



A randomized, multicenter, open-label, blinded end point trial comparing the effects of spironolactone to chlorthalidone on left ventricular mass in patients with early-stage chronic kidney disease: Rationale and design of the SPIRO-CKD trial

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Background Chronic kidney disease (CKD) is associated with increased left ventricular (LV) mass and arterial stiffness. In a previous trial, spironolactone improved these end points compared with placebo in subjects with early-stage CKD, but it is not known whether these effects were specific to the drug or secondary to blood pressure lowering.

Aim The aim was to investigate the hypothesis that spironolactone is superior to chlorthalidone in the reduction of LV mass while exerting similar effects on blood pressure.

Design This is a multicenter, prospective, randomized, open-label, blinded end point clinical trial initially designed to compare the effects of 40 weeks of treatment with spironolactone 25 mg once daily to chlorthalidone 25 mg once daily on the co-primary end points of change in pulse wave velocity and change in LV mass in 350 patients with stages 2 and 3 CKD on established treatment with an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker. Because of slow recruitment rates, it became apparent that it would not be possible to recruit this sample size within the funded time period. The study design was therefore changed to one with a single primary end point of LV mass requiring 150 patients. Recruitment was completed on 31 December 2016, at which time 154 patients had been recruited. Investigations included cardiac magnetic resonance imaging, applanation tonometry, 24-hour ambulatory blood pressure monitoring, and laboratory tests. Subjects are assessed before and after 40 weeks of randomly allocated drug therapy and at 46 weeks after discontinuation of the study drug. (*Am Heart J* 2017;191:37-46.)

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Trial registration: This trial is registered with the European Union Drug Regulating Authorities Clinical Trials: EudraCT No. 2013-002636-25 and Current Controlled Trials: ISRCTN 94696478. UK Medicines and Healthcare Regulatory Agency Clinical Trials Authorization No. 21761/0295/001-0001.

EudraCT No. 2013-002636-25, current controlled trials: ISRCTN 94696478.

Submitted February 13, 2017; accepted May 18, 2017.

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<http://dx.doi.org/10.1016/j.ahj.2017.05.008>

Background

Levels of cardiovascular mortality and morbidity are high in chronic kidney disease (CKD) with a graded inverse relationship with glomerular filtration rate.^{1,2} This has a large public health impact because of the high prevalence of early-stage CKD which affects about 1 in 7 people in the United States.³ Although patients with CKD have a clustering of atherosclerotic risk factors, the majority of deaths are due to heart failure and arrhythmia.⁴ This suggests that the underlying mechanism for heart disease in patients with CKD is not coronary atherosclerosis but myocardial disease, so-called uremic cardiomyopathy. In the early stages of CKD, sensitive markers of systolic (strain) and diastolic function are often abnormal, and there is an increased prevalence of left ventricular hypertrophy (LVH).^{5,6} Causative factors are thought to include increased

arterial stiffness, hypertension, sympathetic neural influences, and circulating factors including mediators of the renin-angiotensin-aldosterone system. These factors are already present in stage 2 to 3 CKD and provide potential targets for treatment aimed at preventing the development and progression of myocardial hypertrophy and fibrosis.⁷

Aldosterone is as a key mediator of cardiovascular disease in many conditions including heart failure and CKD. This hormone causes vascular and myocardial injury and fibrosis, particularly in the presence of sodium excess as occurs in CKD.⁸ Mineralocorticoid receptor blocker (MRB) drugs ameliorate these actions in cellular and animal models and improve clinical outcomes in people with heart failure.⁸ Like heart failure, CKD is characterized by sodium overload and high aldosterone concentrations due to aldosterone escape (unsuppressed levels of aldosterone despite chronic sodium overload) and aldosterone breakthrough (high circulating aldosterone levels despite suppression with angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor blocker [ARB] drugs).⁴ In the CRIB-2 trial of 112 patients with stages 2 and 3 CKD, we showed that, compared with placebo, spironolactone reduced LV mass, arterial stiffness, and collagen turnover and improved myocardial diastolic function.^{9,10} As blood pressure was also reduced by spironolactone with a mean fall in systolic pressure of 11 mm Hg, it is possible that the effects of spironolactone on cardiovascular structure and function were nonspecific and mediated by blood pressure lowering alone. To address whether the benefits of spironolactone in CRIB-2 were specific to mineralocorticoid blockade or as a result of a reduction in blood pressure, we designed the Spironolactone in Chronic Kidney Disease (SPIRO-CKD) trial to include an active control drug to lower blood pressure to similar levels. Chlorthalidone was chosen as the control drug because of its proven antihypertensive action in patients with early-stage CKD with an effect size in the ALLHAT substudy in this patient group about equal to that of spironolactone in CRIB-2.¹¹ The SPIRO-CKD trial was initially designed to investigate the hypothesis that spironolactone is superior to chlorthalidone in the reduction of a co-primary end point consisting of LV mass and arterial stiffness. Recruitment was slower than anticipated because of smaller numbers of patients with early-stage CKD being reviewed routinely in a number of participating centers. Following discussions with the British Heart Foundation (funding body) and the Trial Steering Committee, it was decided that it would not be possible to recruit a sample size sufficient to provide adequate statistical power to detect a change in arterial stiffness. The study design has therefore changed to one with a single primary end point of LV mass.

Methods

Study design

This multicenter, prospective, randomized, open-label, blinded end point (PROBE) clinical trial was initially

designed to compare the effects of 40 weeks of treatment with spironolactone 25 mg once daily to chlorthalidone 25 mg once daily on the co-primary end point of change in LV mass using cardiac magnetic resonance imaging (MRI) and pulse wave velocity (PWV) in patients with stages 2 and 3 CKD, without known cardiovascular disease or diabetes mellitus and on established treatment with an ACE inhibitor or an ARB with controlled blood pressure on study entry. Nested substudies were also designed to compare the effects of these drugs on changes in LV systolic and diastolic deformation (global longitudinal strain) and in LV interstitial fibrosis (T1 mapping), both measured noninvasively by cardiac MRI. Calculation of estimated glomerular filtration rate (eGFR) has been performed using the 4-variable Modification of Diet in Renal Disease formula. CKD stages 2 and 3 have been defined as an eGFR of 60-89 mL/min/1.73 m² in the presence of another abnormality, for example, albuminuria or a structural abnormality of the kidney, and 30-59 mL/min/1.73 m², respectively.¹² At the time of recruitment, creatinine was measured from blood tests performed within the last 12 months on 2 occasions at least 90 days apart. Details of the inclusion and exclusion criteria, and the study outcome measures are listed in [Tables I and II](#), respectively. The academic centers participating in the trial will be the University of Birmingham, the University of Cambridge, University College London, and the University of Edinburgh, UK. Patients have been recruited from the Queen Elizabeth Hospital Birmingham; Addenbrookes Hospital, Cambridge; the Royal Free Hospital, London; the Western General Hospital Edinburgh; and primary care practices in Edinburgh.

The trial started recruitment in June 2014 and aimed to recruit 350 patients over a 2-year period. However, the rate of recruitment was slower than anticipated, and it became evident by November 2015 that recruitment of this number would not be completed within the funded time, and the decision was taken to change the study design to one with the single primary end point of change in LV mass. This allowed a sample size which could be recruited within the funded time frame (see sample size calculations section). This decision was made following discussions with the funder, that is, the British Heart Foundation; the Trial Management Group; and the Trial Steering Committee who remain blind to any interim data analyses.

Ethical approval for this study was awarded by the West Midlands National Research Ethics Service Committee in September 2013 (13/WM/0304). The study is funded by the British Heart Foundation (SP/12/8/29620) and is registered with Medicines and Healthcare products Regulatory Agency (Clinical Trials Authorization No. 21761/0295/001-0001). The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the article, and its final contents.

Table 1. Inclusion and exclusion criteria
Inclusion criteria

Age >18 y and willing to undergo investigations
CKD stage 2 or 3 (eGFR 30-89 mL/min/1.73 m²) from blood tests performed within the last 12 m on 2 occasions at least 90 d apart.
(For stage 2 CKD, no criteria for urinary or blood test or structural abnormalities were mandated; these criteria were left to the discretion of the local principal investigator.)
Controlled blood pressure (no current indication for additional antihypertensive therapy in the opinion of the local principal investigator)
On established (>6 wk) treatment with ACE inhibitors or ARBs
Clinically stable (no hospital admission or other significant acute illness within 3 m) and no recent (<6 m) acute myocardial infarction
Females of childbearing potential must not be pregnant or breast feeding, and must agree to avoid pregnancy and to use adequate, medically approved contraceptive precautions during and for 6 wk following the last dose of study treatment.
Males with a partner of childbearing potential must agree to use medically approved contraception during and for 6 wk following the last dose of study treatment.

Exclusion criteria

Diabetes mellitus
Clinical evidence of hypovolemia
On current regular treatment with nonsteroidal anti-inflammatory drugs or other agents (except ACE inhibitors, ARBs, or low-dose aspirin) that might cause a reduction in eGFR
Recent (<6 m) acute myocardial infarction or other major adverse cardiovascular event (STEMI, NSTEMI, unstable angina, coronary revascularization, stroke, transient ischemic attack)
Known LV systolic dysfunction (ejection fraction <50%) or severe valvular heart disease or evidence of heart failure
Active malignant disease with a life expectancy of <5 y
Previous hyperkalemia (K⁺ ≥6.0 mmol/L) without precipitating cause
Serum K⁺ >5.0 at entry
Serum sodium <130 mmol/L at entry
Atrial fibrillation on screening ECG
Current treatment with spironolactone or other mineralocorticoid receptor blocker
Use of a thiazide or loop diuretic in the 6 wk prior to enrolment
Pregnant or breastfeeding
Known alcohol or drug abuse
Active chronic diarrhea
Recent active gout (within 3 m)
Acute kidney injury in previous 3 m
Documented Addison disease
Treatment with fludrocortisone, cotrimoxazole, or lithium
Combination treatment with ACE inhibitor and ARB
Office blood pressure <115 mm Hg systolic or <50 mm Hg diastolic
Office blood pressure uncontrolled and requiring urgent nontrial treatment
Unable to provide informed consent

STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; ECG, electrocardiogram.

Recruitment and screening

Recruitment of 154 patients was completed by 31 December 2016. Eligible patients (Table 1) were identified using hospital and primary care medical records. All recruitment took place within hospital outpatient clinics in the aforementioned institutions in 2 stages. Firstly, all patients apparently fulfilling the eligibility criteria were asked for written consent for additional screening procedures to be undertaken. Screening procedures were as follows:

1. Ensuring that potential participants met the study's inclusion and exclusion criteria.
2. Physical examination to check pulse, office blood pressure, and signs of hypovolemia, and a cardiovascular examination to exclude signs of heart failure or valvular disease. Echocardiography was performed only in cases of clinical uncertainty about the presence of heart failure or valve disease.

3. Recording an electrocardiogram.
4. Blood tests for routine biochemical and hematological parameters including eGFR.
5. Females of childbearing potential underwent a pregnancy test.

When patients fulfilled the eligibility criteria, informed written consent was obtained for randomization into the main SPIRO-CKD trial in keeping with the principles set out by the Declaration of Helsinki.

Run-in phase

For those patients wanting to take part but not immediately eligible because they are either on existing diuretic therapy or not taking ACE inhibitor or ARB therapy or taking both of these agents, a 4- to 6-week run-in phase is used. For patients on existing loop or thiazide diuretic therapy who wish to take part in the trial, after obtaining consent, diuretic therapy is stopped, and the patient is reviewed after 4 weeks to ensure that

Table II. Primary and secondary outcome measures

Primary outcome measures
Change between baseline and 40 wk in LV mass measured by cardiac MRI
Secondary outcome measures
Change between baseline and 40 wk in arterial stiffness measured by carotid-femoral PWV
Change between baseline and 40 wk in office, central, and ambulatory blood pressures
Change between baseline and 40 wk in urinary albumin-creatinine ratio
Changes between baseline and 40 wk in LV volumes and systolic function
Changes between baseline and 40 wk in plasma NT-pro-BNP
Incidence of hyperkalemia
Change between baseline and 40 wk in eGFR

he/she meets the eligibility criteria (Table D). For patients not on ACE inhibitor or ARB therapy, after obtaining consent, an ACE inhibitor or ARB of the physician's choice is introduced and titrated to a well-tolerated therapeutic dose over a 4-week period. The patient is then reviewed to ensure eligibility. For patients on dual ACE inhibitor and ARB therapy, after obtaining consent, either the ACE inhibitor or the ARB is stopped. Patients are then reviewed to ensure eligibility. Those patients who fulfill all entry criteria are consented and randomized into the main SPIRO-CKD trial.

Randomization

Once informed consent is received and the baseline assessments completed, patients are entered into the main SPIRO-CKD trial. Participants are randomized in a 1:1 ratio to either spironolactone (25 mg once a day) or chlorthalidone (half a 50-mg tablet once a day, as there are no 25-mg tablets available for use in the UK) for 40 weeks without blinding. A secure central randomization service was provided by the Birmingham Clinical Trials Unit (University of Birmingham) using a computer-generated program, using a minimization algorithm to ensure balance between the arms with regard to the important clinical variables of blood pressure, age, and gender. Compliance with treatment is monitored by study coordinators using tablet counting.

Investigations

The trial design and schedule of investigations are summarized in Figure 1, and further information is available in Appendix 1. All baseline investigations have now been completed, and patients are being followed as per the study schedule. The trial consists of a 40-week period of randomized treatment followed by a 6-week period designed to detect effects caused by prolonged treatment rather than direct pharmacological effects. At the baseline visit, informed consent is taken, and weight and heart rate are recorded. Office blood pressure is measured using a British Hypertension Society-validated semiautomated device on 3 occasions in the seated position after 5 minutes of rest with research staff present during the measurement; the mean of the last 2 readings

is used for analysis. Participants undergo 24-hour ambulatory blood pressure monitoring at baseline using a British Hypertension Society-validated oscillometric recorder set to make measurements every 30 minutes between 8:00AM and 10:00PM and hourly during the remaining hours. In addition, all patients undergo blood and urine tests, a cardiac MRI scan, and PWV and pulse wave analysis testing, after which the trial medication is given to the patient. More detail on the study investigations is given below. The measurement and analysis of end points are performed by observers blinded to treatment allocation.

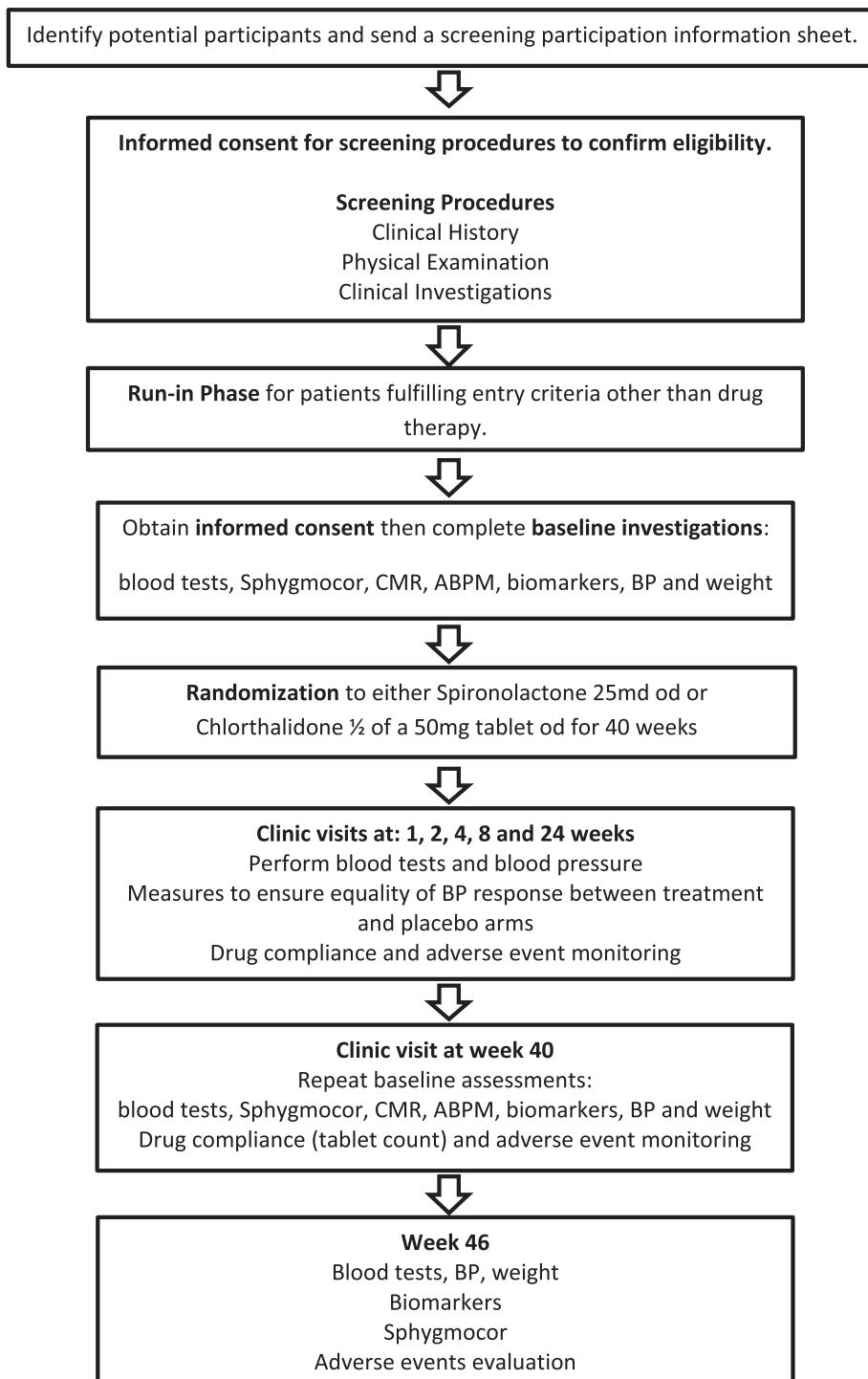
Participants are followed up at weeks 1, 2, 4, 8, 24, 40, and 46 postrandomization. In the event of participants being unable to attend for scheduled visits because of other intercurrent issues, they are asked to attend at the closest possible date, whenever possible within 2 weeks of the due date. Where a participant cannot attend their week 40 study visit and investigations, they are asked either to undertake this visit up to 3 weeks before the due date or, alternatively, to continue the study medication until the scheduled investigations can be undertaken (whenever possible within 4 weeks of the planned date).

The investigations listed below are carried out at time intervals during the trial as listed in Figure 1 and Appendix 1. All end points including SphygmoCor and cardiac MRI values are measured by investigators blinded to treatment allocation.

Blood and urine. Routine hematological and biochemical parameters, including plasma lipids, are recorded at weeks 0, 1, 2, 4, 8, 24, 40, and 46 as indicated in Appendix 1. Plasma is stored for measurement assays of NT-pro-BNP and other biomarkers. Separate consent is also sought to take blood for DNA extraction to allow future analysis for genetic influences on kidney disease and response to treatment. Urine samples are collected for analysis of albumin-creatinine ratio and other biomarkers.

Pulse wave velocity. SphygmoCor (AtCor Medical, Sydney, Australia) studies are performed at weeks 0, 4, 24, 40, and 46. Carotid femoral PWV is the current standard technique for measuring aortic stiffness.¹³ Subjects are studied in a quiet, temperature-controlled

Figure 1



Trial procedure flowchart.

room after 15 minutes of lying supine. Firstly, supine blood pressure is measured 3 times in the nondominant arm, and the final 2 readings are averaged and entered into the machine software. PWV (SphygmoCor) is determined by sequential acquisition of pressure waveforms from the carotid and femoral arteries by using a high-fidelity micromanometer (SPC-301; Millar Instruments, Houston, TX).^{14,15} The path length is calculated by subtracting the distance between the sternal notch and the carotid recording site from the distance between the sternal notch and the femoral site.¹³

Pulse wave analysis. Participants are requested to rest in a supine position for 5 minutes before measuring seated blood pressure 3 times in the nondominant arm. Again, an average of the final 2 blood pressures is entered into the machine software prior to undertaking applanation tonometry to record high-fidelity arterial pressure waveforms, from which indices relating to large artery stiffness can be calculated.^{14,16} A micromanometer is used to flatten but not occlude the radial artery of the nondominant arm using gentle pressure. An averaged peripheral waveform and the corresponding central waveform are generated after 11 seconds of data capture. The central waveform will then be analyzed to determine the augmentation index (the difference between the second and first peaks of the central pressure waveform, expressed as a percentage of the pulse pressure) and central aortic pressures. This method has been shown to be reproducible both in healthy subjects and in patients with CKD.^{14,16}

Cardiac MRI. Cardiac MRI is performed using standard clinical 1.5-T (Siemens Aera and Avanto—London, Birmingham; GE Discovery MR450—Cambridge) or 3-T (Siemens Verio—Edinburgh) scanners at each site at weeks 0 and 40.

Image acquisition. The standard protocol is estimated to take 30 minutes. Serial contiguous short-axis cines are piloted from the vertical long-axis and horizontal short-axis images of the left and right ventricles for assessment of dimensions, volumes, LV function (ejection fraction, deformation), and mass in line with the standard cardiovascular MRI protocol.^{17,18} Regional aortic distensibility will be assessed on cine imaging in the proximal ascending aorta using the following formula: aortic distensibility = Δ aortic area/(minimum aortic area \times pulse pressure). Peripheral blood pressure is performed synchronously in triplicate at the brachial artery at the time of scanning for determination of pulse pressure.

Subjects are also asked for consent to participate in additional cardiac MRI substudies (detailed below). Participation in both substudies lengthens the cardiac MRI scan duration to approximately 40 and 50 minutes respectively.

Substudy A: tagging (cine spatial modulation of magnetization). Cardiac MRI is used to assess regional myocardial function (deformation) and is the recognized reference standard for measuring strain. This sensitive measure of regional and global LV contractile function permits the early detection of subtle LV dysfunction which

precedes decreases in ejection fraction.^{19,21} Cine spatial modulation of magnetization is used to generate a uniform grid pattern with 8-mm tag separation on the LV myocardium at 3 short-axis sections (basal, mid, and apex) and the horizontal long-axis image using a fast field echo multishot sequence (minimum number of 15 phases per cardiac cycle) with prospective electrocardiogram gating.

Substudy B. T1 mapping. T1 mapping using modified Look-Locker inversion recovery sequence is performed to characterize the myocardial tissue and quantify the extent of diffuse interstitial fibrosis.^{22,23} Pixel-based T1 maps will be reconstructed using inline motion correction in the LV horizontal long axis. Basal and mid short-axis slices will be acquired before and 15 minutes after contrast administration for myocardial T1 times and calculation of extracellular volume (ECV) using a 5(3)3 sampling protocol (average breath hold 10-15 seconds). A single, weight-adjusted dose (0.15 mmol/kg) of nonionic, macrocyclic intravenous gadolinium contrast (Gadavist; Bayer Healthcare, Berkshire, England) is given to assess coarse irreversible fibrosis (late gadolinium enhancement) using standard inversion recovery imaging. In the event of a fall in eGFR to <30 mL/min/ 1.73 m², gadolinium contrast will not be administered on safety grounds.

Image analysis. Analysis of ventricular volumes, function, and mass is performed offline using cvi42 software (Circle Cardiovascular Imaging, Calgary, Canada) at a central cardiac MRI laboratory by a single experienced clinician blinded to all trial data. Measurement of aortic cross-sectional area in systole and diastole is assessed using automated software (Matlab; MathWorks Inc, Natick, MA).²⁴ Measurement of aortic distensibility using cardiac MRI has low intraobserver variability and good reproducibility.²⁵ Tagging analysis is performed using CIMTag2D; University of Auckland, New Zealand and Tissue Tracking, cvi42 for LV strain, strain rate, and torsion calculation.³³ For T1 mapping, myocardial and blood relaxation times pre- and 15 minutes after gadolinium contrast are measured offline to calculate native T1 times and ECV using cvi42 software.²⁶ Segmental and global T1 values are obtained using the AHA 6 segment model in short-axis slices and a manual region of interest in the basal septum from the 4-chamber image. Meticulous care will be taken to avoid the blood-myocardial boundary (10% offset from both the epicardial and endocardial borders) and any areas of LGE. ECV will be calculated using myocardial and blood T1 values before and after contrast using the following validated formula²⁷:

$$ECV = \lambda \times (1 - Hct).$$

Hct refers to the hematocrit recorded on a venous blood sample at the time of scan, $\Delta R1 = 1/T1$ time postcontrast - $1/T1$ time precontrast. Lambda (λ) refers to $(1/T1$ myocardium postcontrast - $1/T1$ myocardium precontrast)/($1/T1$ blood postcontrast - $1/T1$ blood precontrast). Normal reference ranges for T1 and ECV

(mean \pm 2 SDs) are defined using the healthy volunteers from a previously published study.²⁸

Withdrawal

Patients may withdraw consent from the study at any time. Patients may also withdraw from trial treatment but continue with study follow-up and data collection as per the protocol.

If the withdrawal is initiated by a health care professional, full details for the reason for withdrawal are recorded on the case report forms. In all other cases, a simple statement reflecting patient preference is noted.

Pharmacovigilance

This trial is categorized by the Medicines and Healthcare products Regulatory Agency as type A (no higher than the risk of standard medical care). Patients are being followed up closely throughout this study, and an ongoing evaluation of risk will continue throughout the recruitment period. Both spironolactone and chlorthalidone are considered investigational medicinal products (IMPs) within SPIRO-CKD trial. Any adverse events or serious adverse events that occur during this trial are reportable to the SPIRO-CKD Trials Office at the trials unit up to 6 weeks following last administration of the IMP. Any suspected unexpected serious adverse reactions related to the IMP will be reported irrespective of how long after IMP administration the reaction occurred. Responses to abnormalities of serum sodium, potassium, and eGFR will be guided by predetermined management plans (see Appendix 2).

Blood pressure monitoring

To confirm or deny the trial hypothesis, it is essential that the change in blood pressure during the treatment period is not significantly different in each arm of the trial. A tight blood pressure target was thought impractical; instead, a blood pressure monitoring committee (BPMC) reviews the blood pressure data after each block of 20 patients for the first 100 patients and then after each block of 30 patients to the end of trial recruitment. The precise frequency of review may change on the advice of the BPMC following its independent review of the data. Patients enter the trial with controlled blood pressure so that there are not anticipated to be clinical reasons for adding further drugs for blood pressure control during the randomized treatment phase. In the event of a difference in blood pressure change becoming evident, the BPMC will advise on changes to medication in either arm.

Data Monitoring Committee

An independent Data Monitoring Committee (DMC) has been convened for the trial. Interim analyses of major outcome measures and safety data are conducted and provided in strict confidence to the DMC. Any decision to stop the trial early will be based on the balance of efficacy and safety.

The DMC advises the chair of the Trial Steering Committee if, in its view, any of the randomized comparisons in the trial have provided both (a) proof beyond reasonable doubt that for all, or for some, types of participant, 1 particular intervention is definitely indicated or definitely contraindicated in terms of a net difference of the major end point and (b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results.

Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least $P < .001$ (similar to a Haybittle-Peto stopping boundary) in an interim analysis of a major end point may be required to justify halting, or modifying, the study prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, so no fixed schedule is proposed. Given these relatively strict stopping criteria, no adjustment for multiple testing (to control the overall type I error rate) is proposed.

Sample size

Data from the CRIB-2 study has been used to inform the sample size.⁹ The SD of change in arterial stiffness measured by PWV was 1.0 m/s in the spironolactone group and 0.9 m/s in the placebo group (with a mean difference between groups of 0.7 m/s). Using the larger of these SDs (1.0 m/s) for the sample size, to detect a minimum relevant difference (MRD) of 0.4 m/s (the smallest difference that is of clinical significance and that can be detected within the limits of accuracy of the equipment used) in PWV (with 90% power, 2-sided $\alpha = .025$) required 157 per arm. Allowing for 10% dropout, this required recruitment of 350 participants. The SD of change in LV mass was 13 g in the spironolactone group and 11 g in the placebo group (with a mean difference between groups of 17 g). Again, using the larger of these SDs (13 g) for the sample size calculation, to detect an MRD of 7 g in LV mass (with 90% power, 2-sided $\alpha = .025$) required 87 per arm. Allowing for 10% dropout, this required recruitment of 200 participants.

The initial design of the study used a co-primary end point of change in LV mass and change in PWV. A sample size of 350 patients was planned to give 90% power to detect a difference in PWV and >90% power to detect a change in LV mass with a P value of .025. When it became evident that this sample size was not achievable within the funded time, the primary outcome of the study was changed to the single end point of change in LV mass again using an MRD of 7 g. With a 2-sided P value of .05 and a power of 85%, it was calculated that 63 patients per group would be required. Allowing for a 15% dropout and missing data, this requires 150 participants.

Statistical analysis

The primary comparison groups are composed of those randomized to spironolactone and those randomized to chlorthalidone. All analyses will be based on the

intention-to-treat principle, with all patients analyzed in the treatment groups to which they were allocated irrespective of compliance with the randomized allocated treatment, and all patients will be included in the analyses. For all tests, summary statistics (eg, mean differences, relative risks) will be reported, and 95% CIs will be constructed where appropriate. A *P* value of $<.05$ will be considered statistically significant, and there will be no adjustment for multiple comparisons.

Primary outcome analysis

LV mass is measured at baseline and 40 weeks. Any missing cardiac MR data will be counted as missing in the first instance. A regression model with LV mass at 40 weeks as the outcome variable, and treatment group and baseline LV mass included as covariates in the model will be fitted. Results will be presented as a mean difference between groups with a 95% CI. These analyses assume that the data will be normally distributed (as is expected). Details of nonparametric analysis methods that will be used should the assumption of normality not hold will be provided in the Statistical Analysis Plan.

Secondary outcome analysis

Arterial stiffness is measured at baseline and at weeks 4, 24, and 40. The primary analysis for arterial stiffness will be as per the primary outcome. A regression model with arterial stiffness at 40 weeks as the outcome variable, and treatment group and baseline arterial stiffness included as covariates in the model will be fitted. A secondary analysis will also be conducted using a longitudinal repeated-measures analysis without the random statement. The variables treatment group (with chlorthalidone as the reference group) and baseline arterial stiffness will be included in the model as a covariates. The repeated statement variable will be time. Analyses will be conducted in Stata using the xtreg command or SAS using the proc. mixed command.

Safety evaluation

The proportion of patients reporting hyperkalemia, a decline in renal function (requiring discontinuation of trial therapy), symptomatic hypotension (requiring discontinuation of trial therapy), and proportion of patients reporting adverse effects (requiring discontinuation of trial therapy) will be analyzed as categorical variables using a χ^2 test, with relative risks and 95% CIs reported. The proportion of patients who died and the proportion of patients who experienced a cardiovascular event will be compared in the 2 treatment groups. A relative risk and 95% CI will be reported, but no hypothesis testing will be performed.

Impact

For most subjects with early-stage CKD, the risk of death greatly exceeds the risk of progression to end-stage renal disease, and much of the premature mortality is due

to cardiovascular disease.²⁹ There is a pressing need, therefore, for research into treatments to reduce the cardiovascular mortality and morbidity of this high-risk group. Published randomized trials of treatments to reduce cardiovascular risk in subjects with early-stage CKD are few. In the SHARP trial, statins reduced atherosclerotic events but had a disappointing impact on total cardiovascular mortality, suggesting that much cardiovascular disease in CKD is not atherosclerotic.³⁰ This result is in line with epidemiological data suggesting that, in CKD, sudden death, heart failure, and stroke are much more common than myocardial infarction.⁴ Although ACE inhibitors are commonly used in subjects with CKD and may have risk-reducing effects similar to those seen in the general population, physicians have tended to avoid MRB drugs because of concerns about hyperkalemia.

In a previous study, we showed that LV mass and arterial stiffness were improved with spironolactone with few hyperkalemic problems in subjects with stages 2 and 3 CKD under close monitoring. This trial will further examine the use of spironolactone in a similar cohort and will specifically test the hypothesis that the effects of spironolactone on LV mass demonstrated in the CRIB-2 study were due to specific MRB-mediated effects and not to nonspecific blood pressure-lowering effects. This hypothesis has biological plausibility in view of the known cardiovascular inflammatory, fibrotic, and hypertrophic actions of aldosterone and the antagonistic effects of MRB drugs on these processes.¹² Furthermore, in the 4E study of subjects with LVH, the addition of eplerenone to enalapril caused significant reduction in LV mass with little effect on blood pressure.³¹ Cardiac MRI is the method of choice for determining changes in LV mass in response to treatment because of its high interstudy reproducibility, lack of dependence on geometric assumptions, and independence of changes in volume.^{32,33} Spironolactone may be a powerful treatment to reverse or delay the onset of LVH and myocardial fibrosis in patients with CKD. As both hypertrophy and fibrosis are likely key intermediate phenotypic changes that result in an increased risk of heart failure and arrhythmia in many patient groups, the data will be of great value in establishing a mode of action of these drugs that may be relevant to subjects with CKD and other at-risk groups.³⁴ The range of secondary end points including arterial stiffness, aortic distensibility, LV fibrosis, systolic and diastolic function, kidney function, and biomarkers may also provide powerful evidence of differences in the effects of MRB and diuretic drugs.

The effect of thiazide-like drugs on LV mass in early-stage CKD has not previously been examined, although they are effective in lowering blood pressure in this group. The study will also provide evidence on the safety of both spironolactone and chlorthalidone in subjects with early-stage CKD, giving valuable data on the effects of both drugs on kidney function measured by eGFR and on changes in serum potassium and sodium

concentrations. If safety and efficacy are confirmed, the rationale would be provided for a larger clinical trial designed to examine the effects of MRB drugs on cardiovascular morbidity and mortality end points. It is acknowledged that the nonblinded study design increases the risk of bias, but the PROBE design maintains the benefits associated with a strict randomization procedure, whereas the blinded end points help to eliminate bias. In a meta-analysis of trials of an ARB, changes in mean 24-hour ambulatory blood pressure in double-blind and PROBE trials were not significantly different.⁵⁵

Acknowledgements

We acknowledge the assistance and facilities provided by the NIHR/Wellcome Trust Birmingham Clinical Research Facility.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ahj.2017.05.008>.

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