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

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:
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

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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 surprisngly 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 avaialble 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?
Protocol article	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