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The Cardiac CARE Trial – can heart muscle injury related to chemotherapy be prevented?

Submission date 07/08/2017	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 08/08/2017	**Overall study status** Completed	
Last Edited 15/08/2025	**Condition category** Circulatory System	

Plain English summary of protocol

Background and study aims
Breast cancer is common. The lifetime risk of women developing breast cancer in the UK is 1 in 8. Survival continues to improve. This improved survival is in part down to chemotherapy drugs called anthracyclines. This medication can cause the unwanted side effect of heart muscle injury. Breast cancer and lymphoma survivors have increased rates of heart problems including heart muscle failure. The aim of this study is to test whether tablet medications called angiotensin receptor blockers (ARBs) and B-blockers can prevent heart muscle injury related to chemotherapy. These medications are well established treatments for improving symptoms and survival in patients with heart failure. A blood test called cardiac troponin I is used to detect very slight heart muscle injury. In this study only patients with increased levels of this marker are treated with ARBs and B-blockers.

Who can participate?
Breast cancer or non-Hodgkin lymphoma patients aged over 18 who are scheduled for anthracycline treatment

What does the study involve?
Participants undergo a detailed magnetic resonance imaging (MRI) scan of their heart before starting chemotherapy. Patients receiving anthracycline have blood samples taken routinely up to a week before each cycle. Cardiac troponin I levels are measured using these blood samples. Patients who have increased levels of cardiac troponin I are randomly allocated to treatment with either a combination of ARB and B-blocker or standard care. Heart muscle function is measured using an MRI scan 6 months later to find out whether ARBs and B-blockers can prevent the decline. Patients are followed up to measure health events such as heart failure.

What are the possible benefits and risks of participating?
The study will show whether a convenient blood test can detect those at risk of heart failure. It is not known whether patients will benefit directly from taking part in this study but they will have more regular monitoring of how their heart is working compared to other patients receiving anthracycline treatment. Participants have to make 4-5 extra visits to the cancer centre

to complete questionnaires and have additional blood samples taken. The patients who are allocated to receive the study medication will have an additional 3-4 visits to provide a blood sample and have the dose of study medication changed.

Where is the study run from?
University of Edinburgh (UK)

When is the study starting and how long is it expected to run for?
April 2017 to November 2020

Who is funding the study?
National Institute for Health Research (UK)

Who is the main contact?
Dr Morag MacLean
Cardiac-CARE@ed.ac.uk

Study website
http://edin.ac/cardiac-care-trial

Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
2017-000896-99

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
35705; AC16148

Study information

Scientific Title
A multicentre prospective randomised open-label blinded end-point controlled trial of high-sensitivity cardiac troponin I-guided combination angiotensin receptor blockade and beta blocker therapy to prevent cardiac toxicity in breast cancer and lymphoma patients receiving anthracycline adjuvant therapy (Cardiac CARE)

Acronym
Cardiac CARE

Study objectives
Current hypothesis as of 17/01/2019:
Angiotensin receptor blockers (ARB) and B-blockers can prevent heart muscle injury related to chemotherapy in breast cancer and lymphoma patients, and cardiac Troponin I levels can predict those patients at risk of ventricular dysfunction.

Previous hypothesis:
Angiotensin receptor blockers (ARB) and B-blockers can prevent heart muscle injury related to chemotherapy in breast cancer patients, and cardiac Troponin I levels can predict those patients at risk of ventricular dysfunction.

For pilot study protocol, see additional file ISRCTN24439460_PROTOCOL_PILOT_v3.0_11Apr2017.docx

Ethics approval required
Old ethics approval format

Ethics approval(s)
East of Scotland Research Ethics Service REC 2, 19/06/2017, ref: 17/ES/0071

Study design
Randomized; Interventional; Design type: Treatment, Prevention, Drug

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 patient information sheet

Health condition(s) or problem(s) studied
Heart muscle injury in patients receiving chemotherapy for breast cancer or non-Hodgkin lymphoma

Interventions
Current interventions as of 17/01/2019:
Breast cancer and non-Hodgkin lymphoma patients scheduled for anthracycline treatment will be approached to take part. If they give consent they will have a detailed magnetic resonance imaging (MRI) scan of their heart prior to starting chemotherapy. Patients not in the trial may routinely have radionuclide scans or ECHO to monitor heart function. Patients receiving anthracycline have blood taken routinely up to a week before each cycle. Cardiac troponin I levels will be measured on these blood samples. It is estimated a third of enrolled patients (n= ~56) will develop an elevated plasma cTnI concentration and they will be randomised (1:1 randomised group design minimized by binary criteria [age, baseline LVEF, and planned cumulative epirubicin equivalent) to receive either:

1. Treatment with a combination of ARB (Candesartan) and B-blocker (Carvedilol). Candesartan will be started at 8 mg o.d. and increased at 3-day intervals to 16 mg and 32 mg o.d. Carvedilol will be initiated simultaneously at 6.25 mg b.d., and increased to 12.5 mg b.d. and 25 mg b.d.
2. Standard care: no intervention, LVEF monitored according to local SOPs. Participants in the standard care arm will additionally have study-specific procedures: cTnI measurements and patient questionnaires at 2, 4 and 6 months post-anthracycline treatment, and a cardiac MRI at 6 months post-anthracycline treatment.

IMP will be dispensed on the day of randomisation and will continue until completion /withdrawal from the study.

Duration of treatment: 25 – 37 weeks
Duration of follow-up: None

Previous interventions:
Breast cancer patients scheduled for anthracycline treatment will be approached to take part. If they give consent they will have a detailed magnetic resonance imaging (MRI) scan of their heart prior to starting chemotherapy. Patients not in the trial would routinely have radionuclide scans to monitor heart function. Patients receiving anthracycline have blood taken routinely 2 to 3 days before each cycle. Cardiac troponin I levels will be measured on these blood samples. It is estimated a third of enrolled patients (n= ~56) will develop an elevated plasma cTnI concentration and they will be randomised (1:1 randomised group design minimized by binary criteria [age, baseline LVEF, and randomisation at cycle 2 or 6]) to receive either:

1. Treatment with a combination of ARB (Candesartan) and B-blocker (Carvedilol). Candesartan will be started at 8 mg o.d. and increased at 3-day intervals to 16 mg and 32 mg o.d. Carvedilol will be initiated simultaneously at 6.25 mg b.d., and increased to 12.5 mg b.d. and 25 mg b.d.
2. Standard care: no intervention, LVEF monitored according to local SOPs. Participants in the standard care arm will additionally have study-specific procedures: cTnI measurements and

patient questionnaires at 2, 4 and 6 months post-anthracycline treatment, and a cardiac MRI at 6 months post-anthracycline treatment.

IMP will be dispensed on the day of randomisation and will continue until completion /withdrawal from the study.

Duration of treatment: 25 – 37 weeks
Duration of follow-up: None

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Candesartan, carvedilol

Primary outcome measure
LVEF measured using cardiac MRI scan at baseline and 6 months after final anthracycline dose

Secondary outcome measures
1. Specificity of cTnI assay for left ventricular dysfunction: 6-months post treatment LVEF will be recorded with cardiac MRI in all non-randomised participants and compared to baseline LVEF to define the specificity of the hs-cTnI assay for identifying low-risk participants who do not develop left ventricular systolic dysfunction
2. The development of asymptomatic left ventricular dysfunction (a 10 percentage point fall or an LVEF less than 50%), measured with cardiac MRI at 6 months post-anthracycline treatment compared to baseline
3. Resolution of myocardial injury: whether plasma cTnI concentrations return to the normal reference range (<5 ng/L) at 2, 4 and 6 months after chemotherapy
4. Clinical endpoints of death, cardiovascular death and heart failure. Heart failure will be defined by the diagnosis of clinical (symptomatic) heart failure
5. Health economics: the feasibility of data capture and the quality of data obtainable in this patient population, to inform the design of further research including sample size calculation and /or value of information analysis
6. Heart rate and blood pressure at 2, 4 and 6 months following final dose of anthracycline

Overall study start date
01/04/2017

Completion date
01/11/2021

Eligibility

Key inclusion criteria
Current inclusion criteria as of 17/01/2019:
1. Female or male aged ≥18 years
2. Histological diagnosis of invasive breast cancer or non-Hodgkin lymphoma

3. ECOG performance status 0-1
4. Planned to commence anthracycline containing therapy:
4.1. For adjuvant or neo-adjuvant treatment of breast cancer. Breast cancer patients scheduled for ≥300 mg/m2 cumulative dose epirubicin, or equivalent, over 3, 4 or 6 cycles
or
4.2. NHL patients planned to commence ≥3 cycles of CHOP or R-CHOP therapy containing ≥300mg/m2 epirubicin equivalent cumulative dose of anthracycline.
5. A life expectancy of at least 12 months
6. LVEF ≥ 50% on baseline MRI
7. Systolic blood pressure ≥ 105 mmHg and ≤170 mmHg
8. An eGFR >45 mL/min/1.73 m2
9. Provide written consent to take part in the study

Previous inclusion criteria:
1. Female or male aged ≥18 years
2. Histological diagnosis of invasive breast cancer
3. ECOG performance status 0-1
4. Planned to commence anthracycline for adjuvant or neo-adjuvant treatment of breast cancer. Patients scheduled for >300 mg/m2 cumulative dose epirubicin or equivalent.
5. A life expectancy of at least 12 months
6. LVEF ≥ 50% on baseline MRI
7. Systolic blood pressure ≥ 105 mmHg and ≤170 mmHg
8. An eGFR >45 mL/min/1.73 m2
9. Provide written consent to take part in the study

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
168

Total final enrolment
175

Key exclusion criteria
1. Pregnancy or breastfeeding
2. HER2 positive disease with planned trastuzumab therapy
3. Uncontrolled arterial hypertension defined as systolic blood pressure on treatment of >170 mmHg
3. Patients already taking B-blockers, ACEi or ARBs
4. Contra-indication to ARBs (eGFR ≤ 45 mL/min/1.73 m2, previous hypersensitivity, renal artery stenosis) or B-blockers (asthma, pathological heart block and pathological sinus bradycardia)

5. Clinically proven intolerance to lactose monohydrate
6. A history of symptomatic heart failure
7. Contraindication to or inability to tolerate MRI scanning
8. Suspected poor drug compliance
9. Active alcohol or drug abuse
10. Patients previously treated with anthracyclines or trastuzumab
11. Uncontrolled concomitant serious illness, as determined by the investigator
12. Female or male aged <18 years
13. Not provided written consent to take part in the study
14. Previously randomised into this trial

Date of first enrolment
01/09/2017

Date of final enrolment
01/09/2020

Locations

Countries of recruitment
England

Scotland

United Kingdom

Wales

Study participating centre
Edinburgh Cancer Centre
Edinburgh
United Kingdom
EH4 2XU

Study participating centre
Beatson Institute for Cancer Research
Glasgow
United Kingdom
G12 0YN

Study participating centre
Velindre Hospital
Cardiff
United Kingdom
CF14 2TL

Study participating centre
University Hospital Wales
Cardiff
United Kingdom
CF14 4XW

Study participating centre
Oxford University Hospitals
Oxford
United Kingdom
OX3 9DU

Study participating centre
The Christie Hospital
Manchester
United Kingdom
M20 4BX

Study participating centre
Milton Keynes University Hospital
Standing Way
Eaglestone
Milton Keynes
United Kingdom
MK6 5LD

Study participating centre
Mount Vernon Cancer Centre
Rickmansworth Rd
Northwood
United Kingdom
HA6 2RN

Sponsor information

Organisation
ACCORD - University of Edinburgh & NHS Lothian co-sponsors

Sponsor details
The Queen’s Medical Research Institute
47 Little France Crescent
Edinburgh
Scotland
United Kingdom
EH16 4TJ

Sponsor type
University/education

Website
http://accord.scot/

ROR
https://ror.org/03q82t418

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research; Grant Codes: 15_48_20

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
A manuscript is being prepared for publishing the protocol. Once recruitment starts the protocol will also be available on the department website (http://www.ed.ac.uk/usher/edinburgh-clinical-trials/our-studies/ukcrc-studies/cardiac-care). Any study documents can be requested by emailing cardiac-CARE@ed.ac.uk.

On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be submitted to the NIHR (funder) by 01/11/2020. A report will also be submitted to the REC within 1 year of the end of the study and results will be uploaded to the European clinical trials database. Following publication of the NIHR report the study team will disseminate the results to participating sites and prepare any possible articles for peer reviewed journals. The study results may also be presented at scientific meetings. A lay summary of results will be published on the trial website and provided to the participating sites for dissemination to participants and within their clinics generally (where appropriate and according to their discretion).

Intention to publish date
01/01/2022

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from the CI Dr Peter Henriksen (Cardiac-CARE@ed.ac.uk). Following publication of the primary paper, a de-identified individual participant dataset will be submitted to data archiving for sharing purposes. The format of the data is currently unknown but will likely be available in common formats in use by statisticians working in UK universities. The de-identified dataset will remain available indefinitely. Access to the dataset will be under a controlled access model in line with ECTU (Edinburgh University) policies at the time.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version v3.0	11/04/2017		No	No
HRA research summary			28/06/2023	No	No
Results article		25/09/2023	25/09/2023	Yes	No
Results article		14/08/2025	15/08/2025	Yes	No