# A randomised multicentre open label blinded end point trial to compare the effects of spironolactone to chlortalidone on left ventricular mass in stage 2 and stage 3 chronic kidney disease

Submission date	Recruitment status	<ul><li>Prospectively registered</li></ul>
16/01/2014	No longer recruiting	[X] Protocol
Registration date	Overall study status	Statistical analysis plan
16/01/2014	Completed	[X] Results
<b>Last Edited</b> 20/05/2022	<b>Condition category</b> Circulatory System	[] Individual participant data

#### Plain English summary of protocol

Current plain English summary as of 26/03/2019:

Background and study aims

Chronic kidney disease (CKD) is a major risk factor for heart and blood vessel disease. Mild CKD is surprisingly common, affecting almost 1 in 7 of the population. The adverse cardiovascular (heart) effects of CKD are caused mainly by damage and thickening of the heart muscle and an increase in artery stiffness, which together cause stroke, heart failure and sudden cardiac death. We have previously shown that an old and inexpensive drug called spironolactone reduces the heart thickening and arterial stiffening in CKD compared to an inactive (placebo) tablet. During treatment with spironolactone however, blood pressure fell and it is not clear whether the beneficial effects of this drug on the heart and arteries were caused by this fall in blood pressure or were specific to the effects of spironolactone. The aim of this study is to compare the effects of spironolactone to a different blood pressure lowering drug called chlortalidone on patients with early CKD.

Who can participate?

Patients aged over 18 with early CKD

What does the study involve?

Participants are randomly allocated to take either spironolactone or chlortalidone for 40 weeks. Changes in heart muscle weight and arterial stiffness are measured.

What are the possible benefits and risks of participating?

The results should show whether or not the effects of spironolactone on the arteries and heart in patients with CKD are due to blood pressure lowering alone or are due to the special effects

of spironolactone. If the effects are specific to spironolactone and occur over and above the blood pressure lowering effects, the drug may be a very effective and inexpensive way to prevent death and disability due to heart and artery disease in patients with CKD.

Where is the study run from? Birmingham Clinical Trials Unit (UK)

When is the study starting and how long is it expected to run for? January 2014 to June 2019

Who is funding the study?
British Heart Foundation (BHF) (UK)

Who is the main contact? Dr Rebekah Wale spiro-ckd@trials.bham.ac.uk

Previous plain English summary:

Background and study aims

Chronic kidney disease (CKD) is a major risk factor for heart and blood vessel disease. Mild CKD is surprisingly common, affecting almost 1 in 7 of the population. The adverse cardiovascular (heart) effects of CKD are caused mainly by damage and thickening of the heart muscle and an increase in artery stiffness, which together cause stroke, heart failure and sudden cardiac death. We have previously shown that an old and inexpensive drug called spironolactone reduces the heart thickening and arterial stiffening in CKD compared to an inactive (placebo) tablet. During treatment with spironolactone however, blood pressure fell and it is not clear whether the beneficial effects of this drug on the heart and arteries were caused by this fall in blood pressure or were specific to the effects of spironolactone. The aim of this study is to compare the effects of spironolactone to a different blood pressure lowering drug called chlortalidone on patients with early CKD.

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Where is the study run from? Birmingham Clinical Trials Unit (UK)

When is the study starting and how long is it expected to run for? January 2014 to March 2018

Who is funding the study?
British Heart Foundation (BHF) (UK)

Who is the main contact? Dr Rebekah Wale spiro-ckd@trials.bham.ac.uk

#### Study website

https://www.birmingham.ac.uk/spiro-ckd

## Contact information

#### Type(s)

Scientific

#### Contact name

Dr Rebekah Wale

#### Contact details

Institute of Applied Health Research College of Medical and Dental Sciences Public Health Building University of Birmingham Birmingham United Kingdom B15 2TT

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spiro-ckd@trials.bham.ac.uk

## Additional identifiers

EudraCT/CTIS number

2013-002636-25

**IRAS** number

ClinicalTrials.gov number

Secondary identifying numbers

15739

# Study information

#### Scientific Title

A randomised multicentre open label blinded end point trial to compare the effects of spironolactone to chlortalidone on left ventricular mass in stage 2 and stage 3 chronic kidney disease

#### Acronym

SPIRO - CKD

#### Study objectives

Chronic kidney disease (CKD) is a major but poorly recognised risk factor for heart and blood vessel disease. Mild CKD is surprisingly common affecting almost 1 in 7 of the population. The adverse cardiovascular effects of CKD are caused mainly by damage and thickening of heart muscle and an increase in artery stiffness which together cause stroke, heart failure and sudden cardiac death. We have previously shown that an old and inexpensive drug called spironolactone reduces the heart thickening and arterial stiffening in CKD compared to an inactive placebo tablet. During treatment with spironolactone however, blood pressure fell and it is not clear whether the beneficial effects of this drug on the heart and arteries were caused by this fall in blood pressure or were specific to the effects of spironolactone.

#### Ethics approval required

Old ethics approval format

#### Ethics approval(s)

13/WM/0304; First MREC approval date 09/09/2013

#### Study design

Randomised; Interventional; Design type: Not specified, Treatment

#### Primary study design

Interventional

#### Secondary study design

Randomised controlled trial

#### Study setting(s)

Hospital

#### Study type(s)

Treatment

#### Participant information sheet

Not available in web format, please use contact details to request a participant information sheet

#### Health condition(s) or problem(s) studied

Topic: Cardiovascular, Renal and Urogenital; Subtopic: Cardiovascular (all Subtopics), Renal and Urogenital (all Subtopics); Disease: Cardiovascular, Renal

#### Interventions

Participants are randomly allocated to treatment with either spironolactone (25 mg od.) or chlortalidone (half a 50 mg tablet od.) for 40 weeks.

12-lead ECG: 12-lead ECG to be performed at the screening visit according to standard clinical practice. The primary function of the ECG is to detect any evidence of Q-wave myocardial infarction or atrial fibrillation (which would exclude the participant from the study).

Ambulatory BP: A mobilograph will be used to record 24 hour brachial and central blood pressure, cardiac output and other indices derived from pulse wave analysis; Arterial

haemodynamics, SphygmoCor system to be used to record central blood pressure and arterial stiffness.

Cardiac MRI scan: CMR scans will be performed at the randomisation/baseline visit and visit 6

Laboratory assessments: Standard clinical lab investigations done at: screening visit; visit 3; visit 6.

Additional clinical lab investigations for renal function and safety to be done at: randomisation visit; visit 1; visit 2; visit 4 and visit 5.

Blood and urine for cardiovascular biomarkers to be taken at: randomisation visit; visit 3; visit 5; visit 6 and visit 7

#### Intervention Type

Drug

#### Phase

Not Applicable

#### Drug/device/biological/vaccine name(s)

Spironolactone, chlortalidone

#### Primary outcome measure

Current primary outcome measure as of 26/04/2018:

Change between baseline and 40 weeks in left ventricular mass measured by cardiac magnetic resonance imaging at 40 weeks.

This change is per protocol v4.0, 28/11/2016

Previous primary outcome measure as of 13/02/2018:

Change between baseline and 40 weeks in left ventricular mass measured by cardiac magnetic resonance imaging at 40 weeks

Previous primary outcome measure:

Change between baseline and 40 weeks in arterial stiffness measured by carotid-femoral PWV; Timepoint(s): 40 weeks

#### Secondary outcome measures

Current secondary outcome measures as of 13/02/2018:

- 1. Change between baseline and 40 weeks in arterial stiffness measured by carotid-femoral PWV (following change to single primary end point); Timepoint(s): 40 weeks
- 2. Incidence of hyperkalaemia; Timepoint(s): 46 weeks
- 3. Change between baseline and 40 weeks in blood pressure; Timepoint(s): 40 weeks
- 4. Change between baseline and 40 weeks in urinary albumin:creatinine ratio; Timepoint(s): 40 weeks
- 5. Decline in renal function (requiring discontinuation from the trial therapy); Timepoint(s): 40 weeks
- 6. Symptomatic hypotension (requiring discontinuation from trial therapy); Timepoint(s): 40 weeks
- 7. Incidence of side-effects (requiring discontinuation from trial therapy); Timepoint(s): 40 weeks
- 8. Changes between baseline and 40 weeks in left ventricular volumes and systolic function;

Timepoint(s): 40 weeks

- 9. Changes between baseline and 40 weeks in plasma NT-pro-BNP therapy; Timepoint(s): 40 weeks
- 10. Changes in plasma NT-pro-BNP and arterial stiffness measures including PWV, augmentation index and central blood pressure measured at 24 weeks; Timepoint(s): 24 weeks

Previous secondary outcome measures:

- 1. Change between baseline and 40 weeks in blood pressure; Timepoint(s): 40 weeks
- 2. Change between baseline and 40 weeks in LV mass measured by cardiac MRI (co-primary outcome); Timepoint(s): 40 weeks
- 3. Change between baseline and 40 weeks in urinary albumin:creatinine ratio; Timepoint(s): 40 weeks
- 4. Changes between baseline and 40 weeks in plasma NT-pro-BNP therapy; Timepoint(s): 40 weeks
- 5. Changes in plasma NT-pro-BNP and arterial stiffness measures; Timepoint(s): 24 weeks
- 6. Decline in renal function (requiring discontinuation from trial therapy); Timepoint(s): 40 weeks
- 7. Incidence of hyperkalaemia; Timepoint(s): 46 weeks
- 8. Incidence of side-effects (requiring discontinuation from trial therapy); Timepoint(s): 40 weeks
- 9. Symptomatic hypotension (requiring discontinuation from trial therapy); Timepoint(s): 40 weeks

#### Overall study start date

15/01/2014

#### Completion date

30/06/2019

# Eligibility

#### Key inclusion criteria

Current inclusion criteria as of 13/02/2018:

- 1. Aged over 18 years
- 2. Willingness to undertake all procedural investigations
- 3. Patients with either stage 2 or stage 3 CKD (eGFR by 4 MDRD equation of 30-89 ml/min/1.732, from blood tests performed within the last 12 months, on 2 occasions, at least 90 days apart)
- 4. Controlled blood pressure. The local PI must be satisfied that BP control will be clinically satisfactory during the 46 week study period
- 5. On established (>6 weeks) treatment with ACE inhibitors or ARBs
- 6. Clinically stable (no hospital admission or significant acute illness within 3 months and no recent (<6 months) acute myocardial infarction or symptoms, or other evidence, of heart failure and/or left ventricular dysfunction)
- 7. Written informed consent

#### Previous inclusion criteria:

- 1. Aged over 18 years
- 2. Diagnosis of stage 3 CKD [estimated glomerular filtration rate (eGFR) by 4 variable Modification of Diet in Renal Disease (MDRD) of 3059ml/min/1.73m2 on 2 occasions, at least 3 months apart]
- 3. Well controlled blood pressure (office reading of <150/90 mmHg, i.e. within 10 mmHg of the systolic level recommended in the Renal Association Clinical Practice Guideline, Fifth edition)
- 4. On established (>6 weeks) treatment with angiotensin-converting-enzyme (ACE) inhibitors or

angiotensin receptor blockers (ARBs)

5. Written informed consent

#### Participant type(s)

**Patient** 

#### Age group

Adult

#### Lower age limit

18 Years

#### Sex

Both

#### Target number of participants

Planned Sample Size: 350; UK Sample Size: 350;

#### Total final enrolment

154

#### Key exclusion criteria

Current exclusion criteria as of 13/02/2018:

- 1. Diabetes mellitus
- 2. Clinical evidence of hypovolaemia
- 3. On current regular treatment with non-steroidal anti-inflammatory drugs, or other agents (except ACEi, ARB or low-dose aspirin) that might cause a reduction in GFR.
- 4. Recent (<6 months) acute myocardial infarction or other major adverse cardiovascular event
- 5. Known left ventricular systolic dysfunction or severe valvular disease
- 6. Active malignant disease with a life expectancy of <5 years
- 7. Previous hyperkalaemia (K+ =6.0 mmol/l without precipitating cause)
- 8. Serum K+=5.0 mmol/l at entry
- 9. Serum sodium <130 mmol/l at entry
- 10. Current treatment with spironolactone or other MRB
- 11. Atrial fibrillation on screening ECG
- 12. Use of a thiazide or loop diuretic in the 6 weeks prior to enrolment
- 13. Pregnant or breast feeding
- 14. Known alcohol or drug abuse
- 15. Active chronic diarrhoea
- 16. Recent active gout (within 3 months)
- 17. Episode of acute kidney injury within 3 months
- 18. Documented Addisons disease
- 19. Current treatment with fludrocortisone, lithium, or cotrimoxasole
- 20. Combination treatment with ACE inhibitor and ARB
- 21. Office blood pressure <115 mmHg systolic or <50 mmHg diastolic
- 22. Office blood pressure uncontrolled and requiring urgent non trial treatment in the opinion of the clinical investigator

#### Previous exclusion criteria:

- 1. Diabetes mellitus
- 2. Clinical evidence of hypovolaemia

- 3. Recent (<6 months) acute myocardial infarction or other major adverse cardiovascular event
- 4. Established diagnosis of left ventricular dysfunction or heart failure
- 5. Active malignant disease with a life expectancy of <5 years
- 6. Previous hyperkalaemia (K+ =6.0 mmol/l without precipitating cause)
- 7. Serum K+ =5.0 mmol/l at entry
- 8. Serum sodium <132 mmol/l at entry
- 9. Atrial fibrillation on screening ECG
- 10. Use of a thiazide or loop diuretic in the 6 weeks prior to enrolment
- 11. Pregnancy
- 12. Known alcohol or drug abuse
- 13. Active chronic diarrhoeal illness
- 14. Recent active gout (within 3 months)
- 15. Episode of acute kidney injury within 3 months
- 16. Documented Addisons disease
- 17. Current treatment with fludrocortisone or cotrimoxasole
- 18. Office blood pressure <115 mmHg systolic or <50 mmHg diastolic

#### Date of first enrolment

15/01/2014

#### Date of final enrolment

15/01/2017

### Locations

#### Countries of recruitment

England

United Kingdom

# Study participating centre Birmingham Clinical Trials Unit

Birmingham United Kingdom B15 2TT

# Sponsor information

#### Organisation

University of Birmingham (UK)

#### Sponsor details

Edgbaston Birmingham England United Kingdom B15 2TT

#### Sponsor type

University/education

#### **ROR**

https://ror.org/03angcq70

# Funder(s)

#### Funder type

Charity

#### **Funder Name**

British Heart Foundation (BHF) (UK); Grant Codes: SP/12/8/29620

#### Alternative Name(s)

the bhf, The British Heart Foundation, BHF

#### **Funding Body Type**

Private sector organisation

#### **Funding Body Subtype**

Trusts, charities, foundations (both public and private)

#### Location

**United Kingdom** 

## **Results and Publications**

### Publication and dissemination plan

Planned publication in a high-impact peer reviewed journal by 01/01/2019.

#### Intention to publish date

31/07/2020

#### Individual participant data (IPD) sharing plan

Participant level data sharing is guided by normal CTU policy. It is available upon request from The CI.

#### IPD sharing plan summary

Available on request

## Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<u>Protocol article</u>	protocol	01/09/2017	17/12/2020	Yes	No
Basic results		25/06/2020	20/05/2022	No	No
HRA research summary			28/06/2023	No	No