ISRCTN44522369 https://doi.org/10.1186/ISRCTN44522369

Benefits of Aldosterone Receptor Antagonism in Chronic Kidney Disease (BARACK-D) Trial: A potential new treatment for kidney disease

Submission date
28/06/2013

Recruitment status
No longer recruiting

Registration date
28/06/2013

Overall study status
Completed

Last Edited
25/03/2025

Condition category
Urological and Genital Diseases

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Current plain English summary as of 17/10/2022:
Background and study aims
Chronic Kidney Disease (CKD) affects around 10% of the UK population. It is linked with increasing age and is more common in people with other illnesses such as hypertension, diabetes mellitus, obesity and primary renal disorders. Of interest to this study, CKD is a major contributor to cardiovascular disease, with CKD patients showing a greater incidence of heart failure and sudden cardiac death. Conventional treatments for cardiovascular disease have been disappointing in CKD patients. There are also limited treatment options to prevent further decline in kidney function. Established drugs called aldosterone receptor antagonists reduce deaths in patients with heart disease. There is also evidence that these drugs may reduce kidney damage attributed to circulating aldosterone. In order to answer the research question, we will conduct a prospective randomised open-blinded endpoint (PROBE) trial using a low dose of the aldosterone receptor antagonist, spironolactone.

Who can participate?
Six NIHR School for Primary Care Research departments will recruit approximately 300 GP practices which in turn will aim to recruit approximately 3022 men and women who meet the criteria for a diagnosis of CKD stage 3b (ascertained from their last 2 blood tests); the participants also need to meet full trial inclusion criteria.

What does the study involve?
Participants will be seen over a period of 3 years. They will be randomly allocated (by a computer programme) to one of two groups of the trial, either a) to receive routine care only or b) to receive the aldosterone receptor antagonist Spironolactone (25mg daily dose) on top of routine care. After their initial visit and random allocation to one of the two groups, the follow-up schedule of visits will be at weeks 1, 2, 4, 12, and 26 and then at intervals of once every 13 weeks until the end of their participation at 156 weeks.

The trial measurements will vary according to the schedule but will consist of a combination of:
- blood pressure measurement

- blood tests
- side-effect monitoring
- questionnaires
- drug monitoring diary card completion
- home blood pressures diary card completion
- A subgroup of participants will take part in some additional procedures at intervals:
- 24-hour ambulatory blood pressure measurements
- pulse wave velocity and other arterial wall measurements

What are the possible benefits and risks of participating?
The group receiving Spironolactone potentially may derive protection against further kidney damage and heart disease. However, this will not be known until after trial completion. The group not receiving Spironolactone will receive no potential additional benefit on top of routine care, but do have the knowledge that their contribution to research helps towards the development of better treatments for people suffering from chronic kidney disease. The group not receiving trial medication will continue to receive routine care from their GP and therefore will be at no additional risk by taking part in the trial.

As with all medications, there are potential side effects from taking Spironolactone, but it is a medication that has been used for various conditions for many years and is considered safe to take for people with no sensitivity to it. Participants are closely monitored during the trial for any side effects. The main safety concern would be an increased potassium level in the blood (previous research has shown approximately 2 in 100 people may develop high potassium), therefore frequent blood samples are taken in the early part of the trial to check the level.

Where is the study run from?
University of Oxford Primary Care Clinical Trials Unit (UK)

When is the study starting and how long is it expected to run for?
June 2013 to December 2021

Who is funding the study?
National Institute for Health Research Health Technology Assessment Programme (UK)

Who is the main contact?
Ms Joy Rahman (Senior Clinical Trials Manager) (UK)
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Previous plain English summary:
Background and study aims
Chronic Kidney Disease (CKD) affects around 10% of the population. Cardiovascular disease (CVD) is a major cause of morbidity (the relative occurrence of disease) and death in CKD, although this is of a different phenotype (composition) from the general CVD population. Currently, few therapies have proved effective in modifying the increased CVD risk or the rate of renal decline in CKD. There are accumulating data that aldosterone receptor antagonists (ARAs) may offer cardio-protection and delay renal impairment in patients with the cardiovascular phenotype in CKD. The use of an aldosterone receptor blocker in CKD has therefore been increasingly advocated. The aim of the trial is to determine the effects of an ARA on renal and CVD outcomes.

Who can participate?
Six NIHR School for Primary Care Research departments will recruit approximately 300 GP

practices which in turn will aim to recruit approximately 3022 men and women who meet the criteria for a diagnosis of CKD stage 3b or low stage 3a (ascertained from their last 2 blood tests); the participants also need to meet full trial inclusion criteria.

What does the study involve?
Participants will be seen over a period of 3 years. They will be randomly allocated (by a computer programme) to one of two groups of the trial, either a) to receive routine care only, or b) to receive the aldosterone receptor antagonist Spironolactone (25mg daily dose) on top of routine care. After their initial visit and random allocation to one of the two groups, the follow-up schedule of visits will be at weeks 1, 2, 4, 12, 26 and then at intervals of once every 13 weeks until the end of their participation at 156 weeks.
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The group receiving Spironolactone potentially may derive protection against further kidney damage and heart disease. However, this will not be known until after trial completion. The group not receiving Spironolactone will receive no potential additional benefit on top of routine care, but do have the knowledge that their contribution to research helps towards the development of better treatments for people suffering from chronic kidney disease. The group not receiving trial medication will continue to receive routine care from their GP and therefore will be at no further risk by taking part in the trial.
As will all medications, there are potential side-effects from taking Spironolactone, but it is a medication that has been used for various conditions for many years and is considered safe to take for people with no sensitivity to it. Participants are closely monitored during the trial for any side-effects. The main safety concern would be an increased level of potassium in the blood (previous research has shown approximately 2 in 100 people may develop high potassium), therefore frequent blood samples are taken in the early part of the trial to check the level.

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University of Oxford Primary Care Clinical Trials Unit (UK)

When is the study starting and how long is it expected to run for?
June 2013 to December 2021

Who is funding the study?
The National Institute for Health Research School for Primary Care Research (UK)

Who is the main contact?
Mr Charles Vicary
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Contact information

Type(s)
Scientific

Contact name
Mr Charles Vicary

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Type(s)
Public

Contact name
Ms Joy Rahman

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Additional identifiers

Clinical Trials Information System (CTIS)
2012-002672-13

Integrated Research Application System (IRAS)
107072

Protocol serial number
14611, IRAS 107072

Study information

Scientific Title
Benefits of Aldosterone Receptor Antagonism in Chronic Kidney Disease (BARACK-D) Trial: a prospective randomised open-blinded endpoint trial to determine the effect of aldosterone receptor antagonism on mortality and cardiovascular outcomes in patients with stage IIIb chronic kidney disease

Acronym
BARACK-D

Study objectives
Hypothesis as of 17/10/2022:
BARACK-D is a prospective randomised open blinded endpoint trial (PROBE) of eligible patients from 300 practices recruited by 6 NIHR School for Primary Care Research departments. Patients identified by their GPs with a diagnosis of Chronic Kidney Disease (CKD) stage 3b will be invited to participate in the full trial and those declining will be asked for written consent to review their records only, for comparative data.
The trial aims to determine whether the addition of an aldosterone receptor antagonist in patients with moderate Chronic Kidney Disease (CKD Stage 3b):
1. Reduces death
2. Reduces onset, or progression of, cardiovascular disease
3. Improves measures of vascular resistance
4. Improves left ventricular function
5. Reduces decline in renal function, based upon measurement of estimated glomerular filtration rate (eGFR) on MDRD criteria

Hypothesis as of 09/12/2016:
BARACK D is a prospective randomised open blinded endpoint trial (PROBE) of eligible patients from 300 practices recruited by 6 NIHR School for Primary Care Research departments. Patients identified by their GPs with a diagnosis of Chronic Kidney Disease (CKD) stage 3b and low stage 3a will be invited to participate in the full trial and those declining will be asked for written consent to review their records only, for comparative data.

The trial aims to determine whether the addition of an aldosterone receptor antagonist in patients with moderate Chronic Kidney Disease (CKD Stage 3b and low 3a):
1. Reduces death
2. Reduces onset, or progression of, cardiovascular disease
3. Improves measures of vascular resistance
4. Improves left ventricular function
5. Reduces decline in renal function, based upon measurement of estimated glomerular filtration rate (eGFR) on MDRD criteria

Original hypothesis:
BARACK D is a prospective randomised open blinded endpoint trial (PROBE) of eligible patients from 120 practices recruited by 6 NIHR School for Primary Care Research departments. Patients identified by their GPs with a diagnosis of Chronic Kidney Disease (CKD) stage 3b will be invited to participate in the full trial and those declining will be asked for written consent to review their records only, for comparative data.

The trial aims to determine whether the addition of an aldosterone receptor antagonist in patients with moderate Chronic Kidney Disease (CKD Stage 3b):

reduces death
reduces onset, or progression of, cardiovascular disease
improves measures of vascular resistance
improves left ventricular function
reduces decline in renal function, based upon measurement of estimated glomerular filtration rate (eGFR) on MDRD criteria.

More details can be found at: http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=14611

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 09/04/2013 NRES Committee South Central Oxford B (Level 3, Block B, Whitefriars Building, Lewins Mead, Bristol, BS1 2NT, UK; +44 (0)207 104 8178, 0207104 8360, 0207 104 8283; oxfordb.rec@hra.nhs.uk), ref: 13/SC/0114

Study design
Prospective randomized open-blinded endpoint trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Chronic kidney disease

Interventions
Once-a-day treatment, This is provided on top of routine care.

The daily treatment is the licenced drug Spironolactone 25g (aldosterone receptor antagonist). This is a candidate for potential cardio-protection in CKD and delay of renal impairment in patients with the cardiovascular disease phenotype in CKD.

Routine Care: Routine care alone

Intervention Type
Drug

Phase
Phase III

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

Primary outcome(s)

Current primary outcome measure as of 17/10/2022:
Effect of aldosterone receptor antagonism on mortality and cardiovascular outcomes (onset or progression of cardiovascular disease); Timepoint(s): Randomisation to first occurrence. Subsequent assessments at weeks: 1, 2, 4, 12, 26.

Primary long-term: Effect of aldosterone receptor antagonism (even short-term use) on long-term mortality and cardiovascular outcomes; Timepoint(s): annual rates collected via medical notes review.

Previous primary outcome measure:
Effect of aldosterone receptor antagonism on mortality and cardiovascular outcomes; Timepoint (s): Baseline assessment (visit 0) and randomisation.
Subsequent assessments at weeks: 1, 2, 4, 12, 26

Key secondary outcome(s))

Current secondary outcome measures as of 17/10/2022:
1. The individual components of the composite primary outcome:
Total occurrences of hospitalisation or new onset heart disease (coronary heart disease, arrhythmia, atrial fibrillation, sudden death, resuscitated sudden death), stroke, transient ischaemic attack, peripheral arterial disease or heart failure.
2. Measures of cardiovascular haemodynamics:
Change in blood pressure annually and at the final visit
3. Measures of renal function:
Change from baseline, annually and to final visit for changes in natriuretic peptide, albumin: creatinine ratio, and estimated glomerular filtration rate.
4. Healthcare cost evaluation:
Change from baseline, annually and to final visit in health status on EQ-5D-5L, KDQol, (ICECAP-A and Qol VAS – Oxford only) and NHS resource use (records).
5. Safety of ARA in patients with stage 3b CKD on:
5.1. Rates of hypotension (<100mmHg systolic or >20 mmHg systolic drop on standing)
5.2. Rates of adverse events
5.3. Rates of hyperkalaemia

Previous secondary outcome measures:
Measures of cardiovascular haemodynamics
1. Change in carotid-femoral pulse wave velocity from baseline to final visit intensively phenotyped group.
2. Change in blood pressure annually and at final visit
3. Rates of hypotension (<100mgHg systolic or >20mmHg systolic drop on standing)
4. Mean change in ambulatory blood pressure from randomisation to final visited (measured in mmHg) intensively phenotyped group

Left ventricular function
1. Changes in brain natriuretic peptide (BNP)

Decline in renal function
1. Change in albumin:creatinine ratio (ACR)
2. Changes in estimated glomerular filtration rate (eGFR)

Treatment costs and benefits
1. Change in health status on EQ-5D-5L
2. Cost effectiveness analysis

Incidence of TIA
1. Transient Ischaemic Attack as defined by the American Heart Association (2009)

To determine the safety of ARA in patients with stage 3b CKD
1. Rates of adverse events
2. Rates of hyperkalaemia

Completion date
31/12/2021

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 17/10/2022:
1. Males and females >= 18 years of age
2. Evidence of CKD stage 3b from last 2 recorded blood tests
3. Willing and able to give informed consent for participation in the study
4. Able and willing (in recruiting GP's opinion) to comply with all study requirements
5. Female patients willing to ensure effective contraception for trial period

Previous participant inclusion criteria:
1. Males and females >= 18 years of age
2. Evidence of CKD stage 3b from last 2 recorded blood tests
3. Female patients willing to ensure effective contraception for trial period
4. Able and willing (in recruiting GPs opinion) to comply with all study requirements

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
1434

Key exclusion criteria
Current participant exclusion criteria as of 17/10/2022:
1. Female patient who is pregnant, lactating or planning pregnancy during the trial
2. Type 1 diabetes mellitus
3. Terminal disease or felt otherwise unsuitable by their physician
4. Chronic heart failure clinical diagnosis or known LVSD with EF<40%

5. Recent myocardial infarction (within 6 months)
6. Active cancer with less than 1-year life expectancy or in palliative care
7. Alcohol or drug abuse
7.1. Suspected or known current hazardous or harmful drinking, as defined by an alcohol intake of greater than 42 units every week
7.2. Suspected or known current substance misuse
8. Most recent potassium result >5.5 mmol/L, where not thought to be spurious, or previously raised potassium needing a reduced dose of ACEI/ARB or intolerance to spironolactone
9. eGFR >60 ml/min/1.73m2 in the last 6 months and no identifiable reason for a temporary reduction in eGFR
10. Serum potassium at baseline over 5 mmol/L
11. Documented Addisonian crisis and/or on fludrocortisone
12. Documented symptomatic hypotension or baseline systolic blood pressure under 100mmHg
13. Recent acute kidney injury or admission for renal failure
14. ACR > 70 mg/mmol
15. Prescription of medications with known harmful interactions with spironolactone as documented in the British National Formulary including tacrolimus, lithium and cyclosporine
16. Any other significant disease or disorder which, in the opinion of the recruiting physician, may either put the participants at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study

Previous participant exclusion criteria:
1. Intolerance to Spironolactone or on any prescription medications known to have harmful interactions with Spironolactone.
2. Terminal illness, or other significant medical history deemed unsuitable by GP for this trial.
3. Hyperkalaemia; Type 1 diabetes mellitus; Addisons disease.
4. Chronic heart failure; recent myocardial infarction (within 6 months); documented symptomatic hypotension; baseline systolic BP under 100mmHg.
5. Recent acute kidney injury or admission for renal failure.
6. Alcohol or drug abuse, suspected or known.
7. Female patient who is pregnant, lactating or planning pregnancy during course of the trial.

Date of first enrolment
06/12/2013

Date of final enrolment
31/07/2018

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University of Oxford
Primary Care Clinical Trials Unit
Nuffield Department of Primary Care Health Sciences

University of Oxford Radcliffe Primary Care Building
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Woodstock Road
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United Kingdom
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Sponsor information

Organisation
University of Oxford (UK)

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Government

Funder Name
NIHR (UK) - National School for Primary Care Research; Grant Codes: 118

Results and Publications

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		30/09/2024	02/10/2024	Yes	No
Results article		19/03/2025	25/03/2025	Yes	No
Protocol article	protocol	08/05/2014		Yes	No
HRA research summary			28/06/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes