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The refer for echocardiogram, clinical decision rule and N-terminal pro-B-type natriuretic peptide (NT-proBNP) in the diagnosis of heart failure

Submission date
28/02/2011

Recruitment status
No longer recruiting

Registration date
21/06/2011

Overall study status
Completed

Last Edited
19/02/2021

Condition category
Circulatory System

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

Plain English summary of protocol

Background and study aims
Heart failure is caused by the heart muscle becoming weak or stiff and failing to pump enough blood around the body. It significantly reduces quality of life and life expectancy. The costs to the NHS are high due to frequent hospitalisation and GP visits. Heart failure is a common problem in primary care, but diagnosis is difficult and GPs must decide which patients need further tests. Heart failure can be diagnosed by ultrasound (an echocardiogram) but it is expensive and limited. Therefore, GPs rely on less effective tests, resulting in under-diagnosis. Accurate diagnosis, appropriate treatment and cost–effective use of NHS resources are needed to improve quality of life and life expectancy. However, there is uncertainty in these areas. We aim to find out if a clinical decision rule (CDR) can help GPs determine which patients should be referred for an echocardiogram and if it is cost–effective. The study will tell us if a simple rule involving symptoms, physical examination and blood testing can be used for better diagnosis and targeting of further diagnostic tests for heart failure, helping to improve quality of care and save money.

Who can participate?
Patients aged 55 or over visiting their GP with new symptoms of breathlessness, lethargy (tiredness) or ankle oedema (swelling)

What does the study involve?
The GP refers all patients for chest x–ray (as usual), and then to a central research clinic. Information on symptoms and quality of life are collected, and patients undergo an electrocardiogram (measuring the electrical activity of the heart), an echocardiogram (an ultrasound scan of the heart), and provide a blood sample. We want to find out whether the CDR can correctly identify all cases with heart failure. We follow-up patients after 6 and12 months to collect medical and quality of life information.

What are the possible benefits and risks of participating?
Not provided at time of registration

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

When is the study starting and how long is it expected to run for?
April 2011 to June 2014

Who is funding the study?
Medical Research Council (MRC)/National Institute of Health Research (NIHR) (UK) - Efficacy and Mechanism Evaluation (EME) Programme (UK)

Who is the main contact?
Prof Richard Hobbs

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Protocol serial number
09/160/13

Study information

Scientific Title
The REFer for EchocaRdiogram, clinical decision rule and N-terminal pro-B-type natriuretic peptide (NT-proBNP) in the diagnosis of heart failure: a prospective validation study

Acronym
REFER

Study objectives

The clinical decision rule (CDR) will discriminate between patients who have sufficiently high probability of heart failure (HF) that they should be referred for echo and those who should have a natriuretic peptide (NP) test first, with referral for echo dependent upon the natriuretic peptide results.

Ethics approval required
Old ethics approval format

Ethics approval(s)
The South Birmingham Research Ethics Committee, 15/10/2009

Study design
Multicentre prospective observational diagnostic validation study

Primary study design
Observational

Study type(s)
Diagnostic

Health condition(s) or problem(s) studied
Heart failure

Interventions
The general practitioner (GP) will have arranged for all patients to receive a chest x-ray when consenting patients for referral (as is usual practice). Within 7 days of referral, the research assessment clinical team will obtain written informed consent, collect baseline demographics, administer quality of life questionnaires (EQ-5D and SF12), clinically assess patients, perform a 12-lead electrocardiogram (ECG) and Echo and take blood for N-terminal pro b-type natriuretic peptide (NT-proBNP), along with creatinine for a renal dysfunction test, calculating an estimated Glomerular Filtration Rate (eGFR) (serum profile)

Intervention Type
Other

Phase
Not Applicable

Primary outcome(s)
1. Test performance of the CDR, estimating the sensitivity and specificity, positive predictive value (PPV) and negative predictive value (NPV) of the CDR for diagnosis of HF in symptomatic patients presenting with shortness of breath, lethargy or ankle oedema of over 48 hours duration
2. Test performance of the diagnostic accuracy of NT-proBNP for diagnosis of HF in symptomatic patients, including sensitivity, specificity, PPV and NPV
3. Proportion of patients with left ventricular systolic dysfunction (LVSD) or not, (ejection fraction < 40%) and HF or not

Key secondary outcome(s))

1. Combination of the CDR and NT-proBNP
2. Modelling of CDR test performance and epidemiological data to ascertain the most cost-effective strategy in the diagnosis of HF in primary care, incorporating data on quality of life (EQ-5D and SF12 widely used questionnaires), clinical events and health care resource use
3. Reliability of GP clinical judgment alone in diagnosing HF
4. Reliability of individual clinical features
5. Reliability of ECG interpretation
6. Estimation of the best performing cut-offs for NT-proBNP to maximise diagnostic yield and for maximising cost-effective referrals
7. Determine the use of variable echocardiographic markers of diastolic function in the diagnosis of HF with preserved ejection fraction

Completion date
01/06/2014

Eligibility

Key inclusion criteria
Current inclusion criteria as of 12/12/2011:
1. All patients 55 years of age or over presenting to their GP with new onset symptoms of breathlessness, lethargy or ankle oedema of over 48 hours duration, with no obvious recurrent, acute or self-limiting cause
2. Able to give informed consent

Previous inclusion criteria:
1. All patients 55 years of age or over presenting to their GP with new onset symptoms of breathlessness, lethargy or ankle oedema of over 48 hours duration, with no obvious acute and self-limiting cause
2. Able to give informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Total final enrolment
304

Key exclusion criteria
Current exclusion criteria as of 12/12/2011
1. All patients with known pre-existing heart failure or left ventricular systolic dysfunction of any cause. However, patients with a pre-existing label of heart failure but without objective

evidence (i.e. echocardiography) of this will not be excluded
2. Severe symptoms requiring urgent assessment or stabilisation (e.g. breathless at rest, hypotension, confusion)
3. Obvious clinically determined alternative diagnoses such as chest infection, exacerbation of chronic obstructive pulmonary disease or asthma
4. Recent acute coronary syndrome (within 60 days)
5. Major co-morbidity or other alternative diagnoses of no obvious acute and self-limiting cause (e.g. malignancy, severe respiratory disease, renal diagnosis, mental health problem)
6. Unable to provide informed consent

Previous exclusion criteria
1. All patients with known pre-existing heart failure or left ventricular systolic dysfunction of any cause. However, patients with a pre-existing label of heart failure but without objective evidence (i.e. echocardiography) of this will not be excluded
2. Severe symptoms requiring urgent assessment or stabilisation (e.g. breathless at rest, hypotension, confusion)
3. Obvious clinically determined alternative diagnoses such as chest infection, exacerbation of chronic obstructive pulmonary disease or asthma
4. Recent acute coronary syndrome (within 60 days)
5. Major co-morbidity or other alternative diagnoses of no obvious acute and self-limiting cause (e.g. active malignancy, severe respiratory disease, renal diagnosis, severe psychiatric disease)
6. Unable to provide informed consent

Date of first enrolment
01/04/2011

Date of final enrolment
01/06/2014

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University of Oxford
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Sponsor information

Organisation
Oxford Radcliffe Hospitals NHS Trust (UK)

ROR
https://ror.org/03h2bh287

Funder(s)

Funder type
Government

Funder Name
Medical Research Council (MRC)/National Institute of Health Research (NIHR) (UK) - Efficacy and Mechanism Evaluation (EME) Programme (ref: 09/160/13)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/04/2017	19/02/2021	Yes	No
Protocol article	protocol	30/10/2012		Yes	No