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Angiotensin converting enzyme inhibitor (ACEi) /angiotensin receptor blocker (ARB) withdrawal in advanced renal disease

Submission date
25/02/2014

Recruitment status
No longer recruiting

Registration date
25/02/2014

Overall study status
Completed

Last Edited
07/12/2022

Condition category
Urological and Genital Diseases

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
Chronic kidney disease (CKD) affects 1 in 10 adults in the UK and describes progressive loss of kidney function regardless of the original kidney disease. CKD can have serious effects for those affected, including a risk of CKD progressing to complete kidney failure so that replacement of kidney function by dialysis or transplantation is required. Kidney disease is expensive with a high proportion of the health-care budget spent on CKD; the cost of dialysis alone is about £30,000 per year. Patient quality of life can be poor, with dialysis leading to early death. Treating high blood pressure (BP) is the most important intervention that can slow CKD progression. Some people with CKD gain additional protection from a type of drug, Angiotensin Converting Enzyme inhibitors (ACEi) or Angiotensin Receptor Blockers (ARBs). These drugs treat high BP but also slow CKD progression by other means. However, recent research suggests that in some people with advanced CKD (stages 4 & 5) who are progressing to complete kidney failure and are receiving treatment with an ACEi and/or ARB, stopping these drugs leads to stabilisation and improvement of kidney function and decreases or delays the need for dialysis. This indicates that in some patients the very tablets used to protect the kidneys may be contributing to a harmful decline in their function by some currently unknown mechanism. To date, research on this is observational and a study to confirm the association between stopping these drugs and stabilisation of kidney function is required. In this study we will randomly allocate suitable participants to either continue or stop their ACEi/ARB treatment and follow-up participants for 3 years. This study is needed before this treatment strategy can be put into routine clinical practice. In addition, the study will look at the other effects of stopping these drugs such as cardiovascular effects and participant quality of life.

Who can participate?
Men and women, aged 18 years and older, diagnosed with chronic kidney disease.

What does the study involve?
Participants are randomly allocated to either continue or discontinue their ACEi and/or ARB treatment.

What are the possible benefits and risks of participating?
Participants in studies such as this receive very close monitoring, which will be advantageous to their general health. Although participants may not receive any individual benefit from taking part in the study, the information we get from the study may help us to improve the treatment of all people in the UK with stage 4 or 5 CKD in the future. It is not currently known whether treating people with advanced CKD with ACEi and/or ARBs is beneficial or not. For participants that are allocated to continue with their current ACEi and/or ARB treatment, there will be no additional risk in the study than would normally be encountered in routine clinical care, but if the assumption of this study is correct, there is the risk that the participants CKD may get worse by staying on ACEi and/or ARBs. For participants that are allocated to the discontinuation group, there is the risk that stopping their existing ACEi and/or ARB treatment will cause a loss of the protective effect of ACEi and/or ARBs and an increase in blood pressure. To counteract the loss of antihypertensive therapy (drugs to lower blood pressure), participants that stop their ACEi and/or ARBs will start alternative antihypertensive drugs (e.g. calcium channel blockers, diuretics etc). However, drug withdrawal requires close monitoring and the potential risk of increased cardiovascular events for participants will be carefully assessed throughout the study by the Date Monitoring and Ethics Committee. If the results of the study show a benefit for ACEi /ARB withdrawal, it could have a huge impact on patients, their families and health services, by reducing or delaying the need for dialysis and kidney transplantation. Risk is minimised by ensuring that patients are closely monitored and that blood pressure is controlled by alternative means throughout the study. If the treating clinician feels that ACEi/ARB is required, this will be permitted. In patients with advanced CKD there are theoretical reasons why ACEi/ARB may be useful, useless or harmful. In practice, some clinicians withdraw these agents in patients with advanced CKD but others do not. It is important for care of patients that controversy and debate evolves into evidence-based guidelines.

Where is the study run from?
The study is coordinated from Birmingham Clinical Trials Unit. The study ran at 37 sites across the United Kingdom. For a list of hospitals that took part in the study, please see the study website http://www.birmingham.ac.uk/STOPACEi

When is the study starting and how long is it expected to run for?
The project grant started in Feb 2014, regulatory approvals in place by end of Jan 2014, launch meeting April 2014 and first participant recruited July 2014. Follow-up completed July 2019.

Who is funding the study?
The National Institute for Health and Care Research (NIHR) and Medical Research Council (MRC) Efficacy and Mechanism Evaluation (EME) Programme.

Who is the main contact?
stopacei@trials.bham.ac.uk

Study website
http://www.birmingham.ac.uk/stopacei

Contact information

Type(s)
Scientific

Contact name

Prof Sunil Bhandari

ORCID ID
https://orcid.org/0000-0002-0996-9622

Contact details
Birmingham Clinical Trials Unit
University of Birmingham
Edgbaston
Birmingham
United Kingdom
B15 2TT
-
stopacei@trials.bham.ac.uk

Additional identifiers

EudraCT/CTIS number
2013-003798-82

IRAS number
138827

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
15908; EME 11/30/07, IRAS 138827

Study information

Scientific Title
Multi-centre randomised controlled trial of angiotensin converting enzyme inhibitor (ACEi) /angiotensin receptor blocker (ARB) withdrawal in advanced renal disease: the STOP-ACEi trial

Acronym
STOP-ACEi

Study objectives
That stopping ACEi or ARB treatment, or a combination of both, compared with continuing on these treatments, improves or stabilises renal function in patients with progressive stage 4 or 5 CKD based on assessment of renal function using the Modification of Diet in Renal Disease (MDRD) 4-variable estimated Glomerular Filtration Rate (eGFR) at 3 years follow-up.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Yorkshire and The Humber (Leeds East) Research Ethics Committee, 29/01/2014, ref: 13/YH/0394

Study design
Randomised; Interventional; Design type:Treatment

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
https://www.birmingham.ac.uk/research/bctu/trials/renal/stopacei/investigators/documentation.aspx

Health condition(s) or problem(s) studied
Topic: Renal and Urogenital; Subtopic: Renal and Urogenital (all Subtopics); Disease: Renal

Interventions
Participants will be randomly allocated to either continue or discontinue their ACEi and/or ARB treatment.

Continue ACEi/ARB arm: participants will continue with their current, standard treatment with ACEi and/or ARBs. The choice and dose of ACEi/ARB will be at the treating clinicians discretion. Discontinue ACEi/ARB arm: participants will stop their existing ACEi and/or ARB treatment and will be started on alternative standard antihypertensives to ensure continued blood pressure control. The choice and dose of antihypertensives will be at the treating clinicians discretion.

Follow Up Length: 36 month(s)
Study Entry : Single Randomisation only

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Lisinopril, Enalapril Maleate, Ramipril, Captopril, Cilazopril, Fosinopril Sodium, Moexipril Hydrochloride, Perindopril, Erbumine, Perindopril Arginine, Quinapril, Trandolapril, Imidapril Hydrochloride, Candesartan, Irbesartan, Telmisartan, Eprosartan, Losartan, Olmesartan, Valsartan, Azilsartan

Primary outcome measure
Renal function measured using MDRD 4-variable eGFR at 3 years

Secondary outcome measures

1. Cystatin-C
2. Blood pressure
3. Number of participants starting renal replacement therapy or sustaining a >50% decline in eGFR
4. Time taken to reach ESRD or need for renal replacement therapy
5. Hospitalisation rates from any cause
6. Participant quality of life and wellbeing (measured using the KDQOL-SF™ v1.3 questionnaire)
7. Participant physical function (measured using the 6-minute walk test)
8. That withdrawal of these treatments does not cause excess harm (e.g. increased cardiovascular events such as heart failure, hypertension, myocardial infarction, stroke) and is not associated with an increase in adverse effects
9. Mortality
10. Urine protein excretion
11. Haemoglobin concentration
12. Dose of ESA

Overall study start date
01/04/2014

Completion date
31/12/2021

Eligibility

Key inclusion criteria
1. Aged ≥18 years (male or female)
2. CKD stage 4 or 5 (eGFR <30 ml/minute using the MDRD equation) and not on dialysis therapy
3. Progressive deterioration in renal function (fall in eGFR of >2 ml/min/year over previous 12-24 months) as measured by linear regression analysis. A simple excel spreadsheet for calculation of this will be provided to all sites. A minimum of 3 measurements of eGFR over the previous 12-24 months are required to identify a >2 ml/min/year fall. The last eGFR must be within 3 months of randomisation
4. Treatment with either an ACEi or ARB, or a combination of both, for >6 months with at least 25% of the maximum recommended daily dose on the day of consent
5. Resting blood pressure (BP) ≤160/90 mmHg when measured in accordance with British Hypertension Society guidelines in clinic or home blood pressure readings within the previous month or a 24 h ambulatory blood pressure measurement within the last 3 months are acceptable
6. At least 3 months of specialist renal follow-up at the time of entry into the trial
7. Written, signed informed consent to the trial

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex

Both

Target number of participants
Planned Sample Size: 410; UK Sample Size: 410

Total final enrolment
411

Key exclusion criteria
1. Aged <18 years
2. Uncontrolled hypertension (>160/90 mmHg) or requirement for 5 or more agents to control BP
3. Undergoing dialysis therapy
4. Any condition which, in the opinion of the investigator, makes the participant unsuitable for trial entry due to prognosis/terminal illness with a projected survival of less than 12 months
5. History of myocardial infarction or stroke in preceding 3 months
6. Participation in an interventional research study in preceding 6 weeks
7. Pregnancy, confirmed by positive pregnancy test, or breastfeeding
8. Inability to provide informed consent (e.g. due to cognitive impairment)
9. Immune-mediated renal disease requiring disease-specific treatment
10. Known drug or alcohol abuse
11. Inability to comply with the trial schedule and follow-up

Date of first enrolment
01/04/2014

Date of final enrolment
19/06/2018

Locations

Countries of recruitment
England

Northern Ireland

United Kingdom

Wales

Study participating centre
University of Birmingham
Birmingham
United Kingdom
B15 2TT

Sponsor information

Organisation
Hull University Teaching Hospitals NHS Trust

Sponsor details
Research and Development Office
Office 13
2nd Floor Daisy Building
Castle Hill Hospital
Castle Road
Cottingham
England
United Kingdom
HU16 5JQ

Sponsor type
Hospital/treatment centre

Website
https://www.hey.nhs.uk/

Funder(s)

Funder type
Government

Funder Name
Efficacy and Mechanism Evaluation Programme

Alternative Name(s)
NIHR Efficacy and Mechanism Evaluation Programme, EME

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan

Planned publication in a high-impact peer reviewed journal.

Intention to publish date
31/12/2022

Individual participant data (IPD) sharing plan
The final dataset will be available to members of the TMG and co-applicant group who need access to the data to undertake the final analyses. Any request for data generated in this trial will be considered by BCTU. Data will typically be available 6 months after the primary publication unless it is not possible to share the data (for example: the trial results are to be used as part of a regulatory submission, the release of the data is subject to the approval of a third party who withholds their consent, or BCTU is not the controller of the data).
Only scientifically sound proposals from appropriately qualified Research Groups will be considered for data sharing. The request will be reviewed by BCTU Data Sharing Committee in discussion with the CI and deputy CI and, where appropriate (or in the absence of the CI and deputy CI) any of the following: the trial sponsor, TMG and independent TSC.
A formal Data Sharing Agreement (DSA) may be required between respective organisations once release of the data is approved and before data can be released. The data will be fully de-identified (anonymised) unless the DSA covers transfer of participant identifiable information. Any data transfer will use a secure and encrypted method.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	01/02/2016		Yes	No
Results article		03/11/2022	07/12/2022	Yes	No
HRA research summary			28/06/2023	No	No