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Stopping perioperative angiotensin II converting enzyme inhibitors and/or angiotensin receptor blockers in major noncardiac surgery

Submission date
18/05/2017

Recruitment status
No longer recruiting

Registration date
29/05/2017

Overall study status
Completed

Last Edited
10/06/2025

Condition category
Surgery

[X] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims:
Many patients after major surgery have detectable levels of a natural marker for injury to the heart which is linked to delayed recovery, infections and/or death. This may occur as a result of prolonged stress to the body following surgery. Around 40% of surgical patients most at risk of these complications after surgery are prescribed angiotensin converting enzyme inhibitors (ACE-I) or angiotensin-II receptor blockers (ARB). These drugs are used to treat a range of long term conditions, including high blood pressure, kidney disease and heart failure. However, the same drugs are frequently stopped before surgery in the widely-held belief that this prevents low blood pressure during or after surgery. Doctors are uncertain whether these drugs should be stopped or continued. Some clinical research suggests that stopping ACE-I and/or ARB just before surgery could lead to complications after surgery. The aim of this study is to find out whether continuing or temporarily stopping these drugs reduces injury to the heart, and other complications, after major planned surgery.

Who can participate?
Adults aged 60 years and over who are undergoing major surgery and are currently on angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers therapy.

What does the study involve?
Before surgery, participants are randomly allocated to one of two groups. Those in the first group stop taking their regular angiotensin converting enzyme inhibitor and/or angiotensin receptor blocker. Those in the second group continue as normal to take their medications after surgery. Participants then undergo their surgery as normal. Blood samples collected as part of standard care are collected and patients have their heart rate and blood pressure measured just before surgery and after surgery, to see whether stopping/continuing medication drugs makes any difference. Those who stop taking the drugs restart treatment around 24-48 hours after waking up from the operation. These drugs are continued or restarted as there are no signs that this may affect blood pressure or kidney function. After the first two days, participants are

visited by the researchers to follow their recovery, reviewing medical notes until they leave hospital. Participants are also contacted by telephone in one month and again six months later to ask some simple questions about their wellbeing. The phone call lasts for around five minutes.

What are the possible benefits and risks of participating?
There are no notable benefits involved with participating. The risks of this trial are very small. Many surgeons/anaesthetists instruct patients to stop these drugs, while many advise to continue them. This reflects the uncertainty as to what doctors should actually do. Early studies suggest that continuing these drugs may benefit many patients in this trial. There is a very small risk of high or low blood pressure for some patients. For this reason, patients will be closely monitored throughout the study period and, if necessary, the research team will make adjustments to patients' treatment to make ensure they are safe.

Where is the study run from?
Royal London Hospital (UK)

When is study starting and how long is it expected to run for?
July 2016 to June 2022 (updated 26/05/2022, previously: March 2022; updated 31/03/2021, previously: January 2021; updated 19/07/2019, previously: July 2020)

Who is funding the study?
British Oxygen Company Research Chair Award in Anaesthesia (UK)

Who is the main contact?
Dr Priyanthi Dias
p.dias@qmul.ac.uk

Contact information

Type(s)
Public

Contact name
Dr Priyanthi Dias

ORCID ID
https://orcid.org/0000-0003-0565-5164

Contact details
Adult Critical Care Research
Room 14 Central Tower
The Royal London Hospital
Whitechapel
London
United Kingdom
E1 1BB
+44 20 3594 0352
admin@spacetrial.org

Additional identifiers

EudraCT/CTIS number
2016-004141-90

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
ReDA Ref: 11368

Study information

Scientific Title
Stopping Perioperative Angiotensin II Converting Enzyme inhibitors and/or angiotensin receptor blockers in major non-cardiac surgery (SPACE): A phase III, mechanistic, randomised controlled trial

Acronym
SPACE

Study objectives
The aim of this study is to determine whether continuing angiotensin II converting enzyme inhibitors and/or angiotensin receptor blockers reduces the risk of myocardial injury, identified using high-sensitivity plasma troponin measurement during the first 48 hours after surgery.

Ethics approval required
Old ethics approval format

Ethics approval(s)
London - City & East Research Ethics Committee London, 31/03/2017, ref: 16/LO/1495

Study design
Open multi-centre randomised controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
See additional files

Health condition(s) or problem(s) studied

Patients undergoing major surgery requiring general anaesthesia

Interventions
Following provision of informed consent, participants will be randomly allocated to one of two groups (1:1) using a computer generated dynamic procedure (minimisation) with a random component. Minimisation will be performed by trial centre, angiotensin converting enzyme-inhibitor and/or angiotensin receptor blocker category and surgical procedure.

The trial intervention period will commence 48 hours before surgery and continue for at least 48 hours after surgery. After randomisation, participants will received a patient advice letter confirming their treatment group allocation, to stopping or continuing their angiotensin II converting enzyme inhibitors and/or angiotensin receptor blockers. Participants will also be reminded by telephone call and/or text message, or in person if they are in hospital. If the patients are not in hospital, they will receive a telephone call and/or text message or visit the day before surgery. Angiotensin II converting enzyme inhibitors and/or angiotensin receptor blockers will be continued or discontinued as per treatment group allocation and this will continue until 48 hours after the end of surgery. Since angiotensin II converting enzyme inhibitors and angiotensin receptor blockers have differing durations of action, participants will receive drug-specific instructions as to when to stop. When the angiotensin II converting enzyme inhibitors and/or angiotensin receptor blockers duration of action is equal to, or more than, 24 hours, the drug will be stopped 48 hours prior to surgery. All other angiotensin II converting enzyme inhibitors and/or angiotensin receptor blockers will be stopped on the day before surgery.

Participants will be followed up on days 1, 2 and 3 after surgery and at 30 days after randomisation. The end of the study is defined as the point when the last patient has completed 30-day follow-up. To minimise bias, follow-up data will be collected by a study team member who is blinded to the primary outcome result. Similarly, investigators will review a participant's medical record (paper or electronic) after surgery, unaware of the primary outcome result (which is measured after the end of the trial).

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Any drug listed either as an angiotensin ii converting enzyme inhibitor or angiotensin receptor blocker.

Primary outcome measure
Troponin-T levels will be measured in blood samples collected immediately before the induction of anaesthesia, and then at 24 and 48 hours after surgery.

Secondary outcome measures
1. Highest level of Troponin-T is assessed on plasma high sensitivity Troponin-T, measured within 48 hours of surgery (continuous variable)
2. Infection of Clavien-Dindo grade II or greater, assessed using a patient medical note review and telephone interview, within 30 days from randomisation
3. Myocardial infarction assessed by patient medical note review and telephone interview, within

30 days from randomisation
4. Acute heart failure assessed using a patient medical note review and telephone interview within 30 days from randomisation
5. Stroke within 30 days from randomisation assessed using a patient medical note review and telephone interview

Process measures:
1. Duration of hospital stay (number of days from randomisation until hospital discharge) assessed by a review of the patient's medical records
2. Number of critical care free days*, assessed by a review of the patient's medical records, up to 30 days from randomisation

*A critical care free day is defined as a day in which the patient is alive and is not in a level 2 or level 3 critical care bed.

Overall study start date
01/07/2016

Completion date
30/06/2022

Eligibility

Key inclusion criteria
1. Informed consent (no incapacitated or vulnerable adult or minors will be included)
2. Currently taking angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers therapy
3. Age 60 years and over
4. Patients undergoing major surgery (major joint replacement/ vascular/ gastrointestinal) requiring general anesthesia that is expected to take longer than 120 minutes
5. American Society of Anesthesiologists grade 3 or above

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
260 (130 per arm)

Total final enrolment
260

Key exclusion criteria
1. Current participation in any other trials
2. Recent myocardial infarction (within 3 months)

3. Any condition, which in the opinion of the treating clinician would result in the patient being harmed by the cessation of the angiotensin II converting enzyme inhibitors and/or angiotensin receptor blockers therapy

Date of first enrolment
01/06/2017

Date of final enrolment
31/01/2022

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Royal London Hospital
Barts Health NHS Trust
Adult Critical Care Unit Research Offices
4th Floor Adult Critical Care Unit Research Office 14
Whitechapel Road
London
United Kingdom
E1 1FR

Sponsor information

Organisation
Queen Mary University of London

Sponsor details
Joint Research Management Office
5 Walden Street
London
England
United Kingdom
E1 2EF
+44 20 7882 7250
sponsorsrep@bartshealth.nhs.uk

Sponsor type
University/education

Website

http://bartshealth.nhs.uk/research/about-us/contact-us/

ROR
https://ror.org/026zzn846

Funder(s)

Funder type
Industry

Funder Name
British Oxygen Company Research Chair Award in Anaesthesia

Results and Publications

Publication and dissemination plan
Planned publication in a peer reviewed journal, conference presentations and webcasts. Intent to publish the main paper as soon as possible after completion of the trial.

Intention to publish date
30/06/2023

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Dr Gareth Ackland, Senior Lecturer, Perioperative Medicine. Translational Medicine & Therapeutics (216B), William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, John Vane Science Centre, Charterhouse Square, London EC1M 6BQ.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version V3.0	08/05/2017	13/06/2017	No	Yes
Protocol file	version 2.0	14/12/2016	16/05/2023	No	No
Protocol file	version 3.0	12/05/2017	16/05/2023	No	No
Protocol file	version 4.0	03/10/2017	16/05/2023	No	No
Protocol file	version 5.0	21/05/2019	16/05/2023	No	No
	version 6.0	11/03	16/05		

Protocol file		/2020	/2023	No	No
Protocol file	version 7.0	14/12 /2020	16/05 /2023	No	No
Protocol file	version 8.0	28/01 /2022	16/05 /2023	No	No
Statistical Analysis Plan	version 2.0	17/03 /2022	16/05 /2023	No	No
HRA research summary			28/06 /2023	No	No
Results article		03/11 /2023	12/12 /2023	Yes	No
Other publications	Preoperative N-terminal pro-B-type natriuretic peptide and myocardial injury after stopping or continuing renin–angiotensin system inhibitors in noncardiac surgery: a prespecified analysis of a phase 2 randomised controlled multicentre trial	09/02 /2024	10/06 /2025	Yes	No
Other publications	Preoperative activation of the renin–angiotensin system and myocardial injury in noncardiac surgery: exploratory mechanistic analysis of the SPACE randomised controlled trial	20/12 /2024	10/06 /2025	Yes	No