

The REFER (REFer for EchocaRdiogram) study: a prospective validation and health economic analysis of a clinical decision rule, NT-proBNP or their combination in the diagnosis of heart failure in primary care

Clare J Taylor,¹ Mark Monahan,² Andrea K Roalfe,² Pelham Barton,² Rachel Iles² and FD Richard Hobbs^{1*} on behalf of the other REFER investigators

¹Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

²Institute of Applied Health Research, University of Birmingham, Birmingham, UK

*Corresponding author richard.hobbs@phc.ox.ac.uk

Declared competing interests of authors: FD Richard Hobbs has received grants from Roche Diagnostics outside the submitted work. The work was supported by funding from the National Institute for Health Research Efficacy and Mechanism Evaluation programme. Roche Diagnostics provided the N-terminal pro-B-type natriuretic peptide testing equipment but did not have any influence on study design, conduct or reporting.

Published April 2017

DOI: 10.3310/eme04030

Scientific summary

The REFER (REFer for EchocaRdiogram) study

Efficacy and Mechanism Evaluation 2017; Vol. 4: No. 3

DOI: 10.3310/eme04030

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Heart failure is a chronic disease associated with significant mortality and poor quality of life for patients. There are several evidence-based therapies that will delay heart failure progression, improve quality of life, reduce cardiovascular events and help avoid hospital admissions. A reliable and early diagnosis is, therefore, essential to guide the most appropriate management strategies. However, making an accurate and timely diagnosis requires referral for objective testing, but deciding who to refer can be challenging. The symptoms of heart failure are often non-specific and include gradual-onset breathlessness, fatigue and ankle swelling, symptoms not unique to heart failure and often associated with other conditions, or patients may have several coexisting diseases. Help with deciding who to refer and what tests to use is, therefore, crucial.

Clinical decision rules (CDRs) may help clinicians to assess the probability that a patient has a particular condition. The 'MICE' CDR was developed from an individual patient database meta-analysis of all ($n = 11$) prospective epidemiological studies of heart failure screening in primary care, which was commissioned as a health technology assessment by the National Institute for Health and Care Excellence (NICE). The CDR comprised four clinical elements – Male, history of myocardial Infarction, Crepitations at the lung bases and oEdema – and was combined with natriuretic peptide levels to identify those likely to have heart failure and who should be referred for further diagnostic testing.

Objectives

The REFER (REFer for EchocaRdiogram) trial aimed to assess the performance of the CDR, CDR and N-terminal pro-B-type natriuretic peptide (NT-proBNP) testing or NT-proBNP testing alone in identifying patients with heart failure presenting to primary care. The REFER trial was a prospective, observational, diagnostic validation study of the MICE CDR – with natriuretic peptide testing – for diagnosing heart failure in primary care.

The economic evaluation aimed to assess the cost-effectiveness of using the MICE CDR in heart failure diagnosis in general practice from a NHS and Personal Social Services perspective.

Methods

Primary care patients aged ≥ 55 years presenting to their general practitioner (GP) with symptoms suggestive of heart failure were recruited across 28 general practices in central England. All consenting patients underwent a full clinical assessment, which included a NT-proBNP test, an echocardiogram and a quality-of-life questionnaire, at a research clinic within 1 week of recruitment. Follow-up quality-of-life and resource-use questionnaires were mailed to the patients at 6 and 12 months after attending the clinic.

The diagnosis of 'heart failure' or 'no heart failure' was determined by an expert panel of cardiologists using the European Society of Cardiology 2012 definition. Clinical information, including the variables of the MICE rule and NT-proBNP level, was presented in stages to quantify any incorporation bias.

For the economic evaluation, a decision tree was developed comparing different diagnostic strategies using data from REFER participants to determine which symptomatic patients would receive the correct diagnostic decision. The model used a lifetime horizon and a UK NHS perspective.

Results

In total, 304 participants were recruited; the mean age of participants was 73.9 years (standard deviation 8.8 years) and 124 (40.8%) were male. In total, 104 participants [34.2%, 95% confidence interval (CI) 28.9% to 39.8%] had a confirmed diagnosis of heart failure. The CDR had a sensitivity of 90% (95% CI 83% to 95%) and a specificity of 46% (95% CI 39% to 53%). NT-proBNP level alone with a cut-off point of < 400 pg/ml had a sensitivity of 77% (95% CI 68% to 85%) and specificity of 92% (95% CI 87% to 95%). At the lower cut-off point of 125 pg/ml, sensitivity was 94% (95% CI 88% to 98%) and specificity was 49% (95% CI 42% to 56%).

The economic model used a lifetime horizon and a UK NHS perspective. The results suggest that use of the current recommended NICE guidelines for identifying patients with heart failure is the most cost-effective option, with a cost of £4400 per quality-adjusted life-year (QALY) gained compared with a do nothing strategy. That is, patients presenting with symptoms suggestive of heart failure should be referred straight for echocardiography if they have a history of myocardial infarction or if their NT-proBNP level is \geq 400 pg/ml. The MICE rule was more expensive and less effective than the other comparators. The base-case results were robust to sensitivity analysis.

Conclusions

Natriuretic peptide testing alone performed as well as the validated CDR in determining which patients presenting with symptoms went on to have a diagnosis of heart failure. The current NT-proBNP cut-off level of 400 pg/ml used in the UK is too high and means that one in five patients with heart failure may not be appropriately referred for further investigation and diagnosis.

The economics study represents the first cost-utility analysis comparing heart failure diagnostic strategies for symptomatic patients. Current practice in England is the most cost-effective option for identifying patients for confirmatory heart failure diagnosis. The low number of heart failure with reduced ejection fraction patients (12%) in the REFER patient population limited the benefits of early detection.

Trial registration

This trial is registered as ISRCTN17635379.

Funding

This project was funded by the Efficacy and Mechanism Evaluation (EME) programme, a MRC and NIHR partnership.

Efficacy and Mechanism Evaluation

ISSN 2050-4365 (Print)

ISSN 2050-4373 (Online)

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full EME archive is freely available to view online at www.journalslibrary.nihr.ac.uk/eme. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Efficacy and Mechanism Evaluation* journal

Reports are published in *Efficacy and Mechanism Evaluation* (EME) if (1) they have resulted from work for the EME programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

EME programme

The Efficacy and Mechanism Evaluation (EME) programme was set up in 2008 as part of the National Institute for Health Research (NIHR) and the Medical Research Council (MRC) coordinated strategy for clinical trials. The EME programme is broadly aimed at supporting 'science driven' studies with an expectation of substantial health gain and aims to support excellent clinical science with an ultimate view to improving health or patient care.

Its remit includes evaluations of new treatments, including therapeutics (small molecule and biologic), psychological interventions, public health, diagnostics and medical devices. Treatments or interventions intended to prevent disease are also included.

The EME programme supports laboratory based or similar studies that are embedded within the main study if relevant to the remit of the EME programme. Studies that use validated surrogate markers as indicators of health outcome are also considered.

For more information about the EME programme please visit the website: <http://www.nets.nihr.ac.uk/programmes/eme>

This report

The research reported in this issue of the journal was funded by the EME programme as project number 09/160/13. The contractual start date was in July 2011. The final report began editorial review in August 2015 and was accepted for publication in July 2016. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The EME editors and production house have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research. The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, the MRC, NETSCC, the EME programme or the Department of Health. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the EME programme or the Department of Health.

© Queen's Printer and Controller of HMSO 2017. This work was produced by Taylor *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).

Efficacy and Mechanism Evaluation Editor-in-Chief

Professor David Crossman Bute Professor of Medicine and Dean and Head of Faculty of Medicine, University of St Andrews, and Honorary Consultant Cardiologist, NHS Fife Health Board, UK

NIHR Journals Library Editor-in-Chief

Professor Tom Walley Director, NIHR Evaluation, Trials and Studies and Director of the EME Programme, UK

NIHR Journals Library Editors

Professor Ken Stein Chair of HTA Editorial Board and Professor of Public Health, University of Exeter Medical School, UK

Professor Andree Le May Chair of NIHR Journals Library Editorial Group (EME, HS&DR, PGfAR, PHR journals)

Dr Martin Ashton-Key Consultant in Public Health Medicine/Consultant Advisor, NETSCC, UK

Professor Matthias Beck Chair in Public Sector Management and Subject Leader (Management Group), Queen's University Management School, Queen's University Belfast, UK

Dr Tessa Crilly Director, Crystal Blue Consulting Ltd, UK

Dr Eugenia Cronin Senior Scientific Advisor, Wessex Institute, UK

Ms Tara Lamont Scientific Advisor, NETSCC, UK

Dr Catriona McDaid Senior Research Fellow, York Trials Unit, Department of Health Sciences, University of York, UK

Professor William McGuire Professor of Child Health, Hull York Medical School, University of York, UK

Professor Geoffrey Meads Professor of Health Sciences Research, Health and Wellbeing Research Group, University of Winchester, UK

Professor John Norrie Chair in Medical Statistics, University of Edinburgh, UK

Professor John Powell Consultant Clinical Adviser, National Institute for Health and Care Excellence (NICE), UK

Professor James Raftery Professor of Health Technology Assessment, Wessex Institute, Faculty of Medicine, University of Southampton, UK

Dr Rob Riemsma Reviews Manager, Kleijnen Systematic Reviews Ltd, UK

Professor Helen Roberts Professor of Child Health Research, UCL Institute of Child Health, UK

Professor Jonathan Ross Professor of Sexual Health and HIV, University Hospital Birmingham, UK

Professor Helen Snooks Professor of Health Services Research, Institute of Life Science, College of Medicine, Swansea University, UK

Professor Jim Thornton Professor of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, University of Nottingham, UK

Professor Martin Underwood Director, Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, UK

Please visit the website for a list of members of the NIHR Journals Library Board:
www.journalslibrary.nihr.ac.uk/about/editors

Editorial contact: journals.library@nihr.ac.uk