Clinical trial results:
Phase II mechanistic, randomised controlled trial of Stopping Perioperative Angiotensin II Converting Enzyme inhibitors and/or receptor blockers in major noncardiac surgery

Summary

EudraCT number	2016-004141-90
Trial protocol	GB
Global end of trial date	15 March 2022

Results information

Result version number	v2 (current)
This version publication date	22 October 2023
First version publication date	08 April 2023
Version creation reason	• New data added to full data set Addition information to be added regarding tertiary endpoints
Summary attachment (see zip file)	SPACE Tertiary exploratory analyses (SPACE tertiary exploratory analyses FINAL.pdf)

Trial information

Trial identification

Sponsor protocol code	8.0

Additional study identifiers

ISRCTN number	ISRCTN17251494
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Queen Mary University of London
Sponsor organisation address	Dept W Mile End Road, London, United Kingdom, E1 4UJ
Public contact	Salma Begum, Queen Mary University of London, admin@spacetrial.org
Scientific contact	Professor Gareth Ackland, Queen Mary University of London, g.ackland@qmul.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	18 October 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 October 2021
Global end of trial reached?	Yes
Global end of trial date	15 March 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether continuing ACE-I and/or ARB treatment perioperatively reduces the risk of perioperative myocardial injury in patients undergoing major surgery. This assessment will be based on plasma troponin levels measured in the first 48 hours postoperatively.

Protection of trial subjects:

This trial was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. All subjects provided written informed consent before undergoing any trial related procedures. The trial was reviewed and approved by a Research Ethics Committee (REC) and the Medicines & Healthcare products Regulatory Agency (MHRA).

Background therapy:

N/A

Evidence for comparator: -

Actual start date of recruitment	02 January 2017
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: 260
Worldwide total number of subjects	260
EEA total number of subjects	260

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)	0
From 65 to 84 years	243

85 years and over	17

Subject disposition

Recruitment

Recruitment details:

Recruitment began in January 2017 and ended in October 2021. Patients were recruited from 5 sites in the United Kingdom and were screened from preoperative assessment outpatient clinics and/or referring surgeons according to the eligibility criteria.

Pre-assignment

Screening details:

1110 patients were assessed for eligibility for the study. 262 patients were randomised and 848 patients were excluded. One patient withdrew consent from each arm.

Period 1

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

Blinding implementation details:

This was an open-label trial. Trial participants and staff were not blinded to treatment group allocation. Only the primary outcome (Troponin-T) assessment was blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Stopping ACE-I and/or ARB

Arm description:

Patients in the stop group will stop their ACE-I and/or ARB [according to half-life of each individual drug] prior to the day of surgery through to at least 48 hours after surgery. One patient withdrew consent.

Arm type	Active comparator
Investigational medicinal product name	ACE-I and/or ARB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

As prescribed by patient's responsible clinician

Arm title	Continuing ACE-I and/or ARB

Arm description:

Patients in the continue group will continue with their ACE-I and/or ARB 72 hours prior to the day of surgery and continue for at least 48 hours after surgery. One patient withdrew consent.

Arm type	Active comparator
Investigational medicinal product name	ACE-I and/or ARB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

As prescribed by patients' responsible clinician

Number of subjects in period 1	Stopping ACE-I and/or ARB	Continuing ACE-I and/or ARB
Started	129	131
Completed	129	131

Baseline characteristics

Reporting groups	
Reporting group title	Stopping ACE-I and/or ARB
Reporting group description:	
Patients in the stop group will stop their ACE-I and/or ARB [according to half-life of each individual drug] prior to the day of surgery through to at least 48 hours after surgery. One patient withdrew consent.	
Reporting group title	Continuing ACE-I and/or ARB
Reporting group description:	
Patients in the continue group will continue with their ACE-I and/or ARB 72 hours prior to the day of surgery and continue for at least 48 hours after surgery. One patient withdrew consent.	

Reporting group values	Stopping ACE-I and/or ARB	Continuing ACE-I and/or ARB	Total
Number of subjects	129	131	260
Age categorical Units: Subjects			
From 60-64 years	22	24	46
From 65-84 years	104	99	203
85 years and over	3	8	11
Age continuous Units: years			
arithmetic mean	72.1	71.5	
standard deviation	± 7.1	± 7.2	-
Gender categorical Units: Subjects			
Female	63	63	126
Male	66	68	134

End points

End points reporting groups

Reporting group title	Stopping ACE-I and/or ARB
Reporting group description:	
Patients in the stop group will stop their ACE-I and/or ARB [according to half-life of each individual drug] prior to the day of surgery through to at least 48 hours after surgery. One patient withdrew consent.	
Reporting group title	Continuing ACE-I and/or ARB
Reporting group description:	
Patients in the continue group will continue with their ACE-I and/or ARB 72 hours prior to the day of surgery and continue for at least 48 hours after surgery. One patient withdrew consent.	

Primary: Myocardial injury

End point title	Myocardial injury
End point description:	
In the stop arm 9 patients had missing primary outcomes In the continue arm 10 patients had missing primary outcomes The primary outcome is myocardial injury, a binary variable based on plasma high sensitivity Troponin-T measured in blood samples collected immediately before the induction of anaesthesia, and then postoperative day 1± 6 hours and day 2 ± 6 hours. The primary outcome is met under the following conditions: 1. Troponin-T ≥15 ng/L within 48 hours after surgery with a pre-operative value <15 ng/L OR 2. Troponin-T increase ≥5 ng/L within 48 hours after surgery with a pre-operative value ≥15ng/L	
End point type	Primary
End point timeframe:	
within 48 hours after surgery	

End point values	Stopping ACE-I and/or ARB	Continuing ACE-I and/or ARB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	121		
Units: number of patients	58	50		

Statistical analyses

Statistical analysis title	Myocardial injury
Statistical analysis description:	
The primary outcome, myocardial injury within 48 hours after surgery, was analysed using a mixed effect logistic regression model, with a random intercept for the minimisation variable trial centre. The model was adjusted for minimisation variables as fixed factors which are planned surgical procedure ((a) surgery involving the gut; (b) all other surgery) and class of drug routinely taken ((a) ACE-I; (b) ARB).	
Comparison groups	Stopping ACE-I and/or ARB v Continuing ACE-I and/or ARB

Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [1]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	2-sided

Notes:

[1] - Model taking into account clustering by site did not converge and hence a logistic regression model was fitted ignoring clustering

Secondary: Peak level Troponin-T

End point title	Peak level Troponin-T

End point description:

Peak level of Troponin-T measured within 48 hours of surgery. Peak Troponin-T level (ng/L) will be calculated as the highest Troponin-T from the blood samples collected at 24 hours and 48 hours after surgery.

End point type	Secondary

End point timeframe:

Within 48 hours after surgery

End point values	Stopping ACE-I and/or ARB	Continuing ACE-I and/or ARB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	121		
Units: ng/L	18	17		

Statistical analyses

Statistical analysis title	Peak level Troponin-T

Statistical analysis description:

The mean (SD) peak level of Troponin-T measured within 48 hours of surgery has been reported within each treatment group. Differences between the groups in the mean peak level troponin-t was analysed using multilevel linear regression – adjusted for the same baseline variables as the adjusted analysis of the primary outcome. We have also adjusted for baseline pre-operative Troponin-T as a continuous variable.

Comparison groups	Stopping ACE-I and/or ARB v Continuing ACE-I and/or ARB
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)

Confidence interval	
level	95 %
sides	2-sided

Notes:

[2] - Analyses will follow the intention-to-treat principle: all randomised patients with a recorded outcome will be included in the analysis and analysed according to the treatment to which they were randomised

Secondary: Infection

End point title	Infection

End point description:

End point type	Secondary

End point timeframe:

Within 30 days of surgery

End point values	Stopping ACE-I and/or ARB	Continuing ACE-I and/or ARB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	123		
Units: number of patients	26	24		

Statistical analyses

Statistical analysis title	Infection

Statistical analysis description:

Infection within 30 days of surgery was analysed using a mixed-effect logistic regression model with a random intercept for the minimisation variable trial centre. The model was adjusted for minimisation variables planned surgical procedure ((a) surgery involving the gut; (b) all other surgery) and class of drug routinely taken ((a) ACE-I; (b) ARB).

Comparison groups	Continuing ACE-I and/or ARB v Stopping ACE-I and/or ARB
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [3]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	2-sided

Notes:

[3] - Model taking into account clustering by site did not converge and hence a logistic regression model was fitted ignoring clustering

Secondary: Myocardial infarction

End point title	Myocardial infarction

End point description:

End point type	Secondary

End point timeframe:

Within 30 days of surgery

End point values	Stopping ACE-I and/or ARB	Continuing ACE-I and/or ARB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	123		
Units: proportion	3	0		

Statistical analyses

Statistical analysis title	Myocardial infarction

Statistical analysis description:

The number (%) was presented in each treatment group. An exact unadjusted logistic regression was performed if 10 or more events were reported. No statistical analysis will be performed if there are fewer than 10 events.

Comparison groups	Stopping ACE-I and/or ARB v Continuing ACE-I and/or ARB
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	2-sided

Secondary: Acute heart failure

End point title	Acute heart failure

End point description:

End point type	Secondary

End point timeframe:

Within 30 days of surgery

End point values	Stopping ACE-I and/or ARB	Continuing ACE-I and/or ARB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	123		
Units: Number of patients	2	0		

Statistical analyses

Statistical analysis title	Acute heart failure

Statistical analysis description:

The number (%) was presented in each treatment group. An exact unadjusted logistic regression was performed if 10 or more events were reported. No statistical analysis will be performed if there are fewer than 10 events.

Comparison groups	Stopping ACE-I and/or ARB v Continuing ACE-I and/or ARB
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	2-sided

Secondary: Stroke

End point title	Stroke

End point description:

End point type	Secondary

End point timeframe:

Within 30 days of surgery

End point values	Stopping ACE-I and/or ARB	Continuing ACE-I and/or ARB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	123		
Units: number of patients	1	0		

Statistical analyses

Statistical analysis title	Stroke

Statistical analysis description:

The number (%) was presented in each treatment group. An exact unadjusted logistic regression was performed if 10 or more events were reported. No statistical analysis will be performed if there are fewer than 10 events.

Comparison groups	Stopping ACE-I and/or ARB v Continuing ACE-I and/or ARB
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	2-sided

Secondary: Death

End point title	Death

End point description:

End point type	Secondary

End point timeframe:

Within 30 days of surgery

End point values	Stopping ACE-I and/or ARB	Continuing ACE-I and/or ARB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	123		
Units: number of patients	1	2		

Statistical analyses

Statistical analysis title	Death

Statistical analysis description:

The number (%) was presented in each treatment group. An exact unadjusted logistic regression was performed if 10 or more events were reported. No statistical analysis will be performed if there are fewer than 10 events.

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Comparison groups	Stopping ACE-I and/or ARB v Continuing ACE-I and/or ARB

Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomisation to 30 days post surgery

Adverse event reporting additional description:

1. Systolic BP>180mmHg from randomisation until 48 hours after surgery
2. Diastolic BP> 100mmHg from randomisation until 48 hours after surgery
3. Hypotension requiring pressor via central venous access from randomisation until 48 hours after surgery
4. Acute kidney injury, in the absence of haemorrhage/sepsis (KDIGO grades 1-4) within 30 days

Assessment type	Systematic

Dictionary used

Dictionary name	n/a
Dictionary version	n/a

Reporting groups

Reporting group title	Continuing ACE-I/ARB

Reporting group description:

Continue Group
Patients in the continue group will continue with their ACE-I and/or ARB 72 hours prior to the day of surgery and continue for at least 48 hours after surgery.

Reporting group title	Stopping ACE-I/ARB

Reporting group description:

Stop Group
Patients in the stop group will stop their ACE-I and/or ARB [according to half-life of each individual drug] prior to the day of surgery through to at least 48 hours after surgery.

Serious adverse events	Continuing ACE-I/ARB	Stopping ACE-I/ARB	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 131 (3.05%)	8 / 129 (6.20%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	2	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 131 (0.00%)	3 / 129 (2.33%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 131 (0.76%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			

subjects affected / exposed	0 / 131 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Haemorrhage			
subjects affected / exposed	2 / 131 (1.53%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary oedema			
subjects affected / exposed	0 / 131 (0.00%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 131 (1.53%)	0 / 129 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 131 (0.76%)	1 / 129 (0.78%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Continuing ACE-I/ARB	Stopping ACE-I/ARB	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 131 (22.14%)	40 / 129 (31.01%)	
Vascular disorders			
Hypertension	Additional description: 1) Systolic BP>180mmHg from randomisation until 48 hours after surgery 2) Diastolic BP> 100mmHg from randomisation until 48 hours after surgery. As verified on measurement by study investigators. This is a pre-specified adverse event.		
subjects affected / exposed	8 / 131 (6.11%)	15 / 129 (11.63%)	
occurrences (all)	8	15	
Hypotension	Additional description: Hypotension requiring pressor via central venous access from randomisation until 48 hours after surgery. This is a pre-specified adverse event.		

subjects affected / exposed	10 / 131 (7.63%)	12 / 129 (9.30%)	
occurrences (all)	10	12	
Renal and urinary disorders			
Acute kidney injury	Additional description: Acute kidney injury, in the absence of haemorrhage/sepsis (KDIGO grades 1-4) within 30 days after surgery. This is a pre-specified adverse event.		
subjects affected / exposed	11 / 131 (8.40%)	13 / 129 (10.08%)	
occurrences (all)	11	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 December 2016	Substantial amendment 1 Changes to IRAS Form (v5.3.2): The study category has been changed to Clinical Trial of an Investigational Medicinal Product (CTIMP). The subsequent MHRA form has been completed via IRAS. Changes to Protocol: Format change on the table of contents in accordance to sponsor requirements. Specified this will be a phase III CTIMP clinical trial. Change in the number of patients recruited from 248 to 260. Further information has been added to the protocol on the pre-clinical and clinical data to support the trial. Immune function has been added as a tertiary end point. New section on the IMP including the list of drugs being investigated, formulation, supply, prescription. Informed consent can also be done by the principal investigator or medically qualified person. Section on schedule of treatment for each visit. Laboratory assessments detailing the procedures used, sample analysis and storage. Detailed section on safety reporting and notification of SAE/SUSAR. Section on quality control and assurance. Patient Information Sheet: Patients will receive advice letters confirming their trial allocation to stopping or continuing their medication. We will also provide reminders by telephone, text message or in person if they are in hospital. Additional information on the time frame the drugs will be restarted. Informed consent form: Only the principal investigator or medically qualified person can take consent. Minor Corrections following HRA review: Changes to Protocol: Change in the flow diagram in Section 2.3 to include 'to provide there is no change in creatinine, as >30% of patients on ACE/ARB and undergoing an operation may have underlying CKD, so from the protocol the ACEi would not be restarted' Patient Information Sheet: Changes to accommodate the following conditions set by the original REC letter dated 15 September 2016. Informed consent form: Changes to the title to ensure consistency cross the documentation.

27 November 2017	Substantial amendment 2 Changes to Protocol - Change in trial title. - Clarification on the trial objectives and design. - Clarifications on the study procedures for screening, randomisation patient follow-ups and the schedule of assessment. - Updated the time line on the end of study definition. - Updated the Laboratories and all samples will be measured using a central lab. Specified the time lines for the adverse event reporting - Updated the statistical considerations section. - Updated the data handling and record keeping section. - Updated the data management section. - Updated the trial steering committee and data monitoring and ethics committee section. - Updated appendix 2 detailing the perioperative morbidity definitions. Patient Information Sheet - Change in the study title and added a sentence that patients will be contacted at 30 days to check on their wellbeing. Informed Consent Form - Change in the study title. - Added nurse to the list of people taking consent. - Changed which copy of the signed consent form goes into the investigator file and the medical notes. Patient invitation letter - Letter to inform patients of the SPACE trial to give them more time to consider whether they want to take part in the trial. Patient Advice Letters - treatment continuation - Spelling mistake. - Updated the information for the co-ordinating centre. Patient Advice Letters - treatment discontinuation - Spelling mistake. - Updated the information for the co-ordinating centre.
21 May 2019	Substantial amendment 3 Changes in conduct or management of the trial Previous and new wording:(tracked) Page 2: Statistician Name: Tahania Ahmad New wording: Page 2: Statistician Name: Akshaykumar Patel Comments/ explanation/ reasons for substantial amendment: We have added 'regional anaesthesia with sedation' to the inclusion criteria. This change has been made for clarity/consistency. Regional anaesthesia is a common anaesthetic technique used in combination with general anaesthesia or heavy sedation for patients undergoing orthopaedic surgery. We want to ensure that this patient group is not excluded from the study. This has been updated in all the necessary sections of the protocol. Other minor clarifications to the protocol regarding patient follow up, the addition of the TMG committee and participation in other trials.
11 March 2020	Substantial amendment 4 1. Clarification to the Patient information sheet to section: What will happen to me if I take part? 2. Clarification to the following sections of the protocol: 2.1 Trial objectives, 2.2 Safety outcomes, 2.4 Assessment of primary and secondary outcomes, 3.1 Number of subjects and subject selection, 5.3 Randomisation procedures, 5.6 Schedule of assessment in diagrammatic format, 5.8 Laboratory assessments, 6.1 Central/ local laboratories, 6.2 Sample collection/labelling/logging, 7.1.3 Serious Adverse Event or Serious Adverse Reaction, 9.1 Statistical Primary Endpoint Efficacy Analysis and 10.2 Case Report Form.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
17 March 2020	Recruitment suspension/pause due to the Covid-19 pandemic. The trial restarted on 25/06/2020.	25 June 2020

Notes:

Limitations and caveats

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

Further endpoint plasma samples has been analysed for NT-pro BNP and mediators of the Renin-angiotensin system. An addendum detailing these findings has been attached as a PDF document to version 2 of this report.

Notes: