

# 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

<b>Submission date</b> 16/01/2014	<b>Recruitment status</b> No longer recruiting	<input type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
<b>Registration date</b> 16/01/2014	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
<b>Last Edited</b> 20/05/2022	<b>Condition category</b> Circulatory System	<input type="checkbox"/> 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  
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Previous plain English summary:

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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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Birmingham Clinical Trials Unit (UK)

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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

## Contact information

**Type(s)**  
Scientific

**Contact name**  
Dr Rebekah Wale

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## Additional identifiers

**Clinical Trials Information System (CTIS)**  
2013-002636-25

**Protocol serial number**  
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

### **Study type(s)**

Treatment

### **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(s)**

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

**Key secondary outcome(s)**

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

**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 30-59ml/min/1.73m<sup>2</sup> 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

**Healthy volunteers allowed**

No

**Age group**

Adult

**Lower age limit**

18 years

**Sex**

All

**Total final enrolment**

**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 ( $K^+ \geq 6.0$  mmol/l without precipitating cause)
8. Serum  $K^+ \geq 5.0$  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 cotrimoxazole
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 ( $K^+ \geq 6.0$  mmol/l without precipitating cause)
7. Serum  $K^+ \geq 5.0$  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 cotrimoxazole
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**

United Kingdom

England

**Study participating centre**

**Birmingham Clinical Trials Unit**

Birmingham

United Kingdom

B15 2TT

## Sponsor information

**Organisation**

University of Birmingham (UK)

**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 British Heart Foundation, the\_bhf, BHF

**Funding Body Type**

Private sector organisation

**Funding Body Subtype**

Trusts, charities, foundations (both public and private)

**Location**

## Results and Publications

### 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?
<a href="#">Protocol article</a>	protocol	01/09/2017	17/12/2020	Yes	No
<a href="#">Basic results</a>		25/06/2020	20/05/2022	No	No
<a href="#">HRA research summary</a>			28/06/2023	No	No
<a href="#">Study website</a>	Study website	11/11/2025	11/11/2025	No	Yes