Clinical trial results:
Multi-centre Randomised Controlled Trial of Angiotensin Converting Enzyme inhibitor (ACEi) / Angiotensin Receptor Blocker (ARB) withdrawal in advanced renal disease;
The STOP-ACEi Trial

Summary

EudraCT number	2013-003798-82
Trial protocol	GB
Global end of trial date	19 December 2021

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	R1578

Additional study identifiers

ISRCTN number	ISRCTN62869767
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	REC Reference: 13/YH/0394, Funder reference: 11/30/07, IRAS project code: 138827, NIHR CRN Study ID: 15908

Notes:

Sponsors

Sponsor organisation name	Hull University Teaching Hospitals NHS Trust
Sponsor organisation address	Anlaby Rd, Hull, United Kingdom, HU3 2JZ
Public contact	STOP-ACEi Trial Manager, Birmingham Clinical Trials Unit University of Birmingham Edgbaston Birmingham B15 2TT, +44 1214159130, stopacei@trials.bham.ac.uk
Scientific contact	STOP-ACEi Trial Manager, Birmingham Clinical Trials Unit University of Birmingham Edgbaston Birmingham B15 2TT, +44 1214159130, stopacei@trials.bham.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 July 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 December 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To test the hypothesis 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 stages 4 or 5 chronic kidney disease (CKD) based on assessment of renal function using the Modification of Diet in Renal Disease (MDRD) 4-variable estimated Glomerular Filtration Rate (eGFR) over 3 years follow-up.

Protection of trial subjects:

The trial was a clinical evaluation assessing whether discontinuation of ACEi or ARB or combination of both in patients with advanced renal disease was better than continuation of such therapy in a group of people who have decline in kidney function with associated poor outcomes, high morbidity and high healthcare cost. The trial was overseen by a DMEC to ensure that participants were not exposed to inappropriate risks. Information on participant safety data, adverse events, serious adverse events, treatment efficacy data, logistics (participant accrual rates) and quality assurance information (data-entry errors) was provided to the DMEC. The trial had equipoise as; 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. The assessment and management of risk was detailed in the separate STOP-ACEi Risk Assessment document. An on-going evaluation of risk continued throughout the recruitment period. Potential participants were provided with a Participant Information Sheet (PIS) and a covering letter explaining the trial and inviting them to participate, sent 1-2 weeks before their next clinic attendance so as they would have time to decide whether to take part. At their next clinic appointment they had time to discuss the trial further and have any questions answered. It was explained there was no obligation to enter the trial and that trial entry was entirely voluntary. It was explained that they could withdraw at any time, without having to give a reason and that their decision would not affect the standard of care received. Participants were continually encouraged to ask questions and reminded they could withdraw at any time without their clinical care being affected.

Background therapy:

Discontinuation of ACEi and/or ARB treatment.
ACEi and/or ARB treatment was discontinued from the point of randomisation onwards. If a participant was due to take an ACEi/ARB on the morning of the randomisation visit, i.e. before randomisation, it was taken as normal. In order to compensate for the loss of anti-hypertensive activity, additional antihypertensive treatment could be commenced. Any antihypertensives used in routine clinical practice were permitted to control BP throughout trial participation, but excluding ACEi or ARBs, except as a last resort. Any of the following alternative antihypertensives could be prescribed: calcium channel blockers, alpha- and beta-adrenoreceptor antagonists, hydralazine, minoxidil and thiazides. It was acceptable to use aldosterone receptor antagonists e.g. spironolactone. The normal contraindications and safety precautions for use of these treatments should have been adhered to, as per routine care. It was recommended that the Renal Pharmacy Handbook was consulted in combination with the British National Formulary due to the complex prescribing needs of patients with CKD. In all cases, it was considered best to commence treatment at low doses and then increase to a therapeutic level. The choice of anti-hypertensive depended on other treatment being taken by the participant and was at the discretion of the responsible clinician.

Continuation of ACEi and/or ARB treatment.

The choice and dose of ACEi and/or ARB was at the discretion of the responsible clinician.

Evidence for comparator:

Treating high blood pressure (BP) is the most important intervention that can slow progression of CKD. Some people with CKD gain additional protection from angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs). However, recent research suggests that in some people with advanced CKD (stage 4 or 5) who are progressing to complete kidney failure and are receiving treatment with an ACEi or ARB, stopping these drugs leads to stabilisation or improvement of kidney function and decreases or delays the need for dialysis treatment. To date, the research on this is observational and to confirm the association between stopping these drugs and stabilisation of kidney function requires a randomised controlled trial to compare the outcomes of a group of people who have had these drugs stopped with a group who continue on the drugs. The trial population are patients with advanced progressive CKD (stage 4 or 5) treated with ACEi or ARBs or a combination of both.

Actual start date of recruitment	11 July 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 411
Worldwide total number of subjects	411
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	226
From 65 to 84 years	179
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

Between July 11th, 2014 and June 19th, 2018, 17,290 patients were screened at 39 participating centres with kidney services in the UK and 1,210 patients were invited to participate in the trial with 411 patients at 37 centres randomised into the trial; 206 to stop and 205 to continue RASi. Follow up continued until June 19th 2021.

Pre-assignment

Screening details:

Participants were screened using the eligibility criteria as specified in the protocol. 17,290 patients were screened, 1,210 patients were invited to participate in the trial with 411 patients at 37 centres randomised into the trial.

Period 1

Period 1 title	Baseline period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Discontinue ACEi and/or ARB treatment

Arm description:

ACEi and/or ARB treatment will be discontinued from the point of randomisation onwards. If a participant is due to take an ACEi/ARB on the morning of the randomisation visit (i.e. before randomisation), this should be taken as normal. In order to compensate for the loss of anti-hypertensive activity, additional antihypertensive treatment may be commenced. Any antihypertensives used in routine clinical practice are permitted to control BP throughout trial participation, but excluding ACEi or ARBs, except as a last resort. Any of the following alternative antihypertensives can be prescribed: calcium channel blockers, alpha- and beta-adrenoreceptor antagonists, hydralazine, minoxidil and thiazides. It is acceptable to use aldosterone receptor antagonists (e.g. spironolactone). The choice of anti-hypertensive will depend on other treatment being taken by the participant and will be at the discretion of the responsible clinician.

Arm type	Experimental
Investigational medicinal product name	Amlodipine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Discontinuation of ACEi/ARB - the responsible clinician can use any other antihypertensive medication as they see fit to achieve the BP target. Choice and dose of antihypertensive medication will be left with the responsible clinician. Any antihypertensives used in routine clinical practice are permitted to control BP throughout trial participation but excluding agents that inhibit the renin-angiotensin-aldosterone system, except as a last resort. Any of the following alternative antihypertensives can be prescribed: calcium channel blockers, alpha- and beta-adrenoreceptor antagonists, hydralazine, minoxidil and thiazides. The normal contraindications and safety precautions for use of these treatments should be adhered to, as per routine care. We recommend that the Renal Pharmacy Handbook is consulted in combination with the British National Formulary due to the complex prescribing needs of patients with CKD. Amlodipine is given as an example.

Arm title	Continue ACEi and/or ARB treatment

Arm description:

Participants will continue on ‘standard’ care and will continue with their ACEi and/or ARB treatment. The choice and dose of ACEi and/or ARB will be at the discretion of the responsible clinician.

Arm type	Active comparator

Investigational medicinal product name	Lisinopril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Continuation of ACEi/ARB - drugs will be taken orally. The dose and choice of drug will be decided by the responsible clinician and will be titrated to achieve the target BP of ≤140/85 mmHg where possible. The responsible clinician can use any other antihypertensive medication for optimal patient care, as well as the ACEi/ARB, to achieve target BP in those cases which remain difficult to control and the clinician decides it is required. Lisinopril is given as an example of an ACEi.

Number of subjects in period 1	Discontinue ACEi and/or ARB treatment	Continue ACEi and/or ARB treatment
Started	206	205
Completed	165	165
Not completed	41	40
Consent withdrawn by subject	20	10
Died	17	22
Lost to follow-up	4	6
Did not undergo eGFR evaluation at baseline	-	2

Baseline characteristics

Reporting groups

Reporting group title	Discontinue ACEi and/or ARB treatment

Reporting group description:

ACEi and/or ARB treatment will be discontinued from the point of randomisation onwards. If a participant is due to take an ACEi/ARB on the morning of the randomisation visit (i.e. before randomisation), this should be taken as normal. In order to compensate for the loss of anti-hypertensive activity, additional antihypertensive treatment may be commenced. Any antihypertensives used in routine clinical practice are permitted to control BP throughout trial participation, but excluding ACEi or ARBs, except as a last resort. Any of the following alternative antihypertensives can be prescribed: calcium channel blockers, alpha- and beta-adrenoreceptor antagonists, hydralazine, minoxidil and thiazides. It is acceptable to use aldosterone receptor antagonists (e.g. spironolactone). The choice of anti-hypertensive will depend on other treatment being taken by the participant and will be at the discretion of the responsible clinician.

Reporting group title	Continue ACEi and/or ARB treatment

Reporting group description:

Participants will continue on 'standard' care and will continue with their ACEi and/or ARB treatment. The choice and dose of ACEi and/or ARB will be at the discretion of the responsible clinician.

Reporting group values	Discontinue ACEi and/or ARB treatment	Continue ACEi and/or ARB treatment	Total
Number of subjects	206	205	411
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
<65yrs	116	110	226
65 years and over	90	95	185
Age continuous Units: years			
arithmetic mean	62.7	61.4	
standard deviation	± 12.6	± 13.6	-
Gender categorical Units: Subjects			
Female	66	64	130
Male	140	141	281

End points

End points reporting groups

Reporting group title	Discontinue ACEi and/or ARB treatment

Reporting group description:

ACEi and/or ARB treatment will be discontinued from the point of randomisation onwards. If a participant is due to take an ACEi/ARB on the morning of the randomisation visit (i.e. before randomisation), this should be taken as normal. In order to compensate for the loss of anti-hypertensive activity, additional antihypertensive treatment may be commenced. Any antihypertensives used in routine clinical practice are permitted to control BP throughout trial participation, but excluding ACEi or ARBs, except as a last resort. Any of the following alternative antihypertensives can be prescribed: calcium channel blockers, alpha- and beta-adrenoreceptor antagonists, hydralazine, minoxidil and thiazides. It is acceptable to use aldosterone receptor antagonists (e.g. spironolactone). The choice of anti-hypertensive will depend on other treatment being taken by the participant and will be at the discretion of the responsible clinician.

Reporting group title	Continue ACEi and/or ARB treatment

Reporting group description:

Participants will continue on ‘standard’ care and will continue with their ACEi and/or ARB treatment. The choice and dose of ACEi and/or ARB will be at the discretion of the responsible clinician.

Primary: eGFR

End point title	eGFR

End point description:

The primary outcome is the continuous measure eGFR at 3 years. The two groups will be compared at 3 years using a linear regression model with the baseline eGFR score and all the minimisation variables included in the model as covariates. Longitudinal plots of the data over time will also be constructed for visual presentation of the data.

End point type	Primary

End point timeframe:

At 3 yrs

End point values	Discontinue ACEi and/or ARB treatment	Continue ACEi and/or ARB treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	69		
Units: ml/min/1.73m2				
least squares mean (standard error)	12.6 (± 0.7)	13.3 (± 0.6)		

Statistical analyses

Statistical analysis title	eGFR at three years
Comparison groups	Discontinue ACEi and/or ARB treatment v Continue ACEi and/or ARB treatment

Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.42
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	1
Variability estimate	Standard error of the mean

Secondary: ESKD or renal-replacement therapy

End point title	ESKD or renal-replacement therapy
End point description:	
End point type	Secondary
End point timeframe:	
At 3yrs.	

End point values	Discontinue ACEi and/or ARB treatment	Continue ACEi and/or ARB treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	205		
Units: Percentage	62	56		

Statistical analyses

No statistical analyses for this end point

Secondary: Renal replacement therapy

End point title	Renal replacement therapy
End point description:	
Renal-replacement therapy (including patients with ESKD) or >50% decrease in estimated glomerular filtration rate.	
End point type	Secondary
End point timeframe:	
At 3yrs	

End point values	Discontinue ACEi and/or ARB treatment	Continue ACEi and/or ARB treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	202		
Units: Percentage	68	63		

Statistical analyses

No statistical analyses for this end point

Secondary: Death

End point title	Death

End point description:

End point type	Secondary

End point timeframe:

At 3yrs.

End point values	Discontinue ACEi and/or ARB treatment	Continue ACEi and/or ARB treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	205		
Units: Percentge	10	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Hospitalisation - number of patients

End point title	Hospitalisation - number of patients

End point description:

End point type	Secondary

End point timeframe:

At 3yrs.

End point values	Discontinue ACEi and/or ARB treatment	Continue ACEi and/or ARB treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	205		
Units: Percentage	66	72		

Statistical analyses

No statistical analyses for this end point

Secondary: Hospitalisation - No. of events

End point title	Hospitalisation - No. of events

End point description:

End point type	Secondary

End point timeframe:

Over 3 years

End point values	Discontinue ACEi and/or ARB treatment	Continue ACEi and/or ARB treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	205		
Units: Number of hospitalisations	414	413		

Statistical analyses

No statistical analyses for this end point

Secondary: Systolic blood pressure at 3yrs

End point title	Systolic blood pressure at 3yrs

End point description:

End point type	Secondary

End point timeframe:

At 3yrs

End point values	Discontinue ACEi and/or ARB treatment	Continue ACEi and/or ARB treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	145		
Units: mm Hg				
least squares mean (standard error)	140 (± 2)	140 (± 2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Diastolic blood pressure at 3yrs

End point title	Diastolic blood pressure at 3yrs

End point description:

End point type	Secondary

End point timeframe:

At 3 years

End point values	Discontinue ACEi and/or ARB treatment	Continue ACEi and/or ARB treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	145		
Units: mm HG				
least squares mean (standard error)	76 (± 1)	76 (± 1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Distance on 6-minute walk test at 3yrs

End point title	Distance on 6-minute walk test at 3yrs

End point description:

End point type	Secondary

End point timeframe:

At 3yrs.

End point values	Discontinue ACEi and/or ARB treatment	Continue ACEi and/or ARB treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	46		
Units: metres				
least squares mean (standard error)	394 (± 19)	412 (± 9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment with erythropoietin-stimulating agent

End point title	Treatment with erythropoietin-stimulating agent

End point description:

End point type	Secondary

End point timeframe:

Over 3yrs

End point values	Discontinue ACEi and/or ARB treatment	Continue ACEi and/or ARB treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	202		
Units: Percentage	55	55		

Statistical analyses

No statistical analyses for this end point

Secondary: Heamoglobin

End point title	Heamoglobin

End point description:

End point type	Secondary

End point timeframe:

At 3yrs.

End point values	Discontinue ACEi and/or ARB treatment	Continue ACEi and/or ARB treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	161		
Units: g/L				
least squares mean (standard error)	119 (± 1.0)	119 (± 1.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Protein:Creatinine ratio

End point title	Protein:Creatinine ratio

End point description:

End point type	Secondary

End point timeframe:

At 3yrs.

End point values	Discontinue ACEi and/or ARB treatment	Continue ACEi and/or ARB treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	85		
Units: mg/mmol				
least squares mean (standard error)	192 (± 31)	193 (± 22)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

3yrs - from patient consent to participant's final assessment at 3 years post trial entry.

Adverse event reporting additional description:

The adverse event reporting period will commence at the patient's consent and continue until the participant's final assessment at 3 years post trial entry. The participant will not be considered to be on trial treatment after this point.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

Frequency threshold for reporting non-serious adverse events: 0 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Non-serious adverse events were not collected so cannot be entered here. Only Serious Adverse Events were collected.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 May 2014	Protocol release V3.0 Changes to Protocol • Addition of ISRCTN number to front cover • Clarification of wording for primary outcome measure throughout. This is now "eGFR at 3 years" and not "eGFR over 3 years". This isn't a change to the outcome measure, just a clarification of wording. • Expansion of exclusion criteria. Patients that have had a kidney transplant will also be excluded. The patient population under study remains pre-dialysis Chronic Kidney Disease (CKD) patients. This exclusion criterion was added for clarity. • We want to allow participating hospitals to continue to use their standard local measure for proteinuria so will measure either albumin:creatinine ratio or protein:creatinine ratio at each visit and convert ACR to PCR for trial analysis. This has been updated in the protocol. • Clarification of wording regarding calculation of decline in renal function. Measures used to assess decline in renal function will be from within the previous "24 months" and not "12-24 months" as previously. • ACE and renin levels will be analysed in a sample of patients from each arm, rather than from all participants. This is updated in the Trial Design section of the Protocol. • Change of wording for minimisation groups for diabetes. There was some concern that the previous categories might cause confusion for patients with type 2 diabetes that are treated with insulin. The categories will now be Type 1 diabetes, Type 2 diabetes and non-diabetic. • Correction of error in schedule of assessments. • Clarification of advice regarding use of aldosterone receptor antagonists (e.g. spironolactone). These are not ACE inhibitors or ARBs so this isn't a change to the trial treatment, just an expansion of advice for trial treatment. • Correction of error in blood pressure target. • Expansion of explanation of the role of the DMEC.

19 September 2019	• TMG membership updated to reflect changes. • Removal of duplication in sections 3 and 7.4. • Update to projected timeframes for the project since the recruitment period overran by 23 months. • Changes to permitted visit window to facilitate pragmatic follow-up. • Lab results not required for outcome analysis reported if performed for clinical monitoring only, in order to facilitate pragmatic follow-up. • Removal of patient diaries in response to feedback from participating sites. • Additional detail regarding partial withdrawal from follow-up to aid clarity and facilitate data collection from routine medical records and support an intention to treat analysis. • E-mail as secondary option for SAE reporting to accommodate Trusts that no longer use fax. • Changes to pharmacovigilance section to bring in line with updated BCTU standards. • Change to timelines for reporting of Protocol defined expected SAEs in line with a risk-adapted strategy for safety reporting. • Update to list of expected SAEs to include TIA as well as stroke. • Changes to data management section to bring in line with updated BCTU standards. • Change to end of trial • Additional detail relating to the planned statistical analyses. • Finance section updated to reflect changes to per patient payments and an update to the funding body's disclaimer. • Reference to Research Governance Framework updated to UK Policy Framework for Health and Social Care Research. • References to data protection act updated to GDPR. • Update of Sponsor name from Hull and East Yorkshire Hospitals NHS Trust to Hull University Teaching Hospitals NHS Trust. Note that this is not a change of the Sponsor itself, just the organisation's name. • Correction of minor typographical errors and minor formatting change

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Non-white ethnic backgrounds poorly represented so limiting the generalisability of the findings. Open-label nature of the trial may have affected subjective endpoints. Only including patients receiving RAS inhibitors at time of randomization.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/36326117