

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

|  |  |  |
|--|--|--|
| <b>Submission date</b><br>25/02/2014   | <b>Recruitment status</b><br>No longer recruiting            | <input checked="" type="checkbox"/> Prospectively registered<br><input checked="" type="checkbox"/> Protocol |
| <b>Registration date</b><br>25/02/2014 | <b>Overall study status</b><br>Completed                     | <input type="checkbox"/> Statistical analysis plan<br><input checked="" type="checkbox"/> Results            |
| <b>Last Edited</b><br>07/12/2022       | <b>Condition category</b><br>Urological and Genital Diseases | <input type="checkbox"/> 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 Data 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](mailto: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  $\geq 18$  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)  $\leq 160/90$  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? |
|--------------------------------------|----------|--------------|------------|----------------|-----------------|
| <a href="#">Protocol article</a>     | protocol | 01/02/2016   |            | Yes            | No              |
| <a href="#">Results article</a>      |          | 03/11/2022   | 07/12/2022 | Yes            | No              |
| <a href="#">HRA research summary</a> |          |              | 28/06/2023 | No             | No              |