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Effect of spironolactone on cardiovascular morbidity and mortality in patients with hypertension and glucose metabolism disorders (ESCAM): a study protocol for a pragmatic randomised controlled trial

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ABSTRACT

Introduction Hypertension combined with diabetes and hypokalemia is more likely to develop hyperaldosteronism and is at higher risk of cardiovascular events. There is evidence that activation of aldosterone and mineralocorticoid receptors may play a significant role in the occurrence of cardiovascular events in patients with hypertension and diabetes. Clinical studies have demonstrated that spironolactone can reduce the incidence of cardiovascular events in patients with chronic kidney diseases or severe heart failure. However, the effect of spironolactone on cardiovascular risk in patients with hypertension and glucose metabolism disorders (GMD) and low potassium has been scarcely studied. Therefore, this study aims to evaluate whether add-on spironolactone (conventional antihypertensive drugs alone vs conventional antihypertensive drugs+spironolactone) can reduce the morbidity and mortality of cardiovascular events in this population.

Methods and analysis In this multicentre, randomised, parallel-controlled study, a total of 7140 hypertensive patients aged 45–75 years with GMD and low potassium will be randomised in a 1:1 manner to the control or the spironolactone group (20 mg/day or with a maximum dose of 40 mg). The primary objective is to estimate the difference in the HR of composite cardiovascular events between the two groups. We will also assess the effects of spironolactone on individual cardiovascular events and the progression of diabetes and renal dysfunction.

Ethics and dissemination This protocol was approved by the Independent Ethics Committee of People's Hospital of Xinjiang Uygur Autonomous Region (no. 2020020618). The results will be disseminated in peer-reviewed journals and at scientific conferences.

Trial registration number ChiCTR2000028909.

Strengths and limitations of this study

- This randomised controlled trial will be the first large-sample study to directly evaluate the cardiovascular efficacy of spironolactone in patients with hypertension and glucose metabolism disorders.
- This trial has primary end points of cardiovascular events.
- This trial will address a problem with an intervention design, which will be pragmatic and will have high potential application value in real-world setting.
- This study is designed as an open-label trial, and participants and investigators are not blinded to the treatment.

INTRODUCTION

Multiple comorbidities have been associated with hypertension. Studies have found that the prevalence of primary aldosteronism (PA) among patients diagnosed with hypertension is 10%[1 2] and reaches more than 15% in patients with resistant hypertension[3 4]; however, current evidence considers that the prevalence of PA may be underestimated.[5 6] In addition to elevating blood pressure (BP), aldosterone also causes aggravation of insulin resistance and diabetes by lowering the level of potassium.[7 8] Hypertensive patients with PA are more likely to be associated with impaired glucose tolerance and diabetes.[9 10] Therefore, it is reasonable to speculate that patients with hypertension are more prone to hyperaldosteronism when glucose metabolism disorders (GMD) and lower potassium exist simultaneously, and aldosterone may play an important role in the high incidence of cardiovascular events in this specific population. As well known, hypertension and GMD are common comorbidities,[11] and clinicians tend to pay more attention to the known pathogenesis, whereas they ignore the role of aldosterone. Meanwhile, aldosterone-induced

hypokalemia is often falsely attributed to the use of diuretics.

The risk of cardiovascular events is higher when hypertension and GMD coexist than when one of them is alone.[12] The two conditions, concurrently occurring in the majority of patients, show the negative effects of agents in lowering BP, aggravate target organ damages and increase the incidence of cardiovascular events.[13 14] In this process, hypertension and GMD share several common known pathogenesis, including the overactivation of the sympathetic nervous system, the activation of the renin-angiotensin-aldosterone system and insulin resistance.[15] Accordingly, correlative antihypertensive medicines are used against these mechanisms. However, the difficult-to-control BP and disproportionate increase in cardiovascular events in this population suggest that the coexistence of hypertension and GMD may be far more complicated than the simple combination of the two conditions.[16] As evidenced, patients with hypertension and diabetes usually need two or more antihypertensive agents to achieve the target BP as well.

Previous studies have shown that plasma aldosterone concentrations are higher in patients with both hypertension and diabetes than in patients with hypertension alone.[17 18] It has been also observed that the expression and sensibility of mineralocorticoid receptors (MR) are increased in patients with diabetes .[19 20] Furthermore, aldosterone breakthrough, related to endothelial dysfunction, left ventricular function deterioration and renal damage, occurs in about 50% of patients treated with ACE inhibitors or angiotensin receptor blockers, which are the preferred agents for patients with hypertension and GMD.[21–23] The MR-dependent mechanisms of aldosterone are also related to the pathophysiology of hypertension and cardiovascular diseases.[24 25] Evidence from human and animal studies suggests that aldosterone and MR activation play important roles in increasing the risk of cardiovascular events by promoting endothelial dysfunction, inflammation, vascular oxidative stress and fibrosis and by the imbalance of vasomotor factors.[26–28] Aldosterone also impairs arterial compliance, induces cardiac hypertrophy and increases left ventricular mass.[29]

Taken together, it is reasonable to believe that spironolactone, the aldosterone antagonist, can be more effective in patients with hypertension and GDM, and add-on spironolactone would provide a cardiovascular benefit to this population. In several small-sample clinical trials, MR antagonists (MRAs) significantly reduce BP and urinary protein in patients with hypertension and diabetes mellitus.[20 30 31] Increasing clinical studies have shown that MRAs reduce the incidence of cardiovascular events and all-cause mortality in patients with chronic kidney disease or heart failure.[32–35] However, the antihypertensive efficacy and safety of MRAs in patients with hypertension and GDM have not been demonstrated in large clinical trials, and it is unclear whether the MRAs bring an extra cardiovascular benefit for patients with hypertension and GDM and low potassium.

Therefore, this pragmatic clinical trial is designed to evaluate whether add-on spironolactone is more effective than conventional antihypertensive drugs in reducing incident cardiovascular events in patients with hypertension and GDM and low potassium.

METHODS

Overview of study design

The Effect of Spironolactone on CArdiovascular Morbidity and Mortality in patients with hypertension and glucose metabolism disorders (ESCAM) study is a multicentre, parallel-group, pragmatic, randomised controlled trial to be conducted in China. The primary objective is to test the hypothesis that add-on spironolactone is more effective than conventional antihypertensive drugs alone in reducing the incidence of cardiovascular events in patients with hypertension and GDM and low potassium. The study design is shown in figure 1. The schedule for enrolment, interventions and assessments is presented

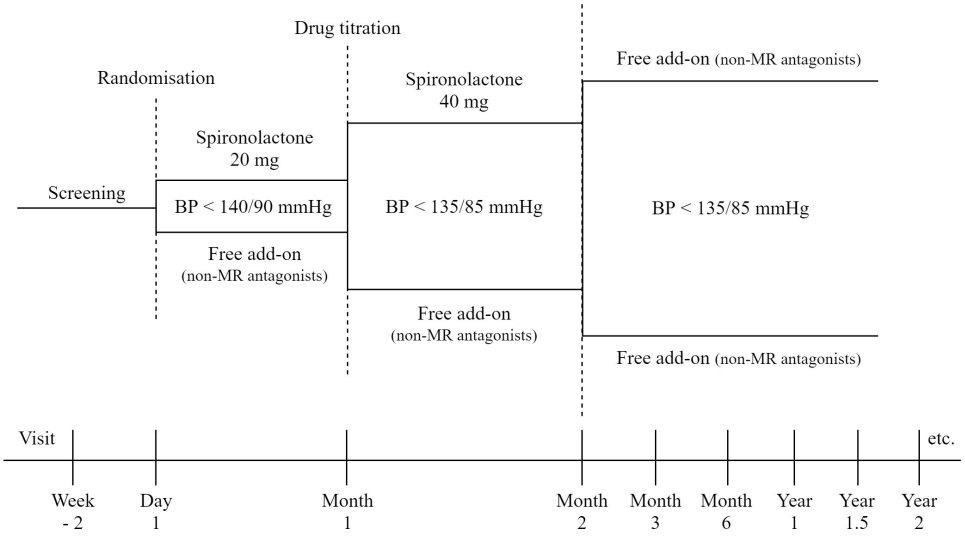

Figure 1 Study design for the ESCAM study. BP, blood pressure; MR, mineralocorticoid receptors.

Table 1 Study schedule for patients

	Study period									
	Screening	Baseline	Follow-up (months)							
Time point	0	0	1	3	6	12	18	24	30	36
Enrolment										
Eligibility screen	X									
Informed consent	X									
Randomisation		X								
Interventions										
Conventional antihypertensive drugs		X	X	X	X	X	X	X	X	X
Conventional antihypertensive drugs+spironolactone		X	X	X	X	X	X	X	X	X
Assessments										
Demographics		X								
Medical history		X								
Records of treatments		X	X	X	X	X	X	X	X	X
Blood pressure		X	X	X	X	X	X	X	X	X
Blood test		X		X	X	X		X		X
Glycometabolism test		X		X	X	X		X		X
Kidney function test		X		X	X	X		X		X
ECG		X			X	X		X		X
Cardiovascular events			X	X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X	X
Concomitant treatment		X	X	X	X	X	X	X	X	X
Adherence			X	X	X	X	X	X	X	X

ECG, electrocardiogram.

in table 1. A checklist in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) is also available in online supplemental table S1.

Eligible participants will be randomised to the spironolactone treatment group or the control group using an allocation ratio of 1:1 after a 2-week screening period. Other necessary treatments are allowed at clinicians' suggestions. Three committees will be established to supervise the whole process of the trial. The Executive Committee will provide guidance and make decisions about the design, execution and publication. The Data Safety and Monitoring Board will review and evaluate the safety and efficacy data of the trial. The Study Protocol Management Committee will address specific challenges in protocol procedures. Study reporting adheres to SPIRIT Reporting.[36]

Study objectives

Primary objective

The primary objective is to evaluate whether add-on spironolactone is more effective than conventional antihypertensive medicines alone in reducing the incidence of composite cardiovascular events in patients with hypertension and GDM and low potassium.

- Composite cardiovascular events include death due to cardiovascular causes, heart failure, myocardial infarction (MI), stroke, unstable angina admission, coronary revascularisation and atrial fibrillation.

Secondary objective

The secondary objective is to evaluate whether add-on spironolactone is more effective than usual antihypertensive medicines alone in reducing the incidence of the following outcomes:

- All-cause death.
- MI (fatal and non-fatal).
- Stroke (fatal and non-fatal).
- Heart failure.
- Atrial fibrillation.

Other objectives

To compare the effects on BP, glucose metabolism and renal function (serum creatinine, estimated glomerular filtration rate, blood urea nitrogen, uric acid, urine

Box 1 Inclusion criteria for the ESCAM study

Inclusion criteria

- Male or female patients aged 45–75 years and able to provide informed consent.
- Office-seated systolic blood pressure (BP) ≥140 mm Hg and/or diastolic BP ≥90 mm Hg, and/or under antihypertension treatment.
- Fasting blood glucose ≥6.1 mmol/L or postprandial glucose ≥7.8 mmol/L, or diagnosed diabetes.
- Plasma potassium <4.0 mmol/L.

protein and the incidence of dialysis) between the two treatment groups.

Study population

Participant recruitment is expected to be completed by 31 December 2020. The means by which participants are recruited are as follows: (1) recruitment advertisement via internet and media, (2) recommended by clinicians, (3) recommended by participants and (4) screening of the hospital electronic medical system and health examination data. Male and female patients aged 45–75 years diagnosed with hypertension and GMD as well as low serum potassium will be included in the study. Hypertension is defined as office systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg, and/or under antihypertension treatment. GMD includes impaired fasting glucose, impaired glucose tolerance and diagnosed diabetes. The details of the inclusion and exclusion criteria are shown in boxes 1 and 2.

Sample size

The ESCAM study is designed to detect a 20% reduction in the primary end point for the add-on spironolactone group, compared with the control group, with 80% power at 5% significance level during a 3-year follow-up. Assuming a cardiovascular event rate of 10% in the control group in a mean follow-up duration of 3 years and a lost-to-follow-up rate of 10%, a sample size of 7140 is required. The sample size was calculated using the PASS software V.11.0, and the parameters are as follows: α=0.05, β=0.2, P1 (treatment group)=8%, P2 (control group)=10% and alternative=two-sided.

Box 2 Exclusion criteria for the ESCAM study

Exclusion criteria

- History of cardiovascular events within the last 3 months (including MI, heart failure, stroke, unstable angina, coronary revascularisation and coronary bypass operation).
- Renal dysfunction (Scr ≥178 µmol/L or eGFR <60 mL/min).
- Hepatic dysfunction (AST/ALT >5 ULN or ALP >5 ULN or BIL >3 ULN).
- Serum uric acid >520 µmol/L.
- Diagnosed with secondary or resistant hypertension (including Cushing syndrome, adrenal tumour, pheochromocytoma, renal hypertension, polycystic ovary syndrome and congenital adrenal disease).
- Diagnosed with primary aldosteronism and is under spironolactone therapy.
- Diagnosed with malignant tumour within the last 5 years.
- Pregnant or breastfeeding women.
- Contraindicated or allergic to spironolactone.
- Severe mental disorders.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BIL, bilirubin; eGFR, estimated glomerular filtration rate; Scr, serum creatinine; ULN, upper limit of normal.

Randomisation

Randomisation of treatment allocation will be accomplished by a phone call to the study centre. Stratified by sex, block randomisation will be used, with random block sizes of 4. Eligible participants will be given a sequential random number based on a list generated by R statistical software and will be assigned to the spironolactone or the control group. The random sequence will be kept by the study centre, and the allocation concealment will be preserved for the participants and study investigators.

Intervention

After the screening visit, participants will enter a prerandomisation phase that lasts up to 2 weeks, and qualified patients will then enter the treatment period. Participants already receiving antihypertensive therapy will remain on their previous regimen. For the spironolactone group, patients will be given an add-on spironolactone of 20 mg, allowing titration to a maximum dose of 40 mg according to the target BP (<135/85 mm Hg) during follow-up. For the control group, patients will be given antihypertensive treatment according to clinicians' suggestions to reach a target BP <135/85 mm Hg, whereas the use of MRAs is limited. A blood glucose target will be set for the treatment of GMD (target fasting blood glucose <8.0 mmol/L, postprandial blood glucose <10 mmol/L), but the hypoglycaemic agents are not specialised. Other appropriate medications for concomitant conditions will be allowed for all participants throughout the study.

Follow-up and data acquisition

All qualified participants will be given a similar schedule of visits. After visit 1 (day 1), participants visit the study centres at month 1, month 2, month 3 and month 6 and thereafter every 6 months until the occurrence of the end points or the end of the study. Follow-up schedule will be planned to end at 31 December 2023. Predesigned structural questionnaires and case report forms (CRF) will be applied to collect all required data, including demographic data, laboratory examination, cardiovascular events, the use of medications and adverse events.

Safety and withdrawal

Safety and tolerability will be assessed by monitoring the occurrence of serious signs and adverse events during visits. Spironolactone will be used to reduce dosage or will to be discontinued when serum potassium rises above 5.0 mmol/L. Serious adverse events, defined as events that are fatal, life-threatening, disabling or will result in malformation, will be recorded in the CRF. Subjects may

withdraw from the trial at any time at their own request or at the decision of the Executive Committee for safe, behavioural or administrative reasons.

Management of the study

The overall responsibility for this trial is vested in the Executive Committee, which will provide guidance and make decisions about the design, execution and publication. The Data and Safety Monitoring Committee will be responsible for monitoring the safety of participants in this trial and for monitoring the relative efficacies of the two groups in terms of the number of cardiovascular events. This committee may recommend that the trial be discontinued prematurely when a sharp therapeutic advantage occurs in one of the treatment groups or when serious adverse events occur. The Study Protocol Management Committee will responsible for specific issues during the study.

Outcomes assessment

Cardiovascular death is defined as sudden death from cardiac cause or death due to heart failure, MI, stroke, cardiovascular invasive procedures, cardiovascular haemorrhage or other known vascular causes. MI needs to meet the criteria for ischaemic symptoms or corresponding electrocardiographic changes plus evidence of myocardial damage. Stroke includes haemorrhagic and ischaemic types, excluding subarachnoid haemorrhage. All-cause death includes death due to any reason. Evidence for death includes death certificates from hospitals or reports from family members.

In the ESCAM study, all outcomes will be identified according to the criteria we set in advance. Source data for all suspected cases will be submitted to the study centre for further verification, including medical records, imaging data and event report forms.

STATISTICAL ANALYSIS

Study data will be locked, and statistical analysis will be performed only with the permission of the principal investigator. The statistician will be blinded for treatment allocation. Any information related to participant identity will be erased before analyses. The primary analysis will be intention-to-treat. The cumulative event rates will be calculated using the Kaplan-Meier method and compared using the log-rank test. The HR and 95% CI will be estimated by the Cox proportional hazards regression model. The secondary end points will be analysed with the same methods used in primary analysis. Other efficacy and safety parameters will be summarised and compared for the differences between the two groups. Subgroup analyses will be performed, including gender, age (<60 years and ≥60 years), the classification of GMD, the absence or the presence of previous cardiovascular events, or the absence or the presence of baseline renal dysfunction. Statistical analyses will be performed using SPSS V.22.0 (SPSS Inc., Chicago, Illinois, USA).

ETHICS AND DISSEMINATION

This protocol was approved by the Independent Ethics Committee of People's Hospital of Xinjiang Uygur Autonomous Region (no. 2020020618). Written informed consent to participate will be obtained from all participants. Patients' family will be allowed to do this when the patient is unable to provide written informed consent. Results will be disseminated in peer-reviewed journals and at scientific conferences.

PATIENT AND PUBLIC INVOLVEMENT STATEMENT

Participants are not directly involved in the design or development of the study and will not be involved in the recruitment and conduct of the study. Results of the therapeutic efficacy will be given to the participants after the study.

DISCUSSION

The morbidity and mortality of cardiovascular diseases remain high in patients with both hypertension and GMD, although several studies have reported that the combination of conventional antihypertensive medicines could reduce the risk of cardiovascular events.[37–39] Therefore, it is necessary to identify the potential risk factors and take interventions to further reduce the incidence of cardiovascular events. This trial will address the problem through a simple intervention, which will be pragmatic and will have high potential application value in real-world setting.

Previous studies have shown that the increase in aldosterone and the activation of MR may be closely associated with the occurrence and development of cardiovascular events.[26–28 40–44] A research on diabetic animals has demonstrated that treatment with spironolactone improves the deterioration of BP and blood glucose, and reduces the production of inflammatory factors.[30] Clinical studies have shown that low-dose spironolactone can effectively reduce BP in patients with diabetes and resistant hypertension[20 45] and also significantly reduce the incidence of cardiovascular events in patients with severe heart failure.[29] MRAs can not only reduce BP by directly blocking the MR[46] but may also bring the beneficial effects on cardiovascular events and mortality through the reduction of cardiovascular remodelling and vascular inflammation,[47 48] the alleviation of vascular calcification and aortic stiffness,[49] and the effects on oxidative stress and endothelial functions.[50] Therefore, it is reasonable to speculate that spironolactone treatment on top of conventional antihypertensive therapy would add further protection against cardiovascular events other than simply provide additional BP-lowering effect.

In the ESCAM study, spironolactone will be the only mandatory intervention drug, and patients' serum potassium will be closely monitored to ensure their safety. Both groups will have equal opportunities to have logical regimens to treat hypertension, GMD, dyslipidaemia

and other disorders, thereby avoiding the inequalities in these reactions, thus causing problems in interpreting outcomes in clinical trials. Moreover, this simple method of intervention is more pragmatic in real-world clinical therapy.

At present, the incidence of cardiovascular events in patients with hypertension and GDM is still high and even increasing in many developing countries. Evidence has shown that aldosterone and MR activation may play a significant role in cardiovascular events. However, it remains unknown whether MRA reduces the risk in this population. Therefore, this large pragmatic clinical trial is established to check the hypothesis that add-on spironolactone would significantly decrease the incidence of cardiovascular events. We expect that the results of the study would provide convincing evidence regarding the treatment in patients with both hypertension and GMD.

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Contributors NL conceived and designed the study, and led the proposal and protocol development. ML, QL, MH, LW, XY, JH and QZ participated in study design and planned the analyses. ML drafted the initial manuscript, and MH, YL and JY revised it carefully. All authors read and approved the final manuscript.

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