BMJ Open

The Rationale and Design of Lowering-hyperUricemia Treatment on Cardiovascular OutcoMes In PeritoNeal DiAlysis Patients: A Prospective, Multicenter, Double-Blind, Randomized Controlled Trial (LUMINA)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-037842
Article Type:	Protocol
Date Submitted by the Author:	20-Feb-2020
Complete List of Authors:	Chen, Wei; Sun Yat-sen University First Affiliated Hospital Department of Nephrology Huang, Naya; Sun Yat-sen University First Affiliated Hospital Department of Nephrology, Mao, Haiping; Sun Yat-sen University First Affiliated Hospital Department of Nephrology Yang, Xiao; Sun Yat-sen University First Affiliated Hospital, Department of Nephrology Zhou, Qian; Sun Yat-sen University First Affiliated Hospital, Department of Medical Statistics, Clinical Trials Unit Jiang, Lanping; Sun Yat-sen University First Affiliated Hospital Department of Nephrology Ding, Jun; Wanbang Pharmaceutical Marketing and Distribution Co., Medical Department Feng, Qiong; Sun Yat-sen University First Affiliated Hospital Department of Nephrology Yu, xueqing; Sun Yat-sen University First Affiliated Hospital, Department of Nephrology; Guangdong Provincial People's Hospital, Department of Nephrology
Keywords:	Nephrology < INTERNAL MEDICINE, Dialysis < NEPHROLOGY, CARDIOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

The Rationale and Design of Lowering-hyperUricemia Treatment on Cardiovascular OutcoMes In PeritoNeal DiAlysis Patients: A Prospective, Multicenter, Double-Blind, Randomized Controlled Trial (LUMINA)

Wei Chen[1#], Naya Huang[1#], Haiping Mao[1], Xiao Yang[1], Qian Zhou[2], Lanping Jiang[1], Jun Ding[3], Qiong Feng[1], Xueqing Yu[1,4*]

1 Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, Key Laboratory of Nephrology, Ministry of Health of China, Guangdong Provincial Key Laboratory of Nephrology, Guangzhou, Guangdong, China

2 Department of Medical Statistics, Clinical Trials Unit, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

3 Medical Department, Wanbang Pharmaceutical Marketing and Distribution Co., Jiangsu, China

4 Guangdong Provincial People's Hospital, School of Medicine, South China University of Technology, Guangzhou, China

# These authors contributed equally to this work.

* Corresponding author

Correspondence to:

Xueqing Yu, M.D., Ph.D

Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, NHC Key Laboratory of Nephrology (Sun Yat-sen University), Guangdong Provincial Key Laboratory

of Nephrology; Guangdong Provincial People's Hospital, School of Medicine, South China University of Technology
Guangzhou 510080, China
Phone: 8620 87766335
Fax: 8620 87769673
E-mail: yuxq@mail.sysu.edu.cn

Word counts: 5186 words.

Keywords: Hyperuricemia, cardiovascular outcomes, peritoneal dialysis

Abstract

Objective

To investigate whether lowering hyperurecimia treatment by febuxostat can lower the risk of cardiovascular events in continuous ambulatory peritoneal dialysis (CAPD) patients.

Study Design and Setting

This prospective, multicenter, double-blind, randomized controlled trial was designed to evaluate the effects of lowering hyperuricemia treatment on cardiovascular event risk in CAPD patients. Based on a power of 80%, with type I error α=0.05, two-sided test, and 1:1 parallel control study, a total of 548 eligible patients are expected to be randomly assigned to either lowering hyperuricemia treatment group (febuxostat) or control group (placebo).

Results

The primary endpoint is cardiovascular events composing of cardiovascular mortality and non-fatal cardiovascular events. All patients will be treated and followed for 3 years.

Conclusion

LUMINA will provide evidence of the effect of lowering-hyperuricemia treatment on cardiovascular outcomes in CAPD patients.

Strengths and limitations of this study

1. To our knowledge, this is the first large sample size randomized clinical trial to evaluate whether high uric acid level is a potentially modifiable risk factor for cardiovascular mortality in peritoneal dialysis patients.

2. It is a prospective, multicenter, double-blind, randomized controlled trial powerful enough to test the hypothesis.

3. The LUMINA study has some limitations. Firstly, we recruit prevent and incident patients concurrently, which might have some bias in baseline characteristics

4. Secondly, since center management capability is not parallel in different centers, thus may lead to center bias in the study.

Trial Registration: ClinicalTrials.gov

Trial number: NCT03200210

Registered: 25 June, 2017

The trial was started on July 13, 2017, and was expected to end by December 31, 2012. Till Jan 20, 2020, a total of 548 patients have been recruited.

Protocol version

The protocol version number and date are YLT-1604-V2.0, December 15, 2016,

Funding

The work was sponsored by WanBang Pharmaceutical Marketing and Distribution Co. China. And this work was supported by the National Key Technology Research and Development Program of China (2016YFC0906101), Operational Grant of Guangdong Provincial Key Laboratory (2017B030314019), Key Laboratory of Nephrology, Guangdong Province, Guangzhou, China (2002B60118), 5010 Clinical Program of Sun Yat-sen University

(2017007), Natural Science Foundation of Guangdong Province, China (Grant no.2017A030310199), National Natural Science Foundation of China (Grant no.81800632), the Natural Science Foundation of China (Grant no. 81600545), National Natural Science Foundation of China (Grant no. 81600592), and Natural Science Foundation of Guangdong Province, China (Grant no.2018A030310273).

Roles and responsibilities:

Author details:

Xueqing Yu is the Corresponding author.

Drs. Wei Chen and Naya Huang contributed equally to this work.

All authors have made substantial contributions to the work. Contributions of the authors were listed below.

Conceptualization: Xueqing Yu

Data curation : Wei Chen,

Formal analysis: Qian Zhou, Naya Huang

Funding acquisition: Xueqing Yu

Investigation: Naya Huang, Wei Chen, Haiping Mao, Xiao Yang, Qiong Feng

Methodology: Naya Huang, Wei Chen, Qian Zhou, Jun Ding

Project administration: Wei Chen, Xueqing Yu

Resources: Xueqing Yu, Jun Ding

Software: Naya Huang, Qian Zhou

Supervision: Xueqing Yu

Validation: Wei Chen, Xueqing Yu

Visualization: Wei Chen, Naya Huang

Roles/Writing - original draft: Naya Huang, Wei Chen

Writing - review &editing: Naya Huang, Wei Chen, Xueqing Yu

Author details were listed below:

1. Wei Chen, Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, Key Laboratory of Nephrology, Ministry of Health of China,Guangdong Provincial Key Laboratory of Nephrology, Guangzhou, Guangdong, China, vvchen66@qq.com;

2. Naya Huang, Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, Key Laboratory of Nephrology, Ministry of Health of China,Guangdong Provincial Key Laboratory of Nephrology, Guangzhou, Guangdong, China, huangnaya@163.com

3.Haiping Mao, Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, Key Laboratory of Nephrology, Ministry of Health of China,Guangdong Provincial Key Laboratory of Nephrology, Guangzhou, Guangdong, China, haipingmao@126.com

4. Xiao Yang, Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, Key Laboratory of Nephrology, Ministry of Health of China,Guangdong Provincial Key Laboratory of Nephrology, Guangzhou, Guangdong, China, yangxsysu@126.com

5. Qian Zhou, Department of Medical Statistics, Clinical Trials Unit, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China, zhouqian2017@163.com

6. Lanping Jiang, Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, Key Laboratory of Nephrology, Ministry of Health of China,Guangdong Provincial Key Laboratory of Nephrology, Guangzhou, Guangdong, China, fuzhi626@126.com

7. Jun Ding, Medical Department, Wanbang Pharmaceutical Marketing and Distribution Co., Jiangsu, China, dingjun0411@163.com

8. Qiong Feng, Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, Key Laboratory of Nephrology, Ministry of Health of China,Guangdong Provincial Key Laboratory of Nephrology, Guangzhou, Guangdong, China, fengqiong2016@126.com

9. Xueqing Yu, Sun Yat-sen University, Key Laboratory of Nephrology, Ministry of Health of China,Guangdong Provincial Key Laboratory of Nephrology, Guangzhou, Guangdong, China, Guangdong Provincial People's Hospital, School of Medicine, South China University of Technology, Guangzhou, China, yuxq@mail.sysu.edu.cn

Name and contact information for the trial sponsor

The work was sponsored by WanBang Pharmaceutical Marketing and Distribution Co. China., No.6 Yangshan Rd, Economic Zone, Xuzhou, Jiangsu, China, 221004.

Role of sponsor

The sponsor participated in the design of the study, but had no role in collection, management, analysis and interpretation of data, writing of the report, and the decision to submit the report for publication.

Composition, roles, and responsibilities of the coordinating centre, steering committee,

endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)

No applicable.

Introduction

Background and study rationale

Elevated serum uric acid (SUA) seen in patients with chronic kidney disease (CKD) is partly due to overproduction of purines due to hypercatabolism, and reduced excretion of uric acid by the kidneys. It was shown that there was a pattern of higher uric acid levels with lower glomerular filtration rate (GFR) [1-3]. Hyperuricemia is highly prevalent in the general population with a prevalence of 13.3-42.1% [4-6]. Based on the epidemiological study in Southern China, prevalence of hyperuricemia in adult population is as high as 31.9% [6]. Reduced GFR seen in CKD patients understandably gives a higher prevalence of hyperuricemia than that of the general population. Our local data showed that the prevalence of hyperuricemia in our peritoneal dialysis (PD) center is 63.1% [6].

A lot of epidemiologic and clinical studies have demonstrated a correlation between hyperuricemia and cardiovascular diseases [7-15]. At the same time, literatures also suggest hyperuricemia is associated with other classical cardiovascular risk factors such as hypertension [16], diabetes mellitus [17], hyperlipidemia[18], obesity and insulin resistance [19, 20]. Evidence shows an elevation in serum uric acid level facilitates oxidation of low density lipoprotein cholesterol [18], also, hyperuricemia is accompanied with an increase in free oxygen radical production that plays a role in inflammation [21]. Besides, elevated uric acid level facilitates the aggregation of platelet, thus increased chance of arterial thrombus

formation [22]. These will contribute to higher risk of cardiovascular events.

Treatment of hyperuricemia has been reported to reduce renal disease progression independently in CKD patients [23, 24]. And treatment of of hyperuricemia was associated with lower mortality among hemodialysis (HD) patients with no history of cardiovascular disease (CVD) in Dialysis Outcomes and Practice Patterns Study (DOPPS) study in Japan [25]. Also, in CKD patients, treatment of hyperuricemia has been shown to reduce cardiovascular risk [26]. However, whether lowering treatment of uric acid would benefit the cardiovascular outcomes in CKD patients, especially in maintenance dialysis patients is not known yet.

Objectives

To investigate whether lowering hyperurecimia therapy by febuxostat could lower the risk of cardiovascular events in CAPD patients.

Trial design

The study is a prospective, multicenter, double-blind, randomized controlled trial.

Methods

Study setting

The study is conducting in mainland China in 24 academic hospitals. List of study sites can be obtained in the acknowledgements.

Inclusion criteria:

1. Subjects who are able to understand and have voluntarily signed the informed consent form (ICF)

2. 18-70 years old at the time of randomization

3. Subjects on PD for more than 3 months

4. Subjects have hyperuricemia, female: 6mg/dl(360μmol/L) <sUA<12mg/dl(720μmol/L)；male: 7mg/dl(420μmol/L)<sUA<12mg/dl(720μmol/L)

Exclusion criteria:

1. Subjects has history of gout

2.Subjects who have a myocardial infarction, unstable angina,cardiovascular reconstructive surgery (such as a stent or bypass surgery), cerebrovascular accident 12 weeks prior to randomization, or plan cardiovascular reconstructive surgery during the trial

3. Subjects who have New York stage IV heart failure occurs4 weeks prior to the screening

4. Subjects who have previously received kidney transplantation and are currently prescribed immunosuppressive therapy

5. Subjects who have severe liver disease, such as acute hepatitis, chronic active hepatitis, cirrhosis

6. Subjects who have alanine aminotransferase (ALT) greater than 2 folds of the upper limited of normal or total bilirubin greater than 1.5 folds of upper limited of normal

7. Subjects who have severe infections 4 weeks prior to the screening, such as pneumonia and peritoneal dialysis-related peritonitis;

8. Subjects who have a major surgery 12 weeks prior to screening or not yet fully recovered from the surgery

9. Subjects who have a malignancy

10. Subjects who report a history of illicit drug use or a regular or daily alcohol consumption of≥4 alcoholic drinks per day in the 2 years before Screening

11. Subjects who are allergic to Febuxostat

12. Subjects who are enrolled in other clinical studies within 4 weeks or currently at randomization

13. Subjects who are currently taking mercaptopurine, azathioprine, vidarabine ordidanosine

14. Subjects who are taking losartan, fenofibrate, thiazide diuretics or loop diuretics within 4 weeks at randomization

15. Subjects who require long-term use of steroids (prednisone <30mg/d, or equivalent amount of other steroids and the use of <2 weeks can be enrolled)

16. Subjects who require long-term use of salicylic acid drugs except low-dose aspirin

17. Fertility, lactation patients unwilling or unable to contraception

Patient and Public Involvement

We state that patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research.

Interventions

Eligible patients will be randomly assigned to febuxostat treatment group or placebo control group

Dose adjustment

Participant is treated by febuxostat/placebo starting at a dose of 20mg /day, once a day. If SUA doesn't reach the target (SUA<6mg/dl), or decrease less than 20% at the 4 weeks' visit,

increase dosage to 40mg/d once per day. If SUA doesn't reach target at 8 weeks' visit, increase dosage to (for those who are at dosage of 20mg/day) or maintain dosage (for those who are at dosage of 40mg/day) at 40mg/d till the end of the study. If at dosage of 40mg/d, SUA >12mg/dl and last for 2 weeks, patients should withdraw from the study for their safety. If at dose of 40mg/d, SUA <3mg/dl, decrease dose to 20mg/d, and check SUA 2 weeks later, if still <3mg/dl, then stop treatment for 2 weeks and check SUA again, if SUA still <3mg/dl, withdraw from the study; if SUA ≥3mg/dl, keep at 20mg/d, till SUA is above target (≥6mg/dl), than increase to 40mg/d.

If SUA reach target or decrease ≥20% at the 4 weeks' visit, maintain at the dose of 20mg/d. If at the dose of 20mg/d, SUA <3mg/dl, then stop treatment and check SUA in 2 weeks, if SUA still <3mg/dl, withdraw from the study. If SUA ≥3mg/dl, keep patients in the study, till the SUA is above the target (≥6mg/dl) and prescribe from 20mg/d again.

Criteria for discontinuing or modifying allocated interventions

1. Subjects with continued withdrawal of more than 2 weeks or intermittently stopping more than one month

2. Subjects who have intolerable side effects

3. Subject who have episodes of gout, if SUA<6mg/dl, remain in the trial after acute treatment; if SUA≥6mg/dl, unblind, treat hyperuricemia and withdraw from the trial

4. Subjects who have no evaluable records available

5. Subjects who have to use prohibited medications due to illness

6. Subjects who have ALT, AST increased to more than 2 times of upper limit of normal or elevated bilirubin to more than 2 times of the upper limit of normal that has persistently elevated for2 weeks

7. Subjects who have SUA>12mg/dl for 2 weeks under the maximum dose of treatment (for how long?)

8. Subjects who have SUA<12mg/dl for 4 weeks under the minimal dose of treatment

9. Subjects who have adverse events and cannot continue the study

10. Subjects who have unexplained complications

11. Subjects who are pregnant during treatment

12. Subjects who have kidney transplantations during the study

13. For safety reasons, the organizers propose to stop the study

14. Ethics Committee decided to discontinue the study subjects

15. The researchers considered unsuitable for continued research subjects

The Investigator may terminate a subject's study participation at any time during the study based on the subject's best interest. In addition, a subject may discontinue his or her participation at any time during the study.

Strategies to improve adherence to interventions

Participants will be followed up monthly at the first 3 months at entry of the study and 3 months thereafter till the end of study. Examinations will involve outpatient appointments in either outpatient clinics or private nephrology practices and will include: History and physical examination, measurement of systolic and diastolic arterial blood pressure, recording of the

frequency, type, severity and duration of adverse events as well as laboratory tests including repeated blood counts.

Relevant concomitant care permitted or prohibited during the trial

Medications to treat concomitant conditions are allowed and are recorded at baseline and each follow-up visit. Participants are encouraged to remain on the same dosage of these medications unless advised otherwise by medical professionals. Participants who used diuretics, losartan should be washed out for 2 weeks before screening, patients who used prednisone≥30mg/d more than 2 weeks and other drugs treat hyperuricemia other than the assigned trial medications are considered to have dropped out of the trial.

Relevant concomitant care permitted or prohibited during the trial included:

1. If taking ACEI/ARB before the trial, can continue but not to increase the dose during the trial; but need to avoid the use of losartan; if not taking ACEI/ARB, do not add during the study.

2. If SBP≥140mmHg or DBP≥90mmHg, adjust the dose of other anti-hypertension drugs except ACEI/ARB

3. Lipid-lowering drugs can be used during the study, use statin to treat high cholesterol and fibrates to treat hypertriglyceridemia mainly in order to maintain normal cholesterol, triglycerides, low-density lipoprotein

4. Anti-glycemic drugs can be used, such as insulin, target glycemic control with HbA1c <7.0%

5. Subjects can use antiplatelet, anticoagulant drugs with LMWH preferred

6. Subjects can use proton pump inhibitors: omeprazole, pantoprazole, etc

7. Subjects can use active vitamin D, calcium, phosphorus lowering drugs

8. Subjects can use folic acid, iron, EPO and other anemia drugs with target Hb 100-120g/L

9. If diuretics needed, avoid thiazide diuretics

10. Avoid long-term use of corticosteroids (subjects use prednisone <30mg/d, or equivalent amount of other hormones and the use of <2 weeks can be enrolled)

11. Avoid using allopurinol, benzbromarone, febuxostat or probenecid

12. Avoid long-term use of salicylic acid drugs (except low-dose aspirin), diuretics, losartan)

13. Avoid the use of immunosuppressive agents, such as cyclophosphamide, MMF, CsA, FK506, azathioprine, vidarabine, leflunomide, Tripterygium glycosides , CD20 antibody, didanosine.

Outcomes

The primary outcome is cardiovascular events composing of cardiovascular mortality and non-fatal cardiovascular events, cardiovascular mortality includes deaths caused by acute myocardial infarction, fatal arrhythmia, sudden death, cardiomyopathy, heart failure, and stroke; non-fatal cardiovascular events includes non-fatal acute myocardial infarction, hospital admission of heart failure, unstable angina, atherosclerotic disease needed hospitalization (including aneurysm, arterial dissection, arteriosclerosis occlusion), non-fatal stroke, transient ischaemic attack or lower limb ischaemia.

Secondary outcomes include all-cause mortality, cardiovascular mortality and non-fatal cardiovascular events separately.

Participant timeline

All participants who are eligible and who have signed the informed consent will be randomized to one of the two treatment groups. Study flowchart was shown in Figure 1. Treatment in both groups and follow-up will last for another 3 years. Examinations will involve outpatient appointments in either outpatient clinics or private nephrology practices and will include: History and physical examination, measurement of systolic and diastolic arterial blood pressure, recording of the frequency, type, severity and duration of adverse events as well as laboratory tests including repeated blood counts. Intervals between examinations vary from monthly (start of study) to 3 monthly (end of study). An overview of examinations is given and obligatory measurements during the trial are given in table 1.

Table 1 Data collection items and activities by visit during the study period of the LUMINA Study

	SCREENING PERIOD visit 1 -3 weeks to day 0		visit 2 1st month(mo) (±7d)	visit 3 2nd mo (±7d)	visit 4 3rd mo (±7d)	visit 5 6th mo (±7d)	visits every 3 mo	v15 36 mo
	washout(-3 weeks to -1week)	Visit 1a(-1 week to day0)						
Physical examination		+		+	+	+	+	+
Blood routine		+		+	+	+	+	+
Urine routine		+		+	+	+	+	+
Uric creatinien		+		+	+	+	+	+
Glycosylated hemoglobin		+				+	+	+
Serum uric acid		+		+	+	+	+	+
Creatinine, potassium, sodium, calcium, phosphorus, bicarbonate, bilirubin, albumin		+		+	+	+	+	+
Parathyroid Hormone		+				+	+	+
Erythropoietin, folic acid, serum feritin, transferrin		+				+	+	+

Serum lipid		+		+	+	+	+	+
24h urine output		+		+	+	+	+	+
Dialysis dose		+		+	+	+	+	+
Kt/V, renal creatinine clearance rate, peritoneal creatinine clearance rate		+		+	+	+	+	+
Peritoneal Equilibrium Test (PET)		+					every 6 mo	+
24h ultrafiltration		+		+	+	+	+	+
Pregnacy test (Female)		+		+	+	+	+	+
Electrocardiograph (ECG)		+				+	+	+
Cardiac uhrasonography and vascular ultrasound		+					every 12m o	+

*Note: Treatment in both groups and follow-up will last for another 3 years. In the first 3 months at the start of study, visit interval will be monthly. After that, visit interval will be three monthly till the end of study. Examinations will involve outpatient appointments in either outpatient clinics or private nephrology practices and will include: History and physical examination, measurement of systolic and diastolic arterial blood pressure, recording of the frequency, type, severity and duration of adverse events as well as laboratory tests including repeated blood counts.

Sample size

According to previous studies, 3-year CVD event-free survival was 55% in non-intervening patients, and 3-year CVD event-free survival was 68% in intervening patients, based on a power of 80%, with type I error α=0.05, two-sided test, and 1:1 parallel control study, a sample size about 219 cases is estimated. But considered a 20% drop-out rate due to loss of contact and quitting, it is designed to recruit 274 patients from each group, and a total of 548 patients will be needed. The patients will be assigned randomly into the intervention group or the control group.

Recruitment

Each center had routine peritoneal dialysis population. These patients were followed up routinely. Each center will screen subjects to achieve the target population is achieved (548 subjects) from these populations. The enrollment period will extend over 24 months. Research assistants and investigators screen participants from the routine clinical visits. The enrollment period was over 24 months. Up to December 31, 2019, all patients have been enrolled.

Allocation

Sequence generation

To ensure that numbers in the intervention group and the control group equal to each other in each center, stratified randomization method will be used according to the center. And patient will be randomly assigned to one of the two treatments in each center. Allocation sequence was generated by computer-generated random numbers with the help of SAS9.2 software.

Allocation concealment mechanism

Tablets of febuxostat and placebo will be made and wrapped in the same appearance. Allocation sequence was generated with the help of SAS9.2 software, When participants were enrolled, investigators would randomly distribute an allocation sequence to the participant using SAS 9.2 software (randomization number), and the corresponding number of study tablets would be distributed to the participants. During these processes, trial participants and investigators are blinded to the treatment,

Implementation

Investigators would randomly distribute an allocation sequence to the participant using SAS 9.2 software (randomization number), and the corresponding number of study tablets would be distributed to the participants.

Blinding

Who will be blinded and how

After assignment to interventions, trial participants, care providers, outcome assessors, data analysts will be blinded. The placebo and febuxostat will be provided in the same tablet and the same packaging (including labels) to protect the blindness. Use the kit number to mark each double-blind treatment. The researchers will obtain the kit number through a random procedure when patients are randomly grouped, At the same time, during treatment and follow-up, patients, researchers and research center staff could not obtain which group the patients were assigned to.

Procedure for unblinding if needed

Blindness can be broken only in order to treat subjects and must know which treatment group they are randomly assigned to.

Blindness can be broken at any time by using the corresponding module of the medical record and/or by calling the sponsor. If the blindness is broken, the researcher should record the date, time, and cause of the unblindness, and report this information (or "required relevant information") on the appropriate page of the case report form (CRF).

When recording the causes of unblindness, the researcher must not provide any detailed information related to the nature of the drug in the study. Until the database is closed, the researcher shall not disclose the details of the research drug to the sponsor representative or

any staff. In addition, when completing forms, research treatments shall not be disclosed in these tables. After breaking the blindness, the patient must withdraw from the study.

Data collection methods

All patients who are eligible and who have signed the informed consent will be randomized to one of the two treatment groups. Treatment in both groups and follow-up will last for another 3 years. Examinations will involve outpatient appointments in either outpatient clinics or private nephrology practices and will include: History and physical examination, measurement ofsystolic and diastolic arterial blood pressure, recording of the frequency, type, severity and duration of adverse events as well as laboratory tests including repeated blood counts. Intervals between examinations vary from monthly (at the first 3 months at entry of the study) to 3 monthly (from 3 months after entry to the end of study). An overview of examinations is given and obligatory measurements during the trial are given in table 1. Baseline characteristic, lab tests and examinations in every visit, adverse events and outcomes etc will be recorded.

Plans to promote participant retention and complete follow-up

Participants would be followed up by clinical visits monthly at the first 3 months at entry of the study and every 3 months thereafter. Research assistants and nurses would follow up the participants' outcome data and adverse events and reported to the investigators.

Data management

A case report form (CRF) is provided for every study participant, where all information about examinations and visits have to be recorded. Following the completion of the form, the original should be sent to the Trial Office and the carbon copy kept by the centre. These

carbon copies may be required should the original be lost and for comparison of the patient data at the end of the study. Documents of the study are subdivided into five categories: recruiting documents,randomization documents, patient books (CRFs), correction documents and evaluation documents. The pages of the CRFs will be originals with integrated carbon copies. Following the completion of the form, the original should be sent to the Trial Office and the carbon copy kept by the centre. All data will be entered into the database. The database is developed and administered centrally by the responsible personnel at the institute of medical statistics, but data entry maybe achieved in a distributed manner within the trial office. The database will provide online plausibility checks, Log file and backup mechanisms. Completeness of the patient data and has to be checked. This is supported by plausibility checks. Double data entry will be conducted. The documentation of the patients will be monitored by the documentation centre. In order to maintain the time course of the follow-up examinations of the participants, each physician will receive, after submitting the initial patient documents (recruitment documentation, consent form, medical history and therapy protocol) a list of preferred dates for follow-up examinations. In the documentation centre all patient data will be checked for completeness and plausibility. Should patient documents be incomplete, contain mistakes or be ambiguous, the documentation centre will send a correction form (if necessary with a copy of the incompletepatient documents) to the treating physician. It is required that the treating physician fills in thecorrection form and returns it to the documentation centre. The execution of each step of the statistical analysis (data modification, data transformation, description of the data, statistical tests) must be logged in a protocol by the documentation and statistical centre.

Statistical methods

Statistical methods for primary and secondary outcomes

Descriptive statistics will be used to analyse the means and distribution between all the study variables. The means of the normal distributed variables will be compared with the student T-test and non-parametric tests (Mann-Whitney U-test for continued and Chi-Square test for nominal variables) will be used for the variables that do not follow a normal distribution. Missing values will be imputed using multiple imputation techniques. Comparisons between groups will be based on types of variables and appropriate methods in analyses. Kaplan Meier survival curve will be used to estimate the difference in survival rates between groups, while Log-rank test and multivariable cox regression will be used to analyze the latter. During the data-analysis, sensitivity analyses will be conducted by adding an additional covariate in the mixed model to account for rescue medication required during the study.

Methods for additional analyses

No applicable.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data

Per-Protocol population (PP) who have protocol adherence between 80%-120%, no serious violation of the protocol, no missing data on the primary outcomes will be included in the analysis. Multiple imputation will be used to handle missing data.

Monitoring

Composition of the data monitoring committee

No applicable. As this study is funded by our university also, there is a scientific research department who is independent of the investigators and will act as safeguard the interests of

trial participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the trial.

Harms

The adverse reactions of febuxostat include liver function damage, allergic reaction such as systemic skin rash, and acute episode of gout. Study drugs should be stopped if the adverse reactions occur and proper treatment should be given. All adverse events, whether related to study drugs or not, should be recorded in detail on the case report form. When the adverse event is considered not related to study drug, possible reasons should be given. The report of adverse event should include the following information: name of the adverse event, occurrence time, end time, study drug information (dose, capacity, treatment date and time or time interval), severity of the adverse event, the relationship of the adverse event and study drugs, treatment of the adverse event, and whether it is serious adverse event. Researchers must track all adverse events until they are resolved or explained by other reasons. Serious adverse events were defined according to the globally accepted definitions in the International Conference on Harmonization Guideline for Clinical Safety Data Management. For serious adverse events, the researchers should fill out the adverse event report form and report them to the principal investigators, security commissioner, the Ethics Committee Report and China Food and Drug Administration (CFDA) within 24 hours. Serious adverse events were recorded from the time the patient consented to be in the study through 30 days after study exit.

Auditing

Auditing would be conducted every 6 months, the process will be independent from

investigators and the sponsor. Representatives of the Sponsor or its designee must be allowed to visit the study centerperiodically to assess the quality of the data and the integrity of the study. The representatives will review study records at the study center and directly compare these with the source documents, discuss the conduct of the study with the Investigator, and verify the appropriateness of the conduct of the study. In addition, the study may be evaluated by the Sponsor's internal auditors who must be allowed access to eCRFs, source documents, and other study files. The Sponsor audit reports will be kept confidential.

The Investigator or a designated member of the Investigator's staff must be available at some time during the monitoring visits to review data, resolve any queries, and allow direct access to subjects' records (eg, medical records, office charts, hospital charts, andstudy-related charts) for source data verification. The eCRFs must be completed before each visit and be made available to the Sponsor's representative in order that the accuracyand completeness of the eCRF may be checked.

Ethics and dissemination

This study has been approved by the Medical Ethics Committee of the First Affiliated Hospital, Sun Yat-sen University and the ethics committees of other participating institutions. The investigators will obtain informed consent or assent from potential trial participants or authorised surrogates. Investigators will go through all the participants case history and lab tests, and screen participants according to inclusion and exclusion criteria, if participant is eligible to the study, the investigator will talk with the participants and their authorized surrogates about the trial, including time scheme, benefits and risks and so on, and answered the questions participants have about the trial, after these, investigators obtained written

informed consent from the potential trial participants or authorised surrogates.

No additional consent provisions for collection and use of participant data and biological specimens in ancillary studies is applicable in this trial.

Confidentiality

All subject information, medical records, and laboratory data will be kept confidential.Information and data may be discussed, analyzed, and reported for the purposes of thisclinical study only. However, code numbers will identify the subject on the eCRFs and inany reports, and the subject's identity will be kept confidential.

Declaration of interests

The work was sponsored by WanBang Pharmaceutical Marketing and Distribution Co. China. All authors declared no conflicts of interest.

Access to data

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

Ancillary and post-trial care

No applicable.

Dissemination policy

Findings will be disseminated through publications in peer-reviewed journals, and presentations at national and international conferences.

Discussion

Hyperuricemia has been reported to be an independent predictor for cardiovascular outcome

in general patients and in CKD patients [7-15]. However, there are limited studies to examine the relationship between serum uric acid levels with cardiovascular mortality in patients on maintenance dialysis. A multicenter observational study from China that included 2264 patients on maintenance PD, with a median follow up of 26.5 months, found that for each 1mg/dl increase in serum uric acid increase 12% risk in cardiovascular death, and a 5% increase in all-cause mortality[4]. From our center, it was found that for each 1mg/dl increase in serum uric acid in male patients, risks of cardiovascular and all-cause mortality increased by 44% and 33% respectively [27].

Lowering serum uric acid was demonstrated to benefit renal outcomes [26, 28]. In the recently published FREED study, febuxostat lowers uric acid and delays the progression of renal dysfunction [29]. However, whether treatment of hyperuricemia could improve their cardiovascular outcomes in dialysis patients, it is still an imperative topic to be explored.

The present LUMINA study is designed to answer this question whether treatment of hypeuricemia will benefit cardiovascular outcomes in PD patients. It will provide evidence on effect of lowering uric acid on cardiovascular outcomes in PD patients.

The LUMINA study has some limitations. Firstly, we recruit prevent and incident patients concurrently, which might have some bias in baseline characteristics. Secondly, since center management capability is not parallel in different centers, thus may lead to center bias in the study. However, it also has some strength. It is a multicenter, randomized, double blinded and controlled design, and has sufficient power to detect a clinically significant difference on effect of cardiovascular events between treatment and not treatment of hyperuricemia in PD patients.

To our knowledge, LUMINA study is the first trial focusing on lowering hyperuricemia treatment and cardiovascular outcomes in PD patients. Results of this study will provide evidence on whether lowering hyperuricemia treatment is of clinical value in PD patients.

Acknowledgments

The authors acknowledge the participants for their time and their extraordinary commitment to the LUMINA trial. The authors also acknowledge all members of the LUMINA Collaborative Research Group, which includes investigators and staff from 24 clinical centers, the Data Coordinating Center, and the primary sponsor, WanBang Pharmaceutical Marketing and Distribution Co. The 24 clinical centers are The First Affiliated Hospital, Sun Yat-Sen University, The Affiliated Tongji Hospital of Tongji University, The Second Affiliated Hospital of Suzhou University, The Second Xiangya Hospital of Central South University, The Third Xiangya Hospital of Central South University, The First Affiliated Hospital of Xi'an Jiaotong University, The First Hospital of Jilin University, Henan Provincial People's Hospital, The First Affiliated Hospital of Nanchang University, Sichuan Provincial People's Hospital, The First Affiliated Hospital of Guangxi Medical University, General Hospital of Ningxia Medical University, Zhejiang Provincial People's Hospital, Nanjing First Hospital, Pingdingshan First People's Hospital, The First Affiliated Hospital of Zhengzhou University, The Second Hospital of Shanxi Medical University, Xiangya Hospital Central South University, Wuxi Second People's Hospital, Chenzhou No.1 People's Hospital, Shengjing Hosptial of China Medical University, Yancheng City No.1 People's Hospital, The First People's Hospital of Kunshan, Zhenjiang First People's Hospital.

Disclosure and conflicts of interest

554 The work was sponsored by WanBang Pharmaceutical Marketing and Distribution Co. China.

555 All authors declared no conflicts of interest.

556

Figure 1. Study flow chart

Reference

[1] Kubo S, Nishida Y, Kubota Y, et al. Higher serum uric acid level is inversely associated with renal function assessed by cystatin C in a Japanese general population without chronic kidney disease: the KOBE study. *BMC Nephrol* 2019; 20:117.

[2] Weiner D E, Tighiouart H, Elsayed E F, et al. Uric acid and incident kidney disease in the community. *J Am Soc Nephrol* 2008; 19:1204-1211.

[3] Iseki K, Oshiro S, Tozawa M, et al. Significance of hyperuricemia on the early detection of renal failure in a cohort of screened subjects. *Hypertens Res* 2001; 24:691-697.

[4] Dong J, Han Q F, Zhu T Y, et al. The associations of uric acid, cardiovascular and all-cause mortality in peritoneal dialysis patients. *PLoS One* 2014; 9:e82342.

[5] Liu R, Han C, Wu D, et al. Prevalence of Hyperuricemia and Gout in Mainland China from 2000 to 2014: A Systematic Review and Meta-Analysis. *Biomed Res Int* 2015; 2015:762820.

[6] Li Z, Liu Q, Mao H, et al. Gender difference in the association of hyperuricemia with chronic kidney disease in southern China. *Kidney Blood Press Res* 2012; 36:98-106.

[7] Chen J H, Chuang S Y, Chen H J, et al. Serum uric acid level as an independent risk factor for all-cause, cardiovascular, and ischemic stroke mortality: a Chinese cohort study. *Arthritis Rheum* 2009; 61:225-232.

[8] Fang J, Alderman M H. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971-1992. National Health and Nutrition Examination Survey. *JAMA* 2000; 283:2404-2410.

[9] Krishnan E, Svendsen K, Neaton J D, et al. Long-term cardiovascular mortality among middle-aged men with gout. *Arch Intern Med* 2008; 168:1104-1110.

[10] Choi H K, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. *Circulation* 2007; 116:894-900.

[11] Liese A D, Hense H W, Lowel H, et al. Association of serum uric acid with all-cause and cardiovascular disease mortality and incident myocardial infarction in the MONICA Augsburg cohort. World Health Organization Monitoring Trends and Determinants in Cardiovascular Diseases. *Epidemiology* 1999; 10:391-397.

[12] Niskanen L K, Laaksonen D E, Nyyssonen K, et al. Uric acid level as a risk factor for cardiovascular and all-cause mortality in middle-aged men: a prospective cohort study. *Arch Intern Med* 2004; 164:1546-1551.

[13] Hoieggen A, Alderman M H, Kjeldsen S E, et al. The impact of serum uric acid on cardiovascular outcomes in the LIFE study. *Kidney Int* 2004; 65:1041-1049.

[14] Hozawa A, Folsom A R, Ibrahim H, et al. Serum uric acid and risk of ischemic stroke: the ARIC Study. *Atherosclerosis* 2006; 187:401-407.

[15] Liu W C, Hung C C, Chen S C, et al. Association of hyperuricemia with renal outcomes, cardiovascular disease, and mortality. *Clin J Am Soc Nephrol* 2012; 7:541-548.

[16] Imazu M, Yamamoto H, Toyofuku M, et al. Hyperinsulinemia for the development of hypertension: data from the Hawaii-Los Angeles-Hiroshima Study. *Hypertens Res* 2001; 24:531-536.

[17] Bonora E, Capaldo B, Perin P C, et al. Hyperinsulinemia and insulin resistance are independently associated with plasma lipids, uric acid and blood pressure in non-diabetic subjects. The GISIR database. *Nutr Metab Cardiovasc Dis* 2008; 18:624-631.

[18] Kuwabara M, Borghi C, Cicero A, et al. Elevated serum uric acid increases risks for developing

high LDL cholesterol and hypertriglyceridemia: A five-year cohort study in Japan. *Int J Cardiol* 2018; 261:183-188.

[19] Lin J D, Chiou W K, Chang H Y, et al. Serum uric acid and leptin levels in metabolic syndrome: a quandary over the role of uric acid. *Metabolism* 2007; 56:751-756.

[20] Wasada T, Katsumori K, Saeki A, et al. Hyperuricemia and insulin resistance. *Nihon Rinsho* 1996; 54:3293-3296.

[21] Zhou Y, Zhao M, Pu Z, et al. Relationship between oxidative stress and inflammation in hyperuricemia: Analysis based on asymptomatic young patients with primary hyperuricemia. *Medicine (Baltimore)* 2018; 97:e13108.

[22] Tomiyama H, Shiina K, Vlachopoulos C, et al. Involvement of Arterial Stiffness and Inflammation in Hyperuricemia-Related Development of Hypertension. *Hypertension* 2018; 72:739-745.

[23] Goicoechea M, de Vinuesa S G, Verdalles U, et al. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. *Clin J Am Soc Nephrol* 2010; 5:1388-1393.

[24] Siu Y P, Leung K T, Tong M K, et al. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. *Am J Kidney Dis* 2006; 47:51-59.

[25] Tsuruta Y, Nitta K, Akizawa T, et al. Association between allopurinol and mortality among Japanese hemodialysis patients: results from the DOPPS. *Int Urol Nephrol* 2014; 46:1833-1841.

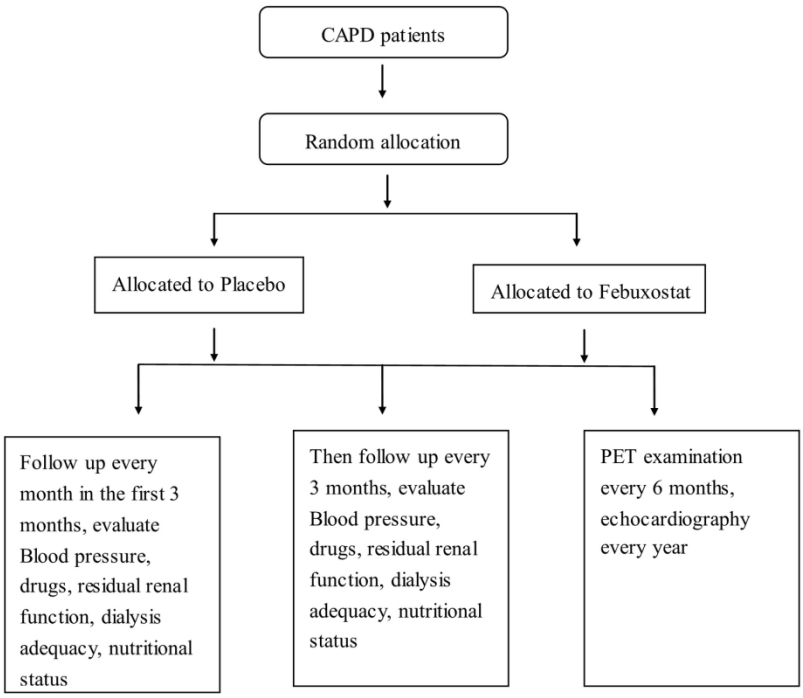
[26] Goicoechea M, de Vinuesa S G, Verdalles U, et al. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. *Clin J Am Soc Nephrol* 2010; 5:1388-1393.

[27] Xia X, He F, Wu X, et al. Relationship between serum uric acid and all-cause and cardiovascular mortality in patients treated with peritoneal dialysis. *Am J Kidney Dis* 2014; 64:257-264.

[28] Bose B, Badve S V, Hiremath S S, et al. Effects of uric acid-lowering therapy on renal outcomes: a systematic review and meta-analysis. *Nephrol Dial Transplant* 2014; 29:406-413.

[29] Kojima S, Matsui K, Hiramitsu S, et al. Febuxostat for Cerebral and CaRdiorenovascular Events PrEvEntion StuDy. *Eur Heart J* 2019; 40:1778-1786.

Figure 1. Study flow chart



Study flow chart

178x167mm (300 x 300 DPI)

BMJ Open

The rationale and design for Lowering-hyperUricemia treatment on cardiovascular outcoMes In peritoNeal diAlysis patients: a prospective, multicentre, double-blind, randomized controlled trial (LUMINA)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-037842.R1
Article Type:	Protocol
Date Submitted by the Author:	28-Jul-2020
Complete List of Authors:	Chen, Wei; Sun Yat-sen University First Affiliated Hospital Department of Nephrology Huang, Naya; Sun Yat-sen University First Affiliated Hospital Department of Nephrology, Mao, Haiping; Sun Yat-sen University First Affiliated Hospital Department of Nephrology Yang, Xiao; Sun Yat-sen University First Affiliated Hospital, Department of Nephrology Zhou, Qian; Sun Yat-sen University First Affiliated Hospital, Department of Medical Statistics, Clinical Trials Unit Jiang, Lanping; Sun Yat-sen University First Affiliated Hospital Department of Nephrology Ding, Jun; Wanbang Pharmaceutical Marketing and Distribution Co., Medical Department Feng, Qiong; Sun Yat-sen University First Affiliated Hospital Department of Nephrology Yu, xueqing; Sun Yat-sen University First Affiliated Hospital, Department of Nephrology; Guangdong Provincial People's Hospital, Department of Nephrology
Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Nephrology < INTERNAL MEDICINE, Dialysis < NEPHROLOGY, CARDIOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

The rationale and design for Lowering-hyperUricemia treatment on cardiovascular outcoMes In peritoNeal diAlysis patients: a prospective, multicentre, double-blind, randomized controlled trial (LUMINA)

Wei Chen[1#], Naya Huang[1#], Haiping Mao[1], Xiao Yang[1], Qian Zhou[2], Lanping Jiang[1], Jun Ding[3], Qiong Feng[1], Xueqing Yu[1,4*]

1 Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, Key Laboratory of Nephrology, Ministry of Health of China, Guangdong Provincial Key Laboratory of Nephrology, Guangzhou, Guangdong, China

2 Department of Medical Statistics, Clinical Trials Unit, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

3 Medical Department, Wanbang Pharmaceutical Marketing and Distribution Co., Jiangsu, China

4 Guangdong Provincial People's Hospital, School of Medicine, South China University of Technology, Guangzhou, China

# These authors contributed equally to this work.

* Corresponding author

Correspondence to:

Xueqing Yu, M.D, PhD

Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, NHC Key Laboratory of Nephrology (Sun Yat-sen University), Guangdong Provincial Key Laboratory

of Nephrology; Guangdong Provincial People's Hospital, School of Medicine, South China University of Technology
Guangzhou 510080, China
Phone: 8620 87766335
Fax: 8620 87769673
E-mail: yuxq@mail.sysu.edu.cn

Word counts: 4439 words.

Keywords: Hyperuricemia, cardiovascular outcomes, peritoneal dialysis

Abstract

Introduction

The prevalence of hyperuricemia in peritoneal dialysis patients is quite high. Studies have demonstrated a correlation between hyperuricemia and cardiovascular disease and treatment of hyperuricemia reportedly reduces cardiovascular risk in chronic kidney disease (CKD) patients. However, whether hyperuricemia treatment benefits cardiovascular outcomes in continuous ambulatory peritoneal dialysis (CAPD) patients is not yet known.

Methods and analyses

This prospective, multicentre, double-blind, randomized controlled trial was designed to evaluate the effects of hyperuricemia treatment on cardiovascular event risk in CAPD patients. Based on a power of 80%, with type I error α=0.05, two-sided test, and 1:1 parallel control study, considering a dropout rate of 20%, a total of 548 eligible patients are expected to be randomly assigned to either the hyperuricemia treatment group (febuxostat) or control group (placebo).

Ethics and dissemination

This study has been approved by the Medical Ethics Committee of the First Affiliated Hospital, Sun Yat-sen University and the ethics committees of other participating institutions. Written informed consent will be obtained from potential trial participants or authorised surrogates.

The findings of the study will be disseminated through publications in peer-reviewed journals, and presentations at national and international conferences.

Trial Registration: ClinicalTrials.gov

Trial number: NCT03200210

Registered: 25 June, 2017

The trial was started on July 13, 2017, and is expected to end by December 31, 2022. Till Jan 20, 2020, a total of 548 patients have been recruited.

Strengths and limitations of this study

1. To our knowledge, this is the first large sample size randomized clinical trial to evaluate whether high uric acid level is a potentially modifiable risk factor for cardiovascular mortality in peritoneal dialysis patients.
2. This is a prospective, multicentre, double-blind, randomized controlled trial powerful enough to test the hypothesis.
3. The LUMINA study has some limitations. First, we recruit prevalent and incident patients concurrently, which might create some bias in baseline characteristics
4. Secondly, since centre management capability is not parallel across different centres, to the potential centre bias exists in this study.

Protocol version

The protocol version number and date are YLT-1604-V2.0, December 15, 2016,

Funding

The work was sponsored by Wanbang Pharmaceutical Marketing and Distribution Co. China, and this work was supported by the National Key Technology Research and Development Program of China (2016YFC0906101), an Operational Grant of Guangdong Provincial Key

Laboratory (2017B030314019), the Key Laboratory of Nephrology, Guangdong Province, Guangzhou, China (2002B60118), 5010 Clinical Program of Sun Yat-sen University (2017007), the Natural Science Foundation of Guangdong Province, China (Grant no.2017A030310199), the National Natural Science Foundation of China (Grant no.81800632), the Natural Science Foundation of China (Grant no. 81600545), National Natural Science Foundation of China (Grant no. 81600592), and the Natural Science Foundation of Guangdong Province, China (Grant no.2018A030310273).

Roles and responsibilities:

Author details:

Xueqing Yu is the corresponding author.

Drs. Wei Chen and Naya Huang contributed equally to this work.

Contributions:

All authors have made substantial contributions to this work. Contributions of the authors are listed below.

Conceptualization: Xueqing Yu

Data curation: Wei Chen,

Formal analysis: Qian Zhou, Naya Huang

Funding acquisition: Xueqing Yu

Investigation: Naya Huang, Wei Chen, Haiping Mao, Xiao Yang, Lanping Jiang, Qiong Feng

Methodology: Naya Huang, Wei Chen, Qian Zhou, Jun Ding

Project administration: Wei Chen, Xueqing Yu

Resources: Xueqing Yu, Jun Ding

Software: Naya Huang, Qian Zhou

Supervision: Xueqing Yu

Validation: Wei Chen, Xueqing Yu

Visualization: Wei Chen, Naya Huang

Roles/Writing - original draft: Naya Huang, Wei Chen

Writing - review &editing: Naya Huang, Wei Chen, Xueqing Yu

Author details are listed below:

1. Wei Chen, Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, Key Laboratory of Nephrology, Ministry of Health of China, Guangdong Provincial Key Laboratory of Nephrology, Guangzhou, Guangdong, China, vvchen66@qq.com;

2. Naya Huang, Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, Key Laboratory of Nephrology, Ministry of Health of China, Guangdong Provincial Key Laboratory of Nephrology, Guangzhou, Guangdong, China, huangnaya@163.com

3.Haiping Mao, Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, Key Laboratory of Nephrology, Ministry of Health of China, Guangdong Provincial Key Laboratory of Nephrology, Guangzhou, Guangdong, China, haipingmao@126.com

4. Xiao Yang, Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, Key Laboratory of Nephrology, Ministry of Health of China, Guangdong

Provincial Key Laboratory of Nephrology, Guangzhou, Guangdong, China, yangxsysu@126.com

5. Qian Zhou, Department of Medical Statistics, Clinical Trials Unit, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China, zhouqian2017@163.com

6. Lanping Jiang, Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, Key Laboratory of Nephrology, Ministry of Health of China, Guangdong Provincial Key Laboratory of Nephrology, Guangzhou, Guangdong, China, fuzhi626@126.com

7. Jun Ding, Medical Department, Wanbang Pharmaceutical Marketing and Distribution Co., Jiangsu, China, dingjun0411@163.com

8. Qiong Feng, Department of Nephrology, The First Affiliated Hospital, Sun Yat-sen University, Key Laboratory of Nephrology, Ministry of Health of China,Guangdong Provincial Key Laboratory of Nephrology, Guangzhou, Guangdong, China, fengqiong2016@126.com

9. Xueqing Yu, Sun Yat-sen University, Key Laboratory of Nephrology, Ministry of Health of China, Guangdong Provincial Key Laboratory of Nephrology, Guangzhou, Guangdong, China, Guangdong Provincial People's Hospital, School of Medicine, South China University of Technology, Guangzhou, China, yuxq@mail.sysu.edu.cn

Name and contact information for the trial sponsor

The work was sponsored by the Wanbang Pharmaceutical Marketing and Distribution Co. China., No.6 Yangshan Rd, Economic Zone, Xuzhou, Jiangsu, China, 221004.

Role of sponsor

The sponsor participated in the design of the study, but had no role in the collection, management, analysis or interpretation of data, writing of the report, or the decision to submit the report for publication.

Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)

Not applicable.

Introduction

Background and study rationale

Elevated serum uric acid (SUA) seen in patients with chronic kidney disease (CKD), partly arises from overproduction of purines due to hypercatabolism, as well as reduced excretion of uric acid by the kidneys. It previously was shown that there was a correlation between higher uric acid levels and lower glomerular filtration rate (GFR) [1-3]. Hyperuricemia is common in the general population with a prevalence of 13.3-42.1% [4-6]. Based on an epidemiological study in Southern China, the prevalence of hyperuricemia in the adult population is as high as 31.9% [6]. Reduced GFR is seen in CKD patients and understandably conveys a higher prevalence of hyperuricemia than tin the general population. Our local data revealed that the prevalence of hyperuricemia at our peritoneal dialysis (PD) center is 63.1% [6].

Many epidemiologic and clinical studies have demonstrated a correlation between hyperuricemia and cardiovascular diseases [7-15]. The literature also suggests hyperuricemia is associated with other classical cardiovascular risk factors, such as hypertension [16],

diabetes mellitus [17], hyperlipidaemia [18], obesity and insulin resistance [19, 20]. Evidence shows that elevated in serum uric acid levels facilitate the oxidation of low density lipoprotein cholesterol [18], and hyperuricemia is accompanied by increased free oxygen radical production, which plays a role in inflammation [21]. Furthermore, elevated uric acid levels facilitate platelet aggregation, increasing the risk for arterial thrombus formation [22]. These features contribute to a higher risk of cardiovascular events.

Treatment of hyperuricemia reportedly independently reduces renal disease progression in CKD patients [23, 24], and treatment of hyperuricemia was associated with reduced mortality among haemodialysis (HD) patients with no history of cardiovascular disease (CVD) in the Dialysis Outcomes and Practice Patterns Study (DOPPS) study in Japan [25]. Additionally, in CKD patients, treatment of hyperuricemia has been shown to reduce cardiovascular risk [26]. However, whether treatment that lowers uric acid would benefit cardiovascular outcomes in CKD patients, especially in maintenance dialysis patients, is not yet known.

Objectives

To investigate whether hyperuricemia-lowering therapy through use of febuxostat reduces the risk of cardiovascular events in CAPD patients.

Trial design

The study is a prospective, multicentre, double-blind, randomized controlled trial.

Methods

Study setting

The study is being conducted in mainland China across 24 academic hospitals. A complete list of study sites is given in the acknowledgements.

Inclusion criteria:

1. Subjects who are able to understand and have voluntarily signed the informed consent form (ICF)

2. Adults aged 18-70 at the time of randomization

3. Subjects on PD for longer than 3 months

4. Subjects with hyperuricemia defined as follows: female: 6mg/dl(360μmol/L) <sUA<12mg/dl(720μmol/L)； male: 7mg/dl(420μmol/L) <sUA<12mg/dl(720μmol/L)

Exclusion criteria:

1. Subjects who have a history of gout

2. Subjects who have a myocardial infarction, unstable angina, cardiovascular reconstructive surgery (such as a stent or bypass surgery), cerebrovascular accident 12 weeks prior to randomization, or planned cardiovascular reconstructive surgery during the trial

3. Subjects who have New York stage IV heart failure within 4 weeks prior to screening

4. Subjects who have previously received kidney transplantation and are currently prescribed immunosuppressive therapy

5. Subjects who have severe liver disease, such as acute hepatitis, chronic active hepatitis, cirrhosis

6. Subjects who have alanine aminotransferase (ALT) levels greater than 2 folds the upper limit of normal or total bilirubin greater than 1.5 folds the upper limit of normal

7. Subjects who have experienced severe infections within 4 weeks prior to the screening, such as pneumonia or peritoneal dialysis-related peritonitis;

8. Subjects who have had a major surgery within 12 weeks prior to screening or who are not yet fully recovered from surgery

9. Subjects who have a malignancy

10. Subjects who report a history of illicit drug use or a regular or daily alcohol consumption of ≥ 4 alcoholic drinks per day in the 2 years prior to screening

11. Subjects who are allergic to febuxostat

12. Subjects who are enrolled in other clinical studies within 4 weeks prior to or at randomization

13. Subjects who are currently taking mercaptopurine, azathioprine, vidarabine ordidanosine

14. Subjects who are taking losartan, fenofibrate, thiazide diuretics or loop diuretics within 4 weeks of randomization

15. Subjects who require long-term use of steroids (prednisone <30mg/d, or equivalent amount of other steroids and use of <2 weeks can be enrolled)

16. Subjects who require long-term use of salicylic acid drugs except low-dose aspirin

17. Fertile, lactating patients who are unwilling or unable to take contraceptives

Patient and Public Involvement

We state that neither patients nor the public WERE involved in the design, conduct, reporting, or dissemination plans of our research.

Interventions

Eligible patients will be randomly assigned to the febuxostat treatment group or the placebo control group

Dose adjustment

Participants are treated with febuxostat/placebo starting at a dose of 20mg /day, once a day. If SUA does not reach the target level (SUA<6mg/dl) or decreases less than 20% at the 4-week visit, the dosage is increased to 40mg/d once per day. If SUA does not reach target at the 8-week visit, the dosage is increased to 40mg/day (for those who are at dosage of 20mg/day) or the dosage is maintained (for those who are at dosage of 40mg/day) until the end of the study. If at dosage of 40mg/d and SUA remains >12mg/dl for 2 weeks, patients are withdrawn from the study for their safety. If SUA reaches <3mg/dl at dose of 40mg/d, the dose decreased to 20mg/d, and SUA is checked 2 weeks later. At that time, if SUA is still <3mg/dl, treatment is stopped for 2 weeks, and SUA is checked again, if SUA still <3mg/dl, patients are withdrawn from the study. if SUA is ≥3mg/dl, the 20mg/d dose is maintained, until SUA is above the target level (≥6mg/dl), at which point the dose is increased to 40mg/d.

Criteria for discontinuing or modifying allocated interventions

1. Subjects with continued withdrawal of more than 2 weeks or intermittently stopping more than one month

2. Subjects who experience intolerable side effects

3. For subjects who have episodes of gout, if SUA remains <6mg/dl, patients are kept in the trial after acute treatment; however, if SUA ≥6mg/dl, patient allocation is unblinded, hyperuricemia is treated, and patients are withdrawn from the trial

4. Subjects who have no evaluable records available

5. Subjects who have to use prohibited medications due to illness

6. Subjects who have ALT, or AST increases to greater than 2 times of upper limit of normal or elevated bilirubin to more than 2 times the upper limit of normal that has been persistently elevated for2 weeks

7. Subjects who have SUA>12mg/dl for 2 weeks who are on the maximum treatment dose

8. Subjects who have SUA<12mg/dl for 4 weeks who are on the minimal dose of treatment

9. Subjects who have adverse events and cannot continue the study

10. Subjects who have unexplained complications

11. Subjects who become pregnant during treatment

12. Subjects who have kidney transplantations during the study

13. If, for safety reasons, the organizers propose to stop the study

14. If the Ethics Committee decides to discontinue the study

15. If the research is considered unsuitable for continued research subjects

The investigator may terminate a subject's study participation at any time during the study based on the subject's best interest. In addition, a subject may discontinue his or her participation at any time during the study.

Strategies to improve adherence to interventions

Participants will be followed up monthly during the first 3 months of the study and every 3 months thereafter until the end of the study. Examinations involve outpatient appointments in either outpatient clinics or private nephrology practices and will include: history and physical examination, measurement of systolic and diastolic arterial blood pressure, recording of the frequency, type, severity and duration of adverse events as well as laboratory tests that include repeated blood counts.

Relevant concomitant care permitted or prohibited during the trial

Medications to treat concomitant conditions are allowed and are recorded at baseline and each follow-up visit. Participants are encouraged to remain on the same dosage of these medications unless advised otherwise by medical professionals. Participants who used diuretics, losartan should be asked to discontinue use for 2 weeks before screening, and patients who used prednisone≥30mg/d for more than 2 weeks and other drugs that treat hyperuricemia other than the assigned trial medications are considered to have dropped out of the trial.

Relevant concomitant care permitted or prohibited during the trial

1. If taking ACEI/ARB before the trial, patients can continue but are not to increase the dose during the trial; however, the need to avoid the use of losartan. If patients are not taking ACEI/ARB at the time of enrolment, it is not to be added during the study.

2. If SBP≥140mmHg or DBP≥90mmHg, the dosages of other anti-hypertension drugs are to be adjusted, except for ACEI/ARB.

3. Lipid-lowering drugs can be used during the study, including statins to treat high cholesterol and fibrates to treat hypertriglyceridemia primarily to maintain normal cholesterol, triglycerides, and low-density lipoprotein levels.

4. Anti-glycaemic drugs can be used, such as insulin, to reach target glycaemia control with HbA1c <7.0%

5. Subjects can use antiplatelet and anticoagulant drugs with LMWH preferred.

6. Subjects can use proton pump inhibitors, such as omeprazole, pantoprazole, etc.

7. Subjects can use active vitamin D, calcium, and phosphorus lowering drugs.

8. Subjects can use folic acid, iron, EPO and other anaemia drugs with target Hb of 100-120g/L

9. If diuretics are needed, patients should avoid thiazide diuretics

10. Avoid long-term use of corticosteroids (subjects using prednisone <30mg/d, or equivalent number of other hormones with use of <2 weeks can be enrolled).

11. Avoid using allopurinol, benzbromarone, febuxostat or probenecid.

12. Avoid long-term use of salicylic acid drugs (except low-dose aspirin), diuretics, and losartan.

13. Avoid use of immunosuppressive agents, such as cyclophosphamide, MMF, CsA, FK506, azathioprine, vidarabine, leflunomide, tripterygium glycosides, CD20 antibody, and didanosine.

Outcomes

The primary outcome is cardiovascular events comprising cardiovascular mortality and non-fatal cardiovascular events. Cardiovascular mortality includes death caused by acute myocardial infarction, fatal arrhythmia, sudden death, cardiomyopathy, heart failure, and stroke, while non-fatal cardiovascular events includes non-fatal acute myocardial infarction, hospital admission for heart failure, unstable angina, atherosclerotic disease requiring hospitalization (including aneurysm, arterial dissection, arteriosclerosis occlusion), non-fatal stroke, transient ischaemic attack or lower limb ischaemia.

Secondary outcomes include all-cause mortality, cardiovascular mortality and non-fatal cardiovascular events separately.

Participant timeline

All participants who are eligible and who have signed the informed consent will be randomized to one of the two treatment groups. A study flowchart was shown in Figure 1. Treatment in both groups and follow-up will last for 3 years. Examinations will involve outpatient appointments in either outpatient clinics or private nephrology practices and will include: history and physical examination, measurement of systolic and diastolic arterial blood pressure, recording of the frequency, type, severity and duration of adverse events as well as laboratory tests including repeated blood counts. Intervals between examinations vary from monthly (start of study) to 3 months (end of study). An overview of examinations is given and obligatory measurements during the trial are shown in Table 1.

Table 1 Data collection items and activities by visit during the study period for LUMINA

	SCREENING PERIOD visit 1 -3 weeks to day 0		visit 2 1st month(mo) (±7d)	visit 3 2nd mo (±7d)	visit 4 3rd mo (±7d)	visit 5 6th mo (±7d)	visits every 3 mo	v15 36 mo
	Washout (-3weeks to -1week)	Visit 1a (-1 week to day0)						
Physical examination		+		+	+	+	+	+
Blood routine		+		+	+	+	+	+
Urine routine		+		+	+	+	+	+
Uric creatinine		+		+	+	+	+	+
Glycosylated haemoglobin		+				+	+	+
Serum uric acid		+		+	+	+	+	+
Creatinine, potassium, sodium, calcium, phosphorus, bicarbonate, bilirubin, albumin		+		+	+	+	+	+
Parathyroid Hormone		+				+	+	+
Erythropoietin, folic acid, serum ferritin, transferrin		+				+	+	+
Serum lipid		+		+	+	+	+	+
24h urine output		+		+	+	+	+	+
Dialysis dose		+		+	+	+	+	+

Kt/V, renal creatinine clearance rate, peritoneal creatinine clearance rate		+		+	+	+	+	+
Peritoneal Equilibrium Test (PET)		+					every 6 mo	+
24h ultrafiltration		+		+	+	+	+	+
Pregnancy test (Female)		+		+	+	+	+	+
Electrocardiograph (ECG)		+				+	+	+
Cardiac ultrasonography and vascular ultrasound		+					every 12m o	+

*Note: Treatment in both groups and follow-up will last for another 3 years. In the first 3 months at the start of the study, visit intervals will be monthly. After that, visit intervals will be every three months untill the end of study. Examinations will involve outpatient appointments in either outpatient clinics or private nephrology practices and will include: history and physical examination, measurement of systolic and diastolic arterial blood pressure, recording of the frequency, type, severity and duration of adverse events as well as laboratory tests including repeated blood counts.

Sample size

According to previous studies, 3-year CVD event-free survival is 55% in untreated patients and 68% in treated patients; therefore, based on a power of 80%, type I error α=0.05, two-sided test, and 1:1 parallel control study, a sample size of approximately 219 cases is estimated. But considering a 20% drop-out rate due to loss of contact and quitting, this study was designed to recruit 274 patients from each group, for a total of 548 patients. Patients will be randomly assigned into the intervention or control group.

Recruitment

Each centre has a routine peritoneal dialysis population, and these patients are followed up routinely. Each centre will screen subjects to ensure the target population is achieved (548 subjects) from these patients. The enrollment period will last 24 months. Research assistants

and investigators screen participants from routine clinical visits. The enrolment period has ended, and as of December 31, 2019, all patients had been enrolled.

Allocation

Sequence generation

To ensure that numbers in the intervention and the control groups were equal in each centre, a stratified randomization method will be used for each centre, and patients will be randomly assigned to one of the two treatment groups at each centre. The allocation sequence was attained using computer-generated random numbers using SAS9.2 software.

Allocation concealment mechanism

Tablets of febuxostat and placebo will be made and wrapped to appear the same. The allocation sequence was generated using SAS9.2 software. When participants were enrolled, investigators randomly distributed an allocation sequence to the participant using SAS 9.2 software (randomization number), and study tablet with the corresponding number would be distributed to the participants. During these processes, both trial participants and investigators are blinded to the treatment,

Implementation

Investigators randomly distribute an allocation sequence to a given participant using SAS 9.2 software (randomization number), and study tablets with the corresponding number are then distributed to the participants.

Blinding

Who will be blinded and how

After assignment to interventions, trial participants, care providers, outcome assessors, and data analysts are blinded. The placebo and febuxostat will be provided in the same tablet and the same packaging (including labels) to protect the blindness, using kit numbers to mark each double-blind treatment. Researchers will obtain the kit number through a random procedure when patients are randomly grouped, At the same time, during treatment and follow-up, patients, researchers and research centre staff are unable to identify to which group the patients were assigned.

Procedure for unblinding if needed

Blindness can only be broken only to treat subjects when a need to know which treatment group they are randomly assigned to arises.

Blindness can be broken at any time using the corresponding module of the medical record and/or by calling the sponsor. If blindness is broken, the researcher should record the date, time, and cause of the unblind, and report this information (or "required relevant information") on the appropriate page of the case report form (CRF).

When recording causes of unblinding, the researcher must not provide any detailed information related to the nature of the drug in the study. Until the database is closed, the researcher shall not disclose the details of the research drug to the sponsor representative or any staff. In addition, when completing forms, research treatments shall not be disclosed in these tables. After breaking the blinding, the patient must withdraw from the study.

Data collection methods

All patients who are eligible and who have signed the informed consent will be randomized to one of the two treatment groups. Treatment in both groups and follow-up will last for another

3 years. Examinations will involve outpatient appointments in either outpatient clinics or private nephrology practices and will include: history and physical examination, measurement of systolic and diastolic arterial blood pressure, recording of the frequency, type, severity and duration of adverse events as well as laboratory tests including repeated blood counts. Intervals between examinations vary from monthly (during the first 3 months of the study) to every 3 months (from 3 months after entry to the end of study). An overview of examinations is given along with obligatory measurements during the trial in Table 1. Baseline characteristics, lab tests and examinations in every visit, adverse events and outcomes etc. will be recorded.

Plans to promote participant retention and complete follow-up

Participants will be followed up by monthly clinical visit during the first 3 months of the study and every 3 months thereafter. Research assistants and nurses will follow up participants outcome data and adverse events, which are reported to the investigators.

Data management

A case report form (CRF) is provided for every study participant, where all information concerning examinations and visits are recorded. Following completion of the form, the original is sent to the Trial Office, and a carbon copy is retained by the centre. These carbon copies may be required should the original be lost and for comparison of patient data at the end of the study. Study documents are subdivided into five categories: recruiting documents, randomization documents, patient books (CRFs), correction documents and evaluation documents. The pages of the CRFs will be originals with integrated carbon copies. Following completion of the form, the original will be sent to the trial office, and a carbon copy is

retained by the center. All data will be entered into the database. The database is developed and administered centrally by the responsible personnel at the institute of medical statistics, but data entry maybe achieved in a distributed manner within the trial office. The database will provide online plausibility checks, log files and backup mechanisms. Completeness of patient data has to be verified. This is supported by plausibility checks. Double data entry will be conducted. Documentation of patients will be monitored by the documentation centre. To maintain the time course of the follow-up examinations of the participants, each physician will receive, a list of preferred dates for follow-up examinations after submitting the initial patient documents (recruitment documentation, consent form, medical history and therapy protocol). In the documentation centre, all patient data will be verified for completeness and plausibility. Should patient documents be incomplete, contain mistakes or be ambiguous, the documentation centre will send a correction form (if necessary, with a copy of the incomplete patient documents) to the treating physician. It is required that the treating physician fills in the correction form and returns it to the documentation centre. Execution of each step of statistical analysis (data modification, data transformation, description of the data, statistical tests) must be logged in a protocol by the documentation and statistical centre.

Statistical methods

Statistical methods for primary and secondary outcomes

Descriptive statistics will be used to analyse the means and distribution between all study variables. The means of the normal distributed variables will be compared to the Student's T-test, and non-parametric tests (Mann-Whitney U-test for continuous and Chi-Square test for nominal variables) will be used for variables that do not follow a normal distribution. Missing values will be imputed using multiple imputation techniques. Comparisons between groups

will be based on types of variables and appropriate methods in analyses. A Kaplan Meier survival curve will be used to estimate difference in survival rates between the groups, while Log-rank test and multivariable Cox regression will be used to analyse the latter. During data-analysis, sensitivity analyses will be conducted by adding an additional covariate in the mixed model to account for rescue medication required during the study.

Methods for additional analyses

Not applicable.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data

Per-Protocol population (PP) that have protocol adherence between 80%-120%, no serious violation of the protocol, and no missing data on primary outcomes will be included in the analysis. Multiple imputation will be used to handle missing data.

Monitoring

Composition of the data monitoring committee

Not applicable. As this study is funded by our university, there is a scientific research department that is independent of the investigators and will act as a monitoring committee, safeguard the interests of trial participants, monitor the primary outcome measures including safety and efficacy, and monitor the overall conduct of the trial.

Interim analyses and stopping guidelines

Not applicable.

Harms

Adverse reactions to febuxostat include liver function damage, allergic reactions such as systemic skin rash, and acute episodes of gout. Study drugs should be stopped if adverse

reactions occur and proper treatment should be administered. All adverse events, whether related to study drugs or not, are recorded in detail on the case report forms. When the adverse event is considered not related to study drug, possible reasons are given. Reporting of adverse events should include the following information: name of the adverse event, occurrence time, end time, study drug information (dose, capacity, treatment date and time or time interval), severity of the adverse event, relationship of the adverse event to study drug, treatment of the adverse event, and whether it is a serious adverse event. Researchers must track all adverse events until they are resolved or explained by other reasons. Serious adverse events are defined according to globally accepted definitions in the International Conference on Harmonization Guideline for Clinical Safety Data Management. For serious adverse events, researchers should fill out the adverse event report form and report them to the principal investigators, security commissioner, and the Ethics Committee Report and China Food and Drug Administration (CFDA) within 24 hours. Serious adverse events are recorded from the time the patient consent to be in the study through 30 days after study exit.

Auditing

Auditing will be conducted every 6 months; and the process will be independent from investigators and the sponsor. Representatives of the sponsor or its designee must be allowed to visit the study centre periodically to assess the quality of the data and the integrity of the study. Representatives will review study records at the study centre and directly compare these with the source documents, discuss the conduct of the study with the investigator, and verify the appropriateness of the conduct of the study. In addition, the study may be evaluated by the sponsor's internal auditors who must be allowed access to eCRFs, source documents,

and other study files. The sponsor audit reports will be kept confidential.

The investigator or a designated member of the investigator's staff must be available at some time during the monitoring visits to review data, resolve any queries, and allow direct access to subjects' records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. eCRFs must be completed before each visit and be made available to the sponsor's representative to ensure that the accuracy and completeness of the eCRF.

Ethics and dissemination

This study has been approved by the Medical Ethics Committee of the First Affiliated Hospital, Sun Yat-sen University and the ethics committees of other participating institutions. Any amendments to the protocol should be reported to the Medical Ethics Committee.

Investigators will obtain informed consent or assent from potential trial participants or authorized surrogates. Investigators will go through all the participants case histories and lab tests, and screen participants according to inclusion and exclusion criteria. If the potential participant is eligible for the study, the investigator will talk with the participants and their authorized surrogates about the trial, including the time scheme, benefits and risks and so on, to answer questions participants have about the trial. After this, investigators obtained written informed consent from the potential trial participants or their authorized surrogates.

No additional consent provisions for collection or use of participant data and biological specimens in ancillary studies is applicable in this trial.

Confidentiality

All subject information, medical records, and laboratory data will be kept confidential. Information and data may be discussed, analyzed, and reported for the purposes of this clinical study only. However, code numbers will identify subject on the eCRFs and in any reports, to keep the subject's identity confidential.

Declaration of interests

This work is sponsored by Wanbang Pharmaceutical Marketing and Distribution Co. China. All authors declare no conflicts of interest.

Access to data

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

Ancillary and post-trial care

Not applicable.

Dissemination policy

Findings will be disseminated through publications in peer-reviewed journals, and presentations at national and international conferences. Authorship eligibility guidelines and any intended use of professional writers, plans of granting public access to the full protocol, participant-level dataset, and statistical code is not yet available.

Discussion

Hyperuricemia is reportedly an independent predictor for cardiovascular outcome in both general and CKD patients [7-15]. However, there are limited studies examining the relationship between serum uric acid levels and cardiovascular mortality in patients on maintenance dialysis. A multicentre observational study from China that included 2,264

patients on maintenance PD, with a median follow up of 26.5 months, found that each 1mg/dl increase in serum uric acid caused a corresponding 12% increased risk of cardiovascular death, and a 5% increase in all-cause mortality [4]. From our centre, each 1mg/dl increase in serum uric acid in male patients, corresponded to increasing the risks of cardiovascular and all-cause mortality by 44% and 33% respectively [27].

Lowering serum uric acid was demonstrated to benefit renal outcomes [26, 28]. In the recently published FREED study, febuxostat lowered uric acid and delayed the progression of renal dysfunction [29]. However, whether treatment of hyperuricemia improves cardiovascular outcomes in dialysis patients remains to be explored.

The present LUMINA study is designed to determine this question whether treatment of hyperuricemia benefits cardiovascular outcomes in PD patients. It will provide evidence for the effect of lowering uric acid on cardiovascular outcomes in PD patients.

The LUMINA study has some limitations. First, we recruit preventative and incidental patients concurrently, which might introduce some bias in baseline characteristics. Secondly, since centre management capability is not parallel across different centres, centre bias may be present in the study. However, this study also has some strengths. This is a multicentre, randomized, double blind and controlled design with sufficient power to detect a clinically significant difference on the effect of cardiovascular events between treatment and not treatment of hyperuricemia in PD patients.

To our knowledge, the LUMINA study is the first trial focusing on treatment to reduce hyperuricemia and its relationship to cardiovascular outcomes in PD patients. Results of this

study will provide evidence on whether hyperuricemia-lowering treatment is of clinically valuable in PD patients.

Acknowledgments

The authors acknowledge the participants for their time and their extraordinary commitment to the LUMINA trial. The authors also acknowledge all members of the LUMINA Collaborative Research Group, which includes investigators and staff from 24 clinical centres, the Data Coordinating Center, and the primary sponsor, Wanbang Pharmaceutical Marketing and Distribution Co. The 24 clinical centres are The First Affiliated Hospital, Sun Yat-Sen University, The Affiliated Tongji Hospital of Tongji University, The Second Affiliated Hospital of Suzhou University, The Second Xiangya Hospital of Central South University, The Third Xiangya Hospital of Central South University, The First Affiliated Hospital of Xi'an Jiaotong University, The First Hospital of Jilin University, Henan Provincial People's Hospital, The First Affiliated Hospital of Nanchang University, Sichuan Provincial People's Hospital, The First Affiliated Hospital of Guangxi Medical University, General Hospital of Ningxia Medical University, Zhejiang Provincial People's Hospital, Nanjing First Hospital, Pingdingshan First People's Hospital, The First Affiliated Hospital of Zhengzhou University, The Second Hospital of Shanxi Medical University, Xiangya Hospital Central South University, Wuxi Second People's Hospital, Chenzhou No.1 People's Hospital, Shengjing Hosptial of China Medical University, Yancheng City No.1 People's Hospital, The First People's Hospital of Kunshan, Zhenjiang First People's Hospital.

Disclosure and conflicts of interest

This work was sponsored by Wanbang Pharmaceutical Marketing and Distribution Co. China.

All authors declare no conflicts of interest.

562 **Figure 1. Study flow chart**

Reference

[1] Kubo S, Nishida Y, Kubota Y, et al. Higher serum uric acid level is inversely associated with renal function assessed by cystatin C in a Japanese general population without chronic kidney disease: the KOBE study. *BMC Nephrol* 2019; 20:117.

[2] Weiner D E, Tighiouart H, Elsayed E F, et al. Uric acid and incident kidney disease in the community. *J Am Soc Nephrol* 2008; 19:1204-1211.

[3] Iseki K, Oshiro S, Tozawa M, et al. Significance of hyperuricemia on the early detection of renal failure in a cohort of screened subjects. *Hypertens Res* 2001; 24:691-697.

[4] Dong J, Han Q F, Zhu T Y, et al. The associations of uric acid, cardiovascular and all-cause mortality in peritoneal dialysis patients. *PLoS One* 2014; 9:e82342.

[5] Liu R, Han C, Wu D, et al. Prevalence of Hyperuricemia and Gout in Mainland China from 2000 to 2014: A Systematic Review and Meta-Analysis. *Biomed Res Int* 2015; 2015:762820.

[6] Li Z, Liu Q, Mao H, et al. Gender difference in the association of hyperuricemia with chronic kidney disease in southern China. *Kidney Blood Press Res* 2012; 36:98-106.

[7] Chen J H, Chuang S Y, Chen H J, et al. Serum uric acid level as an independent risk factor for all-cause, cardiovascular, and ischemic stroke mortality: a Chinese cohort study. *Arthritis Rheum* 2009; 61:225-232.

[8] Fang J, Alderman M H. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971-1992. National Health and Nutrition Examination Survey. *JAMA* 2000; 283:2404-2410.

[9] Krishnan E, Svendsen K, Neaton J D, et al. Long-term cardiovascular mortality among middle-aged men with gout. *Arch Intern Med* 2008; 168:1104-1110.

[10] Choi H K, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. *Circulation* 2007; 116:894-900.

[11] Liese A D, Hense H W, Lowel H, et al. Association of serum uric acid with all-cause and cardiovascular disease mortality and incident myocardial infarction in the MONICA Augsburg cohort. World Health Organization Monitoring Trends and Determinants in Cardiovascular Diseases. *Epidemiology* 1999; 10:391-397.

[12] Niskanen L K, Laaksonen D E, Nyyssonen K, et al. Uric acid level as a risk factor for cardiovascular and all-cause mortality in middle-aged men: a prospective cohort study. *Arch Intern Med* 2004; 164:1546-1551.

[13] Hoieggen A, Alderman M H, Kjeldsen S E, et al. The impact of serum uric acid on cardiovascular outcomes in the LIFE study. *Kidney Int* 2004; 65:1041-1049.

[14] Hozawa A, Folsom A R, Ibrahim H, et al. Serum uric acid and risk of ischemic stroke: the ARIC Study. *Atherosclerosis* 2006; 187:401-407.

[15] Liu W C, Hung C C, Chen S C, et al. Association of hyperuricemia with renal outcomes, cardiovascular disease, and mortality. *Clin J Am Soc Nephrol* 2012; 7:541-548.

[16] Imazu M, Yamamoto H, Toyofuku M, et al. Hyperinsulinemia for the development of hypertension: data from the Hawaii-Los Angeles-Hiroshima Study. *Hypertens Res* 2001; 24:531-536.

[17] Bonora E, Capaldo B, Perin P C, et al. Hyperinsulinemia and insulin resistance are independently associated with plasma lipids, uric acid and blood pressure in non-diabetic subjects. The GISIR database. *Nutr Metab Cardiovasc Dis* 2008; 18:624-631.

[18] Kuwabara M, Borghi C, Cicero A, et al. Elevated serum uric acid increases risks for developing

high LDL cholesterol and hypertriglyceridemia: A five-year cohort study in Japan. *Int J Cardiol* 2018; 261:183-188.

[19] Lin J D, Chiou W K, Chang H Y, et al. Serum uric acid and leptin levels in metabolic syndrome: a quandary over the role of uric acid. *Metabolism* 2007; 56:751-756.

[20] Wasada T, Katsumori K, Saeki A, et al. Hyperuricemia and insulin resistance. *Nihon Rinsho* 1996; 54:3293-3296.

[21] Zhou Y, Zhao M, Pu Z, et al. Relationship between oxidative stress and inflammation in hyperuricemia: Analysis based on asymptomatic young patients with primary hyperuricemia. *Medicine (Baltimore)* 2018; 97:e13108.

[22] Tomiyama H, Shiina K, Vlachopoulos C, et al. Involvement of Arterial Stiffness and Inflammation in Hyperuricemia-Related Development of Hypertension. *Hypertension* 2018; 72:739-745.

[23] Goicoechea M, de Vinuesa S G, Verdalles U, et al. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. *Clin J Am Soc Nephrol* 2010; 5:1388-1393.

[24] Siu Y P, Leung K T, Tong M K, et al. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. *Am J Kidney Dis* 2006; 47:51-59.

[25] Tsuruta Y, Nitta K, Akizawa T, et al. Association between allopurinol and mortality among Japanese hemodialysis patients: results from the DOPPS. *Int Urol Nephrol* 2014; 46:1833-1841.

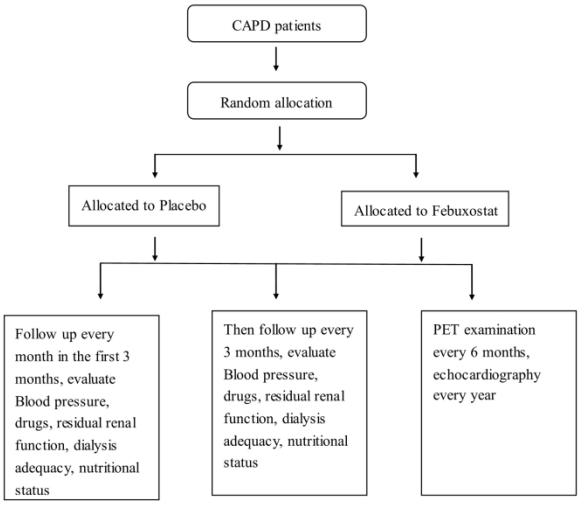
[26] Goicoechea M, de Vinuesa S G, Verdalles U, et al. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. *Clin J Am Soc Nephrol* 2010; 5:1388-1393.

[27] Xia X, He F, Wu X, et al. Relationship between serum uric acid and all-cause and cardiovascular mortality in patients treated with peritoneal dialysis. *Am J Kidney Dis* 2014; 64:257-264.

[28] Bose B, Badve S V, Hiremath S S, et al. Effects of uric acid-lowering therapy on renal outcomes: a systematic review and meta-analysis. *Nephrol Dial Transplant* 2014; 29:406-413.

[29] Kojima S, Matsui K, Hiramitsu S, et al. Febuxostat for Cerebral and CaRdiorenovascular Events PrEvEntion StuDy. *Eur Heart J* 2019; 40:1778-1786.

Figure 1. Study flow chart



Study flow chart

210x297mm (300 x 300 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym ***(Page 1 line 1-3)***
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry ***(Page 3 line 52-page 4 line 56)***
	2b	All items from the World Health Organization Trial Registration Data Set ***(Not applicable)***
Protocol version	3	Date and version identifier ***(Page 4 line 69-70)***
Funding	4	Sources and types of financial, material, and other support ***(Page 4 line 71 – Page 5 line 81)***
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors ***(Page 5 line 82-Page 7 line 133)***
	5b	Name and contact information for the trial sponsor ***(Page 7 line 134-136)***
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities ***(Page 7 line 137 –line 140)***
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) ***(Page 8 line 141-144)***
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention ***(Page 8 line 145- Page 9 line 164)***
	6b	Explanation for choice of comparators ***(Page 9 line 165-171)***

Objectives	7	Specific objectives or hypotheses ***(Page 9 line 172-174)***
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) ***(Page 9 line 175-176)***
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained ***(Page 9 line 177-180)***
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) ***(Page 9 line 181 - Page 11 line 216)***
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered ***(Page 11 line 220 - Page 12 line 234)***
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) ***(Page 12 line 235 -Page 13 line 258)***
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) ***(Page 13 line 259 - line 265)***
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial ***(Page 13 line 266 -Page 15 line 298)***
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended ***(Page 15 line 299-308)***
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) ***(Page 15 line 309 - Page 17 line 325)***
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations ***(Page 17 line 326-332)***

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size ***(Page 17 line 333 - 338)***

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions ***(Page 17 line 339-page 18 line 344)***
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned ***(Page 18 line 345-351)***
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions ***(Page 18 line 352-355)***
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how ***(Page 18 line 356 - 364)***
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial ***(Page 19 line 365-376)***

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol ***(Page 19 line 377-Page 20 line 388)***
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols ***(Page 20 line 389-392)***
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol ***(Page 20 line 393-Page 21 line 417)***

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol ***(Page 21 line 418- 429)***
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) ***(Page 21 line 430-431)***
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) ***(Page 22 line 432-436)***
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed ***(Page 22 line 437-442)***
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial ***(Page 22 line 443-444)***
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct ***(Page 22 line 445 - Page 23 line 461)***
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor ***(Page 23 line 462- Page 24 line 476)***
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval ***(Page 24 line 477-479)***
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) ***(Page 24 line 480)***
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) ***(Page 24 line 481-487)***
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable ***(Page 24 line 488-489)***

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial ***(Page 24 line 490 - 494)***
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site ***(Page 24 line 495-497)***
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators ***(Page 25 line 498-500)***
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation ***(Page 25 line 501-502)***
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions ***(Page 25 line 503-505)***
	31b	Authorship eligibility guidelines and any intended use of professional writers ***(Page 25 line 505-507)***
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code ***(Page 25 line 505-507)***
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates (***See supplement material Inform consent***)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable ***(Not applicable)***

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.