	24.47 ± 2.77	24.67 ± 4.57
Systolic pressure, mmHg	139.15 ± 21.18	142.56 ± 22.64	139.04 ± 21.08	126.75 ± 15.00
Diastolic pressure, mmHg	81.94 ± 13.92	88.19 ± 19.97	80.09 ± 10.84#	78.25 ± 12.92
Tophus, No. (%)	33 (37.90%)	8 (32.00%)	23 (39.70%)	2 (50.00%)
Comorbid conditions, No. (%)				
Hypertension	47 (54.0%)	9 (36.00%)	35 (60.30%)	3 (75.00%)
Diabetic mellitus	10 (11.50%)	2 (8.00%)	8 (13.80%)	–
Hyperlipemia	30 (34.50%)	9 (36.00%)	19 (32.80%)	2 (50.00%)
Cardio-cerebrovascular disease	9 (10.30%)	1 (4.00%)	8 (13.80%)	–
Concomitant medication use, No. (%)				
Colchicine	26 (29.90%)	5 (20.00%)	20 (34.50%)	1 (25.00%)
NSAIDs	8 (9.20%)	4 (16.00%)	4 (6.90%)	–
Glucocorticoid	58 (66.70%)	14 (56.00%)	42 (72.40%)	2 (50.00%)
Previous ULT, No. (%)				
NO	54 (62.10%)	16 (64.00%)	36 (62.10%)	2 (50.00%)
Febuxostat	15 (17.20%)	4 (16.00%)	10 (17.20%)	1 (25.00%)
Allopurinol	14 (16.10%)	4 (16.00%)	9 (15.50%)	1 (25.00%)
Benzbromarone	4 (4.60%)	1 (4.00%)	3 (5.20%)	–
Initial dose of febuxostat, No. (%)				
10~40mg/d	67 (76.90%)	20 (80.00%)	45 (77.60%)	2 (50.00%)
40mg/d	19 (21.80%)	5 (20.00%)	12 (20.70%)	2 (50.00%)
40-80mg/d	1 (1.10%)	–	1 (1.70%)	–

Laboratory data, mean ± SD				
sUA, μmol/L	598.22 ± 95.11	588.56 ± 88.04	593.43 ± 87.70	728.00 ± 165.91[#*]
eGFR, ml/min/1.73m^2	52.37 ± 11.74	64.34 ± 3.54	49.30 ± 8.01[#]	22.04 ± 4.79[#*]
sCr, μmol/L	138.42 ± 42.77	111.72 ± 3.67	139.51 ± 24.64[#]	289.50 ± 66.28[#*]
Nephrolithiasis, No. (%)				
NA	9 (10.30%)	3 (12.00%)	6 (10.30%)	–
YES	42 (48.20%)	14 (56.00%)	26 (44.90%)	2 (50.00%)
NO	36 (41.40%)	8 (32.00%)	26 (44.80%)	2 (50.00%)
Tophus for DECT, No. (%)				
NA	64 (73.60%)	20 (80.00%)	40 (69.00%)	4 (100.00%)
YES	22 (25.30%)	4 (16.00%)	18 (31.00%)	–
NO	1 (1.10%)	1 (4.00%)	–	–
Medical insurance (Yes, %)	60 (69.00%)	17 (68.00%)	41 (70.70%)	2 (50.00%)
Occupation				
retirement	5 (5.70%)	1 (4.00%)	3 (5.20%)	1 (25.00%)
staff	23 (26.40%)	9 (36.00%)	12 (20.70%)	2 (50.00%)
self-employed entrepreneurs	57 (65.50%)	15 (60.00%)	41 (70.70%)	1 (25.00%)
farmer	2 (2.30%)	--	2 (3.40%)	–
Residence				
Hangzhou	55 (63.20%)	17 (68.00%)	37 (63.80%)	1 (25.00%)
[$]Zhejiang Province	22 (25.30%)	4 (16.00%)	16 (27.60%)	2 (50.00%)
Outside Zhejiang Province	10 (11.50%)	4 (16.00%)	5 (8.60%)	1 (25.00%)

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; NSAIDs, Nonsteroidal anti-inflammatory; ULT, urate-lowering treatment; sUA, serum urate; eGFR, estimated glomerular filtration rate; sCr, serum creatinine; NA, not applicable; DECT, Dual energy computed tomography. [#]$P < 0.05$, stage 2 CKD vs. stage 3 CKD or stage 2 CKD vs. stage 4 CKD. [*]$P < 0.05$, stage 3 CKD vs. stage 4 CKD.

[$]Zhejiang Province: Patients were from others areas of Zhejiang province besides Hangzhou.

Table 2. Stratification analysis of level of mean sUA, sCr and eGFR based on hypertension, diabetic mellitus, hyperlipidemia and use of NSAIDs

Hypertension, diabetic mellitus, hyperlipidemia and the usage of NSAIDs are the four risk factors. Group a is defined as subjects who had none of four risk factors, group b is defined as subjects who had one risk factors,

	baseline	4 weeks	8 weeks	12~16 weeks	20~28 weeks	32~36 weeks	≥ 44 weeks
Group a (patients without risk factors, n=27)							
sUA	596.15 ± 87.83	481.5 ± 103.83*	466.67 ± 119.99*	431.06 ± 126.45*	410.39 ± 81.15*	451.91 ± 80.61*	424.22 ± 109.23*
sCr	132.36 ± 29.88	129.75 ± 30.14	110.33 ± 7.05	115.38 ± 29.46*	122.88 ± 36.82	114.90 ± 28.13*	124.96 ± 30.02*
eGFR	54.57 ± 10.81	56.66 ± 13.24	62.72 ± 3.84	65.07 ± 15.33*	60.81 ± 14.04*	64.02 ± 11.20*	58.80 ± 12.92*
Group b (patients with one risk factor, n=30)							
sCr	145.93 ± 58.83	142.73 ± 55.92	134.10 ± 44.56*	132.11 ± 47.65*	135.56 ± 44.55	123.79 ± 37.85*	139.30 ± 64.43
eGFR	50.58 ± 12.71	52.78 ± 14.00	54.78 ± 13.46	55.78 ± 13.34*#	53.64 ± 12.86*	59.02 ± 13.32*	55.11 ± 16.84*
sUA	601.77 ± 107.88	440.53 ± 77.57*	438.62 ± 106.42*	464.59 ± 102.05*	440.54 ± 92.41*	423.42 ± 106.13*	440.33 ± 135.66*
Group c (patients with two risk factors, n=25)							
sCr	132.60 ± 31.66	122.77 ± 18.29*	121.38 ± 14.35#	130.41 ± 25.74	122.61 ± 22.36*	121.23 ± 20.35	128.80 ± 31.74
eGFR	53.65 ± 11.20	57.51 ± 11.16*	57.02 ± 9.15	55.01 ± 13.80	57.51 ± 10.65*	58.18 ± 11.63	56.56 ± 15.71
sUA	586.08 ± 89.29	447.67 ± 107.08*	440.88 ± 98.93*	410.69 ± 118.88*	367.67 ± 92.53*	355.08 ± 101.10*#	424.84 ± 134.27*
Group d (patients with three risk factors, n=5)							
sCr	155.20 ± 34.30	112.50 ± 20.51	133.50 ± 37.08#	122.33 ± 33.62	133.50 ± 22.96	135.75 ± 21.13	134.20 ± 23.92
eGFR	44.80 ± 11.75	64.76 ± 14.66	54.56 ± 18.66	59.84 ± 18.22	52.97 ± 10.72	51.03 ± 11.82	52.25 ± 12.32
sUA	648.80 ± 88.89	457.00 ± 72.13	439.75 ± 92.69*	457.00 ± 136.12	400.75 ± 82.94	477.00 ± 121.51	420.80 ± 90.38

group c is defined as subjects who had two risk factors and group d is defined as subjects who had three risk factors. Data given as mean ± SD. *$P < 0.05$, before vs. after treatment. #$P < 0.05$, group b, c or d vs. group a.

Table 3. Clinical factors related to target sUA achieving by multivariate logistic regression

Factors	multivariate logistic regression		Adjusted[a*]		Adjusted[b*]		Adjusted[c*]	
	OR, 95%CI	P value	OR, 95%CI	P value	OR, 95%CI	P value	OR, 95%CI	P value
body weight	0.951(0.899-1.066)	0.082	0.941(0.884-1.001)	0.055	0.951(0.898-1.006)	0.082	**0.941(0.886-0.999)**	**0.046**
baseline sUA	**0.993(0.987-0.998)**	**0.013**	**0.993(0.986-1.000)**	**0.038**	**0.993(0.987-0.998)**	**0.013**	**0.993(0.988-0.999)**	**0.027**
baseline eGFR	0.958(0.914-1.004)	0.076	0.964(0.916-1.013)	0.049	0.958(0.913-1.005)	0.076	0.959(0.914-1.005)	0.082
Acute arthritis	**3.292(1.171-9.257)**	**0.024**	**3.560(1.006-12.594)**	**0.049**	**3.320(1.166-9.451)**	**0.025**	**3.368(1.132-9.435)**	**0.029**

[a*], adjusted the multivariate logistic regression analysis by age, duration of disease, hypertension, diabetic mellitus, hyperlipidemia, cardio-cerebrovascular disease, the usage of NSAIDs and follow-up time. [b*], adjusted the multivariate logistic regression analysis by tophus. [c*] adjusted the multivariate logistic regression analysis by medical insurance, residence and gout flares after treatment.

Figures

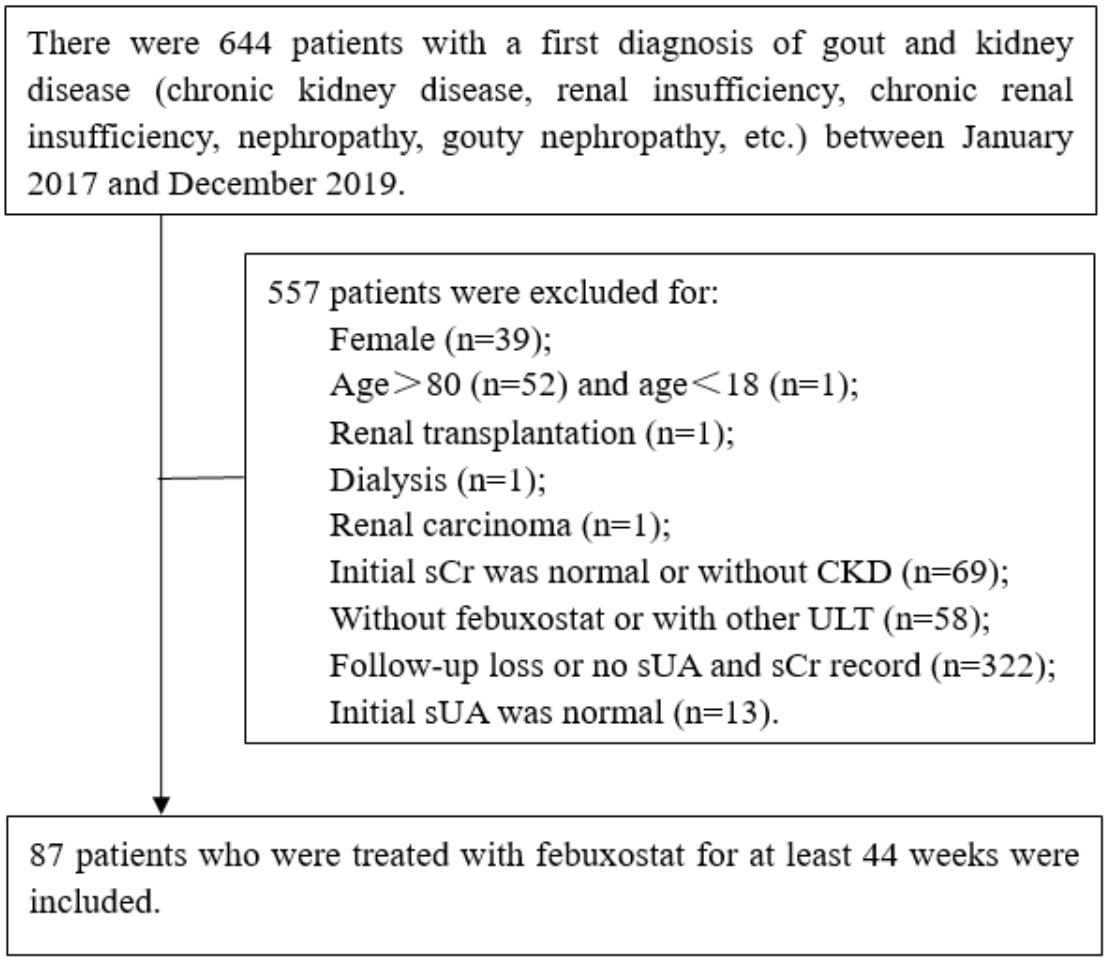

Figure 1

Flow diagrams of study participants.

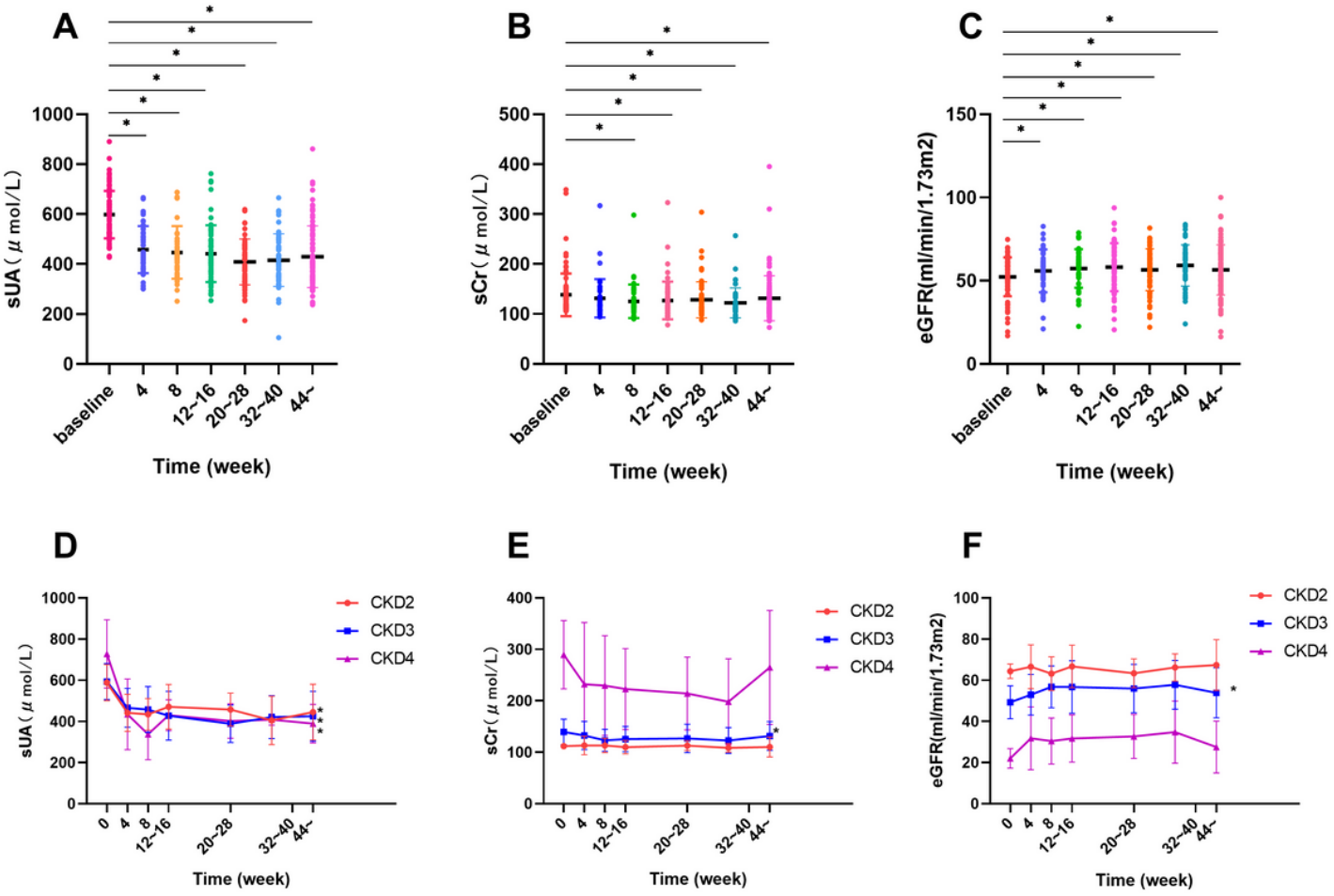

Figure 2

level of mean sUA, sCr and eGFR after ULT with febuxostat. A, mean sUA of all subjects. B, mean sCr of all subjects. C, mean eGFR of all subjects. D, Mean sUA of subjects with different stages of CKD. E, Mean sCr of subjects with different stages of CKD. F, Mean eGFR of subjects with different stages of CKD. *P□0.05□before vs. after treatment (Fig 2. A, B, C). *P□0.05□ before vs. 44~weeks (Fig 2. D, E, F).

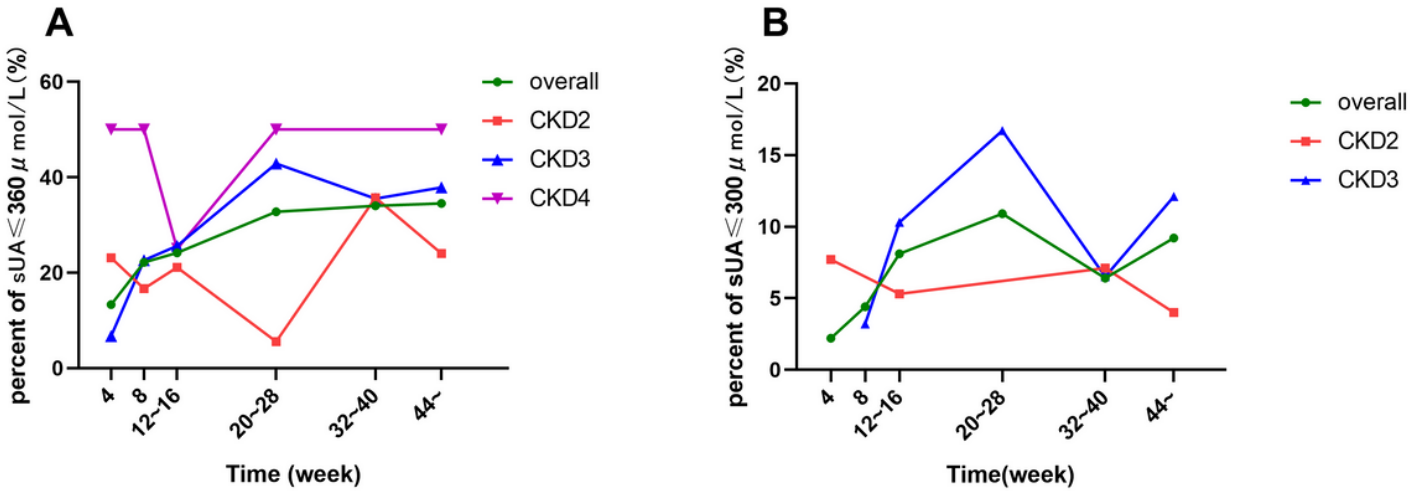

Figure 3

the percentage of target sUA achieving. A, sUA< 360 μmol/L. B, sUA< 300 μmol/L.

Supplementary Files

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