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

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Scientific summary

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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 ≥ 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.

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