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A UK trial for the investigation of stable chest pain: can we improve patient experience, outcomes and NHS cost-efficiency compared to the current NICE guidelines?

Submission date
19/01/2022

Recruitment status
Recruiting

Registration date
24/01/2022

Overall study status
Ongoing

Last Edited
16/07/2025

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

Coronary artery disease (narrowing of the heart arteries) is the typical cause of angina (cardiac chest pain) and is becoming more common as people live longer with multiple heart disease risk factors (e.g. diabetes, smoking, high blood pressure, and high cholesterol). In the UK, about 2 million people have angina and about 200,000 are referred to hospital each year for further investigation. There are lots of different tests to investigate suspected angina, but doctors have different opinions as to the best approach, and international guidelines make very different recommendations. This leads to wide practice variation, inefficiency of healthcare resources and it may adversely impact on patient experience and outcomes. What most doctors agree on is that we do too many invasive X-ray angiograms. About 60% of angiograms performed do not find significant narrowing of the heart arteries, and as such, do not lead to a direct change in management for that patient.

Recent UK NICE guidelines recommend a non-invasive CT angiogram as the first-line test for all patients with suspected angina. This one-size-fits-all approach does not recognise individual patient characteristics, risk factors or likelihood of them having disease. Whilst cardiac CT is an excellent test to exclude narrowing of the heart arteries when they are normal, it can lead to over-estimation of severity when moderate disease is present. It has been suggested that this approach may lead to further increases in the rates of invasive angiography, more additional downstream investigations and increased NHS costs, with no difference in patient outcomes. In addition, the recent UK NICE guidelines if fully adopted would require major service reorganisation in every hospital, and large capital and revenue investment to accommodate the 700% predicted increase in cardiac CT capacity. Thus many doctors believe that this major NHS service reorganisation should first be robustly evaluated in the setting of a clinical trial to demonstrate that it is both appropriate and cost-efficient.

The aim of this study is to try to improve the investigation and management of patients with suspected cardiac chest pain (angina), both in terms of NHS resource use and also patient experience and outcomes; producing results that would be highly generalisable across the NHS.

Who can participate?
Males aged 45 years and over and females aged 50 years and over with atypical or typical angina and at least one major cardiac risk factor (diabetes, peripheral arterial disease, cerebrovascular disease, current or past tobacco use, high blood pressure, dyslipidaemia or a family history of premature coronary artery disease) referred to NHS cardiology outpatient services, requiring further investigation according to NICE CG95 guidelines, and who are deemed suitable for coronary revascularisation if required.

What does the study involve?
Patients will have either a computerised tomography cardioangiogram (a CT scan of the heart), a cardiac MRI scan, a stress echocardiogram (an ultrasound scan of the heart) or a nuclear perfusion scan of the heart with single-photon emission computerised tomography (MPS-SPECT), depending on which group they are randomly allocated to and their calculated risk of having heart disease. Patients will also complete three questionnaires at the start of the study and after 6 and 12 months.

What are the possible benefits and risks of participating?
All of the study procedures are part of routine clinical care and no additional procedures will be undertaken. Participants may be less likely to have unnecessary tests. Patients will also have more contact with the clinical care team and have more opportunities to ask questions and be informed about their health, which some patients find helpful.

Where is the study run from?
University of Leeds and Leeds Clinical Trials Research Unit (UK)

When is the study starting and how long is it expected to run for?
May 2019 to April 2027

Who is funding the study?
1. Heart Research UK
2. British Heart Foundation (UK) (quality of life sub-study)

Who is the main contact?
Dr Laura Jones
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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
302218

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 50598, IRAS 302218

Study information

Scientific Title
A pragmatic approach to the investigation of stable chest pain: a UK, multi-centre, randomised trial to improve patient experience, outcomes and NHS cost efficiency

Acronym
CE-MARC 3

Study objectives
The primary question is: 'can we improve the management of patients with new-onset chest pain, both from a patient perspective and an NHS (payer) perspective?'

The proposed trial will address this by answering the following: compared to the current UK NICE guidelines, can a more pragmatic diagnostic pathway to guide the management of patients with suspected cardiac chest pain, result in a) lower rates of invasive angiography without evidence of obstructive disease, b) less downstream resource utilisation and c) improved patient experience and outcomes.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 01/10/2021, London Bridge Research Ethics Committee (postal address: not available; +44 (0)207 1048202; +44 (0)207 1048124; londonbridge.rec@hra.nhs.uk), REC ref: 21/LO/0666

Study design
Randomized; Both; Design type: Diagnosis, Imaging, Validation of investigation /therapeutic procedures

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Diagnostic

Participant information sheet
See study outputs table

Health condition(s) or problem(s) studied
Stable chest pain

Interventions
People who come to the hospital outpatients department with stable new-onset chest pain or those that have been admitted to cardiology wards will be approached to take part in the trial. If they take part they will be in one of the two arms of the trial and this will be randomly decided (by a computer). The two strategies for the first-line test are:
1. Usual care following the NICE guidelines (this essentially means having a non-invasive CT coronary angiography (CTCA), anatomical test)
2. Pragmatic care following the European Society of Cardiology (ESC) 2019 guidelines whereby a patient could get either a) an MRI scan of the heart (functional test), b) a stress echocardiogram (ultrasound scan) of the heart (functional test), c) a nuclear perfusion scan of the heart (functional test), d) a non-invasive CTCA with added computer calculations (fractional flow reserve [FFR]-CT, anatomical test) which is no different for the patient than having a CTCA. The choice of the first test in this arm would be by shared decision making between the patient and the doctor (cardiologist) guided by contemporary risk stratification determined by the doctor. There will be no extra visits but patients may be asked to complete three short (optional) questionnaires that ask about their health and well-being at baseline, 6 and 12 months. The questionnaires are validated and are expected to take no longer than 20 minutes to complete in total (at each time point). They can be completed during hospital visits or submitted electronically via the Clinical Trials Research portal (the link will be sent out via email or SMS).

In either arm, if the first test is abnormal patients may be asked to go for an invasive angiogram (this would also be the case if a patient was not in the trial). If the first test is normal then NICE guideline-directed medical therapy would be recommended by the doctor. If the first test is inconclusive then the patient could have second-line non-invasive testing or invasive angiography, based upon shared decision-making and in line with current UK NICE guidelines.

The researchers will collect all the test results to see how many of the invasive angiograms were abnormal in each of the trial arms (and how many were normal - i.e. how many showed no evidence of significant disease). They will analyse questionnaire results completed at baseline, 6 and 12 months, and will review medical records at the same intervals.

Patients will also be followed up for up to 10 years to see if they have any further downstream tests, and if they have any health problems like a heart attack (thankfully only very few people have).

Setting: Secondary care cardiology departments that have well-established clinical NHS services for both anatomical and functional cardiac imaging. Initially nine high volume, experienced research centres that are geographically spread and with ethnically diverse populations have been selected (Leeds, Glasgow, Leicester, Bristol, Oxford, Barts (London), Liverpool, Wakefield and Southampton); other centres could join based on their clinical services and trial experience.

Intervention Type
Other

Primary outcome measure
Time to composite endpoint of cardiovascular death, myocardial infarction, unobstructive coronary artery disease (CAD) at invasive angiography, defined as the invasive reference standard FFR measurement of >0.80 (or instantaneous wave-free ratio [iFR] ≥0.90), i.e. no functional ischaemia, at the time of coronary angiography (or no coronary stenosis >70% on quantitative coronary angiography should FFR/iFR be deemed clinically inappropriate/unsafe to perform)

Secondary outcome measures
1. Patient-reported quality of life measured using the Seattle Angina Questionnaire (SAQ), Euroqol EQ-5D-5L, SF12v2 at 0, 6 and 12 months
2. Guideline-directed medical therapy (GDMT) usage measured using patient questionnaire results and/or GP records at 0, 6 and 12 months
3. Major Adverse Cardiovascular Events (all cause death, myocardial infarction [MI], unplanned percutaneous coronary intervention [PCI]/coronary artery bypass graft surgery [CABG]) measured using patient questionnaire results and/or GP records at 3 years
4. Resource use and cost efficiency measured using patient questionnaire results and/or GP records at 12 months

Overall study start date
30/05/2019

Completion date
26/04/2027

Eligibility

Key inclusion criteria
1. Males ≥45 years or females ≥50 years
2. Atypical or typical angina
3. At least one major cardiac risk factor (diabetes, peripheral arterial disease, cerebrovascular disease, current or past tobacco use, hypertension, dyslipidaemia or family history of premature coronary artery disease)
4. Referred to NHS cardiology outpatient services
5. Requiring further investigation according to NICE CG95 guidelines
6. Deemed suitable for coronary revascularisation if required

Participant type(s)
Patient

Age group
Adult

Lower age limit
45 Years

Sex
Both

Target number of participants
Planned Sample Size: 4000; UK Sample Size: 4000

Key exclusion criteria
In order to keep the trial generalisable to the UK population at large, only issues related to patient safety/appropriateness will form the exclusion criteria; these will include:
1. Prior normal CT coronary angiography (CTCA) within the last 2 years or prior CTCA with extensive calcification
2. Clinically unstable cardiac symptoms

3. Known coronary artery disease (including previous myocardial infarction [MI], acute coronary syndrome [ACS] or coronary revascularization)
4. Contraindication to CTCA or functional cardiac imaging
5. Pregnancy and/or breastfeeding
6. Known chronic renal failure (eGFR < 30ml/min/1.73m²)
7. Inability to give written informed consent

Date of first enrolment
27/04/2022

Date of final enrolment
31/07/2025

Locations

Countries of recruitment
England

Scotland

United Kingdom

Study participating centre
United Leeds Teaching Hospital NHS Trust
Trust Hq
Leeds General Infirmary
Great George St
Leeds
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LS1 3EX

Study participating centre
Gartnavel Royal Hospital
1055 Great Western Road
Glasgow
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G12 0XH

Study participating centre
Leicester Royal Infirmary
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Study participating centre
Oxford University Hospitals
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OX3 9DU

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Trust Hq, Rowan House
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WF1 4EE

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Study participating centre
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UB9 6JH

Study participating centre
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EX2 5DW

Study participating centre
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TS5 5AZ

Study participating centre
University Hospital Southampton NHS Foundation Trust
Southampton General Hospital
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United Kingdom
SO16 6YD

Study participating centre
Central Manchester University Hospitals NHS Foundation Trust
Trust Headquarters, Cobbett House
Manchester Royal Infirmary
Oxford Road
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M13 9WL

Study participating centre
Bradford Teaching Hospitals NHS Foundation Trust
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BD9 6RJ

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Study participating centre
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Study participating centre

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Sponsor type
University/education

Website
http://www.leeds.ac.uk/

ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Charity

Funder Name
Heart Research UK; Grant Codes: TR2442/19/24

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype

Other non-profit organizations

Location
United Kingdom

Funder Name
British Heart Foundation

Alternative Name(s)
the_bhf, The British Heart Foundation, BHF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
A copy of the protocol will be available after publication. The researchers will work closely with the communications teams at Leeds Teaching Hospitals NHS Trust, University of Leeds and Heart Research UK to ensure that the findings are conveyed to the general public through mainstream broadcasters, press and patient groups, including online resources and social media (e.g. #NIHR@leeds). Findings will be presented at leading scientific conferences and in high-quality, high impact, peer-reviewed journals. Dissemination to patients will be supported through established national PPIE groups, in conjunction with the PPIE advisors involved with this trial. Lay summaries will be produced and published on the NIHR@Leeds websites, CTRU website, and Institute website. Dissemination will also take place through community engagement via research open days, Café Scientifique, and to other expert patient groups regionally and nationally, as guided by the patient advisors.

Intention to publish date
31/01/2028

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request (Prof. John Greenwood; P.Greenwood@Leeds.ac.uk) following the publication of the pre-specified primary and secondary endpoints. Data will be fully anonymised.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 1.0	16/08/2021	20/01/2022	No	Yes
HRA research summary			26/07/2023	No	No