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A study of two different strategies for handling anticlotting medication in patients who require open-heart surgery to bypass their blocked heart arteries following a heart attack

Submission date
09/06/2022

Recruitment status
No longer recruiting

Registration date
30/08/2022

Overall study status
Completed

Last Edited
17/03/2025

Condition category
Circulatory System

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Most heart attacks are due to blood clots forming within the heart's blood vessels. Two anticlotting medications, aspirin and ticagrelor, are used to treat heart attacks. Some people require open-heart surgery to bypass the blockages in their heart blood vessels. Because of the risk of bleeding associated with this, ticagrelor is usually stopped 5 days before surgery but this may delay surgery and is associated with a small risk of another heart attack as the ticagrelor effects wear off. CytoSorb is a device that is approved for removing ticagrelor from the bloodstream during heart surgery.

Who can participate?
Patients aged 18 years and over who are planned for bypass surgery following a heart attack

What does the study involve?
Participants will be randomly allocated to one of two strategies: 50% will have standard treatment of stopping ticagrelor about 5 days before surgery and just continuing aspirin; and 50% of participants will take their last doses of ticagrelor and aspirin in the morning 48 hours before the planned surgery date, following which CytoSorb will be used to remove ticagrelor during surgery. Blood tests will be performed to study blood clotting and other properties at four timepoints: at randomisation; just before surgery; after patients come off the heart-lung machine during surgery; and 2-4 hours after surgery. A test known as skin bleeding time will also be performed at these time points, which involves pricking the skin on the forearm three times and measuring how long the bleeding lasts. Details of bleeding following surgery and other clinical events will be recorded. All face-to-face visits will be performed during the hospital stay and a single telephone follow-up will be performed at 30 days after surgery.

What are the possible benefits and risks of participating?
The study will provide insights into a potential way of improving the experience and reducing the risks for patients who require open-heart surgery following a heart attack. The risks of

taking part in the study are minimal. There may be a small amount of discomfort when taking the blood samples and bleeding time tests for the study. There is the possibility of bruising around the puncture sites and there is also a very small risk of infection. There is a small risk that patients who are allocated to CytoSorb will have an increased risk of bleeding after the surgery if not all of the ticagrelor is removed; however, this is minimised by patients in this group omitting the dose of aspirin 48 hours before the day of surgery. For patients in the device group who require antibiotics at the time of surgery, there is a small chance the antibiotic treatment may have to be altered to ensure they are best protected from infection and this will be considered by the clinical team as per standard practice with the CytoSorb device.

Where is the study run from?
Sheffield Teaching Hospitals NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
June 2022 to February 2025

Who is funding the study?
Cytosorbents (USA)

Who is the main contact?
Prof. Robert Storey, r.f.storey@sheffield.ac.uk

Contact information

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Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1005625

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
STH21981, IRAS 1005625, CPMS 53872

Study information

Scientific Title
A RandomizEd trial of two diFferent antIplatelet strategies in patieNts with acutE coronary syndromes planned for Coronary Artery Bypass Graft surgery - the REFINE CABG study

Acronym
REFINE CABG

Study objectives
Current study hypothesis as of 05/09/2023:
The primary objective of the trial is to assess whether a novel strategy of stopping the anticlotting medications ticagrelor and aspirin 48 hours before open-heart surgery for treatment of a heart attack or unstable angina and then using a device known as CytoSorb to remove

ticagrelor from the blood during surgery leads to an equivalent anticlotting effect following surgery compared to the standard practice of stopping ticagrelor approximately 5 days before surgery and continuing aspirin up to the day of surgery.

The secondary objectives of the trial are to look at the effects of the different strategies of discontinuing anticlotting medications on:
1. Various blood tests looking at anticlotting effects
2. Levels of inflammation and blood clotting induced by heart surgery
3. Bleeding tendency after surgery as assessed by a skin bleeding test
4. Amount of bleeding and blood transfusion requirements following surgery
5. Changes in blood ticagrelor levels after surgery compared to before surgery

Previous study hypothesis:
The primary objective of the trial is to assess whether a novel strategy of stopping the anticlotting medications ticagrelor and aspirin on the day before open-heart surgery for treatment of a heart attack or unstable angina and then using a device known as CytoSorb to remove ticagrelor from the blood during surgery leads to an equivalent anticlotting effect following surgery compared to the standard practice of stopping ticagrelor approximately 5 days before surgery and continuing aspirin up to the day of surgery.

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Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 29/07/2022, East Midlands - Leicester Central Research Ethics Committee (Equinox House, City Link, Nottingham, NG2 4LA, UK; +44 (0)207 104 8066/+44 (0)207 104 8199; leicestercentral.rec@hra.nhs.uk), ref: 22/EM/0142

Study design
Open randomized controlled parallel-group trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Acute coronary syndrome

Interventions
Current interventions as of 05/09/2023:
The eligible participants in this study will be randomized at Visit 2 in a 50:50 manner to one of two arms using the online randomisation service sealedenvelope.com, and a block size of 8. The treatment arms are as follows:

1. Experimental group
Patients will receive ticagrelor and aspirin (at a standard-of-care dose as prescribed by the clinical care team) until the morning 48 hours before their coronary artery bypass graft (CABG) surgery. They will then discontinue these and will receive treatment with the CytoSorb device during surgery.

2. Standard-of-care group
Patients will discontinue ticagrelor approximately 5 days before CABG surgery and continue to receive aspirin until the day of surgery.

Both groups will return to standard-of-care ticagrelor and aspirin dosing upon completion of surgery. Patients in both groups will have blood samples taken on the day of surgery along with bleeding time assessments. Both groups will be followed up at 24hrs (+/- 4 hrs) post-surgery on the ward and 30 days (+/- 2 days) post-surgery via telephone.

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1. Experimental group
Patients will receive ticagrelor and aspirin (at a standard-of-care dose as prescribed by the clinical care team) until the morning of the day before their coronary artery bypass graft (CABG) surgery. They will then discontinue these and will receive treatment with the CytoSorb device during surgery.

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Patients will discontinue ticagrelor approximately 5 days before CABG surgery and continue to receive aspirin until the day of surgery.

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Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Acetylsalicylic acid, ticagrelor

Primary outcome measure
The absolute level of platelet aggregation in response to collagen 4ug/ml, measured using light transmittance aggregometry immediately following cardiopulmonary bypass

Secondary outcome measures
The two groups will be compared using the following outcomes, where 'pre-surgery' indicates the timepoint on the day of surgery prior to induction of anaesthesia:
1. Absolute light transmission aggregometry (LTA) response to arachidonic acid (AA) 1 mmol/L measured immediately post-CPB
2. Platelet reactivity units (PRU) and % inhibition values assessed using the VerifyNow P2Y12 assay immediately post-CPB
3. Increase in plasma IL-6 level, assessed using ELISA, from pre-surgery to immediately post-CPB
4. Increase in plasma D-dimer level, assessed using immunoturbidimetry, from pre-surgery to immediately post-CPB
5. Absolute skin bleeding time (in minutes) assessed using the bleeding time test immediately post-surgery
6. Total chest tube drainage recorded in millilitres from patient records from immediately post-surgery to 24 hours post-surgery

The following outcomes will be assessed independently in each group:
1. Change in plasma ticagrelor concentration measured using mass spectrometry from pre-surgery to immediately post-CPB
2. Change in plasma ticagrelor active metabolite concentration measured using mass spectrometry from pre-surgery to immediately post-CPB

Overall study start date
07/06/2022

Completion date
28/02/2025

Eligibility

Key inclusion criteria
1. Provision of informed consent prior to any study-specific procedures
2. Male or female aged 18 years or over
3. Currently hospitalised for treatment of an acute coronary syndrome
4. Currently receiving aspirin 75 mg once daily
5. Current treatment or prior treatment during the current hospitalisation with ticagrelor 90 mg twice daily
6. Currently being considered for CABG surgery during the current hospitalisation following coronary angiography with plan to stop ticagrelor approximately 5 days before surgery

Participant type(s)

Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
40

Total final enrolment
48

Key exclusion criteria
1. CABG surgery planned to occur urgently either less than 3 days after cessation of ticagrelor or less than 5 days after cessation of ticagrelor without guidance by platelet function testing
2. Treatment within the last 7 days or planned treatment with any antiplatelet drug other than aspirin and ticagrelor (including prasugrel, clopidogrel, dipyridamole, cilostazol, or glycoprotein IIb/IIIa antagonists) except for a short course of a glycoprotein IIb/IIIa antagonist (tirofiban or eptifibatide) as bridging therapy in those discontinuing ticagrelor at least 3 days prior to scheduled CABG surgery
3. Current or planned treatment prior to CABG surgery with oral or parenteral anti-inflammatory /immunomodulatory drugs (oral corticosteroids; disease-modifying anti-rheumatic drugs, including methotrexate at any dose; immunosuppressants; chemotherapy drugs), oral anti-coagulant medications (warfarin, dabigatran, rivaroxaban, edoxaban, apixaban) or intravenous fibrinolytic agents
4. Current or planned treatment prior to CABG surgery with a non-steroidal anti-inflammatory drug other than aspirin
5. Known hypersensitivity to or intolerance of aspirin, salicylic acid (including certain asthma patients who may suffer an asthma attack or faint), ticagrelor or excipients
6. Clinically significant liver disease, defined as a known or suspected diagnosis of hepatic cirrhosis with current Child-Pugh class B or C; or elevation of serum alanine transferase or aspartate transferase greater than 3 times the upper limit of the normal range for the processing laboratory on blood tests performed during the current hospitalisation
7. Abnormal full blood count on blood tests performed during the current hospitalisation that, in the opinion of the investigator, would preclude safe involvement in the study or compromise its scientific credibility
8. Evidence of active pathological bleeding
9. Participants with clinically significant co-morbidity that, in the opinion of the investigator, would preclude safe involvement in the study or compromise its scientific credibility
10. Any clinically significant abnormal laboratory test results during the current hospitalisation that, in the opinion of the investigator, would preclude safe involvement in the study
11. Pregnant or breastfeeding women
12. Known haemorrhagic diathesis or coagulation disorders such as haemophilia or moderate or severe thrombocytopenia (platelet count < 100 x 10 9/L)
13. Current treatment with a strong CYP3A inhibitor or inducer
14. Current treatment with doses of simvastatin or lovastatin >40 mg/day or CYP3A substrates

with a narrow therapeutic index
15. Any other contraindication for ticagrelor or aspirin treatment as detailed in the respective SmPCs
16. Women of child-bearing potential (WOCBP) unless negative pregnancy test at screening and willing to use highly-effective contraception for the duration of treatment with study medication

Date of first enrolment
01/10/2022

Date of final enrolment
24/10/2024

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Northern General Hospital
Herries Road
Sheffield
United Kingdom
S5 7AU

Sponsor information

Organisation
Sheffield Teaching Hospitals NHS Foundation Trust

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Sponsor type
Hospital/treatment centre

Website
http://www.sth.nhs.uk/

ROR
https://ror.org/018hjpz25

Funder(s)

Funder type
Industry

Funder Name
Cytosorbents

Results and Publications

Publication and dissemination plan
1. Peer-reviewed scientific journals
2. Internal report
3. Conference presentation
4. Publication on website

Intention to publish date
31/12/2025

Individual participant data (IPD) sharing plan
All relevant anonymised study data will be published and available as an open-access article.

IPD sharing plan summary
Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No