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The research reported in this issue of the journal was commissioned by the HTA programme as project number 05/06/01. The contractual start date was in February 2006. The draft report began editorial review in October 2007 and was accepted for publication in January 2009. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

Systematic review and individual patient data meta-analysis of diagnosis of heart failure, with modelling of implications of different diagnostic strategies in primary care

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Objectives: To assess the accuracy in diagnosing heart failure of clinical features and potential primary care investigations, and to perform a decision analysis to test the impact of plausible diagnostic strategies on costs and diagnostic yield in the UK health-care setting.
Data sources: MEDLINE and CINAHL were searched from inception to 7 July 2006. 'Grey literature' databases and conference proceedings were searched and authors of relevant studies contacted for data that could not be extracted from the published papers.
Review methods: A systematic review of the clinical evidence was carried out according to standard methods. Individual patient data (IPD) analysis was performed on nine studies, and a logistic regression model to predict heart failure was developed on one of the data sets and validated on the other data sets. Cost-effectiveness modelling was based on a decision tree that compared different plausible investigation strategies.
Results: Dyspnoea was the only symptom or sign with high sensitivity (89%), but it had poor specificity (51%). Clinical features with relatively high specificity included history of myocardial infarction (89%), orthopnoea (89%), oedema (72%), elevated jugular venous pressure (70%), cardiomegaly (85%), added heart sounds (99%), lung crepitations (81%) and hepatomegaly (97%). However, the sensitivity of these features was low, ranging from 11% (added heart sounds) to 53% (oedema). Electrocardiography (ECG), B-type natriuretic peptides (BNP) and N-terminal pro-B-type natriuretic peptides (NT-proBNP) all had high sensitivities (89%, 93% and 93% respectively). Chest X-ray was moderately specific (76–83%) but insensitive (67–68%). BNP was more accurate than ECG, with a relative diagnostic odds ratio of ECG/BNP of 0.32 (95% CI 0.12–0.87). There was no difference between the diagnostic accuracy of BNP and NT-proBNP. A model based upon simple clinical features and BNP derived from one data set was found to have good validity when applied to other data sets. A model substituting ECG for BNP was less predictive. From this a simple clinical rule was developed: in a patient presenting with symptoms such as breathlessness in whom heart failure is suspected, refer directly to echocardiography if the patient has a history of myocardial infarction or basal crepitations or is a male with ankle oedema; otherwise, carry out a BNP test and refer for echocardiography depending on the results of the test. On the basis of the cost-effectiveness analysis carried out, such a decision rule is likely to be considered cost-effective to the NHS in terms of cost per additional case detected. The cost-effectiveness analysis further suggested that, if likely benefit to the patient in terms of improved life expectancy is taken into account, the optimum strategy would be to refer all patients with symptoms suggestive of heart failure directly for echocardiography.
Conclusions: The analysis suggests the need for important changes to the NICE recommendations. First, BNP (or NT-proBNP) should be recommended over ECG and, second, some patients should be referred straight for echocardiography without undergoing any preliminary investigation. Future work should include evaluation of the clinical rule described above in clinical practice.

Contents

List of abbreviations

ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
AHA	American Heart Association
ARB	angiotensin receptor blocker
AUC	area under the curve (summary measure of diagnostic test performance)
BNF	*British National Formulary*
BNP	B-type natriuretic peptides
CINAHL	Cumulative Index to Nursing and Allied Health Literature
COPD	chronic obstructive pulmonary disease
CXR	chest X-ray
DOR	diagnostic odds ratio
ECG	electrocardiogram
ECHOES	Echocardiographic Heart of England Screening (study)
EMBASE	*E*xcerpta *M*edica data*base*, a biomedical and pharmacological literature database
ESC	European Society of Cardiology
ICER	incremental cost-effectiveness ratio
IHD	ischaemic heart disease
IPD	individual patient data (analysis)
JVP	jugular venous pressure
LV	left ventricle/left ventricular
LVEF	left ventricular ejection fraction
LVSD	left ventricular systolic dysfunction
MEDLINE	medical literature analysis and retrieval system
MI	myocardial infarction
MICE	clinical scoring system to determine risk of heart failure (*m*ale, *i*nfarction, *c*repitations, o*e*dema)
NHANES	National Health and Nutritional Examination Survey
NICE	National Institute for Health and Clinical Excellence
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association (functional classification)
QALY	quality-adjusted life-year
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RCT	randomised controlled trial
ROC	receiver operating characteristic (curve)
SAS®	statistical analysis software
SOB	shortness of breath
SPSS	Statistical Package for the Social Sciences
WTP	willingness to pay

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Heart failure is a syndrome resulting from a structural or functional cardiac disorder. For a diagnosis of heart failure to be made there should be symptoms or signs such as breathlessness, effort intolerance or fluid retention together with objective evidence of cardiac dysfunction. Heart failure is associated with significant morbidity and mortality, and health-care expenditure. However, there is a good evidence base for interventions to improve prognosis. Diagnosis of heart failure in primary care is often inaccurate. Current National Institute for Health and Clinical Excellence (NICE) recommendations are that patients in whom heart failure is suspected should undergo an electrocardiogram (ECG) and/or a B-type natriuretic peptide (BNP) test, where available, and that if either of these is positive, then they should be referred for echocardiography as part of their diagnostic workup. The purpose of this work is to determine the potential value of clinical features in the diagnostic assessment, and the relative value of the different diagnostic tests that are available in primary care, with the aim of producing clear recommendations on the optimal approach to diagnosis of heart failure in primary care in the UK.

Objectives

1. To perform a systematic review to assess the accuracy in diagnosing heart failure of:
   i. clinical features – both singly and, if possible, in combination
   ii. potential primary care investigations – plasma natriuretic peptides, ECG and chest X-ray (CXR) (singly and, if possible, in combination).
2. To perform an individual patient data (IPD) analysis to address the following questions:
   i. Can a clinical scoring system based on symptoms and signs usefully predict the presence of heart failure?
   ii. To rule out heart failure in primary care, what is the optimum decision cut-off point for plasma natriuretic peptides (BNP)?
   iii. Does the diagnostic performance of plasma natriuretic peptides vary according to patient characteristics?
   iv. How accurate is the combination of plasma natriuretic peptides with ECG at diagnosing heart failure?
3. To perform a decision analysis to test the impact of plausible diagnostic strategies for the diagnosis of heart failure in primary care on costs and diagnostic yield in the UK health-care setting.

Methods

Systematic review

Data sources

Primary studies were identified by searching MEDLINE and CINAHL, with supplementary checks of reference lists of all studies that met the inclusion criteria and any review articles. 'Grey literature' databases and conference proceedings were searched, and authors of relevant studies were contacted for data that could not be extracted from the published papers.

Study selection

Studies were included if they estimated the diagnostic accuracy of symptoms, signs or investigations for detecting heart failure. There needed to be an adequate reference standard [e.g. use of European Society of Cardiology (ESC) criteria for diagnosis of heart failure]. Studies in which the reference standard was echocardiographic assessment of left ventricular systolic dysfunction (LVSD) alone were reviewed but were not included in the meta-analysis.

Data extraction

Potentially relevant studies were assessed by two reviewers against the inclusion criteria, with a third reviewer arbitrating when necessary. Data were extracted by both reviewers and quality was assessed using the Quality Assessment of Diagnostic Accuracy of Studies (QUADAS) criteria.

Data synthesis

Sensitivity and specificity were plotted on receiver operating characteristic (ROC) graphs. The data

were pooled using a bivariate random-effects meta-analysis and summary estimates of test accuracy calculated. To explore the impact of setting and prevalence, predictive values were plotted against heart failure prevalence.

Individual patient data analysis

Inclusion criteria for the IPD required the study to be set in primary care and to have a minimum of 100 recently symptomatic patients. A total of 11 studies were identified, and data were obtained from nine of these.

A logistic regression model to predict heart failure was developed on one of the data sets. This was then validated on the other data sets that had the required variables. Validation included calculation of the area under the ROC curve (AUC) and use of goodness-of-fit calibration plots.

The resultant model was then simplified into a decision rule that would be usable in clinical practice.

The impact of potential effect modifiers (e.g. use of drugs, co-morbidity) was examined by their inclusion as interactions with BNP [and N-terminal pro-B-type natriuretic peptide (NT-proBNP)] adjusted for clinical score.

Cost-effectiveness analysis

The cost-effectiveness modelling was based on a decision tree that compared different plausible investigation strategies. The outputs of the model were in terms of investigation costs and cases detected, from which an incremental cost-effectiveness ratio (ICER) was calculated comprising the cost per additional case detected. The amount of money that it would be worth spending to diagnose an extra case of heart failure was calculated in two ways. First, only the costs to the NHS were taken into account (including extra admissions through delayed diagnosis). Second, patient benefit in terms of improved quality-adjusted life-years (QALYs) was also taken into account, based on estimates of improved survival as a result of earlier diagnosis leading to earlier initiation of treatments with proven effects on survival. The robustness of the results of the model was tested by sensitivity analyses that varied the costs of the investigations and the time horizon over which the benefits accrued.

Results

Systematic review

Dyspnoea was the only symptom or sign with high sensitivity (89%), but it had poor specificity (51%). Several clinical features had relatively high specificity, including history of myocardial infarction (89%), orthopnoea (89%), oedema (72%), elevated jugular venous pressure (JVP) (70%), cardiomegaly (85%), added heart sounds (99%), lung crepitations (81%) and hepatomegaly (97%). However, the sensitivity of all of these features was low, ranging from 11% (added heart sounds) to 53% (oedema). ECG, BNP and NT-proBNP all had high sensitivities (89%, 93% and 93% respectively). CXR was moderately specific (76–83%) but insensitive (67–68%). BNP was more accurate than ECG, with a relative diagnostic odds ratio of ECG/BNP of 0.32 (95% CI 0.12–0.87). There was no difference between the diagnostic accuracy of BNP and NT-proBNP.

Individual patient data analysis

A model based upon simple clinical features (*m*ale gender, history of myocardial *i*nfarction, basal *c*repitations, o*e*dema; 'MICE') and BNP derived from one data set was found to have good validity when applied to other data sets, with an AUC between 0.84 and 0.96 and reasonable calibration. A model substituting ECG for BNP was less predictive.

From this a simple clinical rule was developed and is proposed by the authors:

- In a patient presenting with symptoms such as breathlessness in whom heart failure is suspected, refer directly to echocardiography if the patient has any one of:
  - history of myocardial infarction or
  - basal crepitations or
  - male with ankle oedema.
- Otherwise, carry out a BNP test and refer for echocardiography depending on the results of the test:
  - female without ankle oedema – refer if BNP > 210–360 pg/ml depending upon local availability of echocardiography (or NT-proBNP > 620–1060 pg/ml)
  - male without ankle oedema – refer if BNP > 130–220 pg/ml (or NT-proBNP > 390–660 pg/ml)
  - female with ankle oedema – refer if BNP > 100–180 pg/ml (or NT-proBNP > 190–520 pg/ml).

Cost-effectiveness analysis

On the basis of the cost-effectiveness analysis carried out, such a decision rule is likely to be considered cost-effective to the NHS in terms of cost per additional case detected.

The cost-effectiveness analysis further suggested that, if likely patient benefit in terms of improved life expectancy is taken into account, the optimum strategy would be to refer all patients with symptoms suggestive of heart failure directly for echocardiography.

Conclusions

The analysis that we have performed points to the need for important changes to the NICE recommendations. First, BNP (or NT-proBNP) should be recommended over ECG and, second, some patients should be referred straight for echocardiography without undergoing any preliminary investigation.

Implications for health care

- If there is sufficient local capacity, the evidence synthesised here suggests that the optimal diagnostic strategy for many patients with symptoms indicating possible heart failure would be direct referral for echocardiography.
- In the presence of a limited supply of echocardiography the authors suggest the following:
  - patients with symptoms suggestive of heart failure should be referred directly for echocardiography only if they have a history of myocardial infarction or if they have basal crepitations on examination or if they are male and have ankle oedema
  - otherwise, they should have a BNP (or NT-proBNP) test performed and the decision to refer for echocardiography should depend upon the BNP (or NT-proBNP) result, interpreted in the light of their gender and the presence or absence of ankle oedema.
- There is no need to perform an ECG as part of the assessment of whether or not heart failure is present (although it is recognised that there may be other indications for performing an ECG).

Recommendations for research

1. Evaluation of the usability of the clinical rule described above in clinical practice.
2. Evaluation of the diagnostic value of repeated BNP (or NT-proBNP) measurements for the diagnosis of heart failure.
3. Evaluation of the diagnostic accuracy of automated ECG readings in the diagnosis of heart failure compared with ECG reading by a specialist.
4. Further development of methods to conduct IPD meta-analysis for diagnostic tests.

Chapter 1
Background

Introduction

Heart failure is a syndrome resulting from a structural or functional cardiac disorder. For a diagnosis of heart failure to be made there should be symptoms or signs such as breathlessness, effort intolerance or fluid retention together with objective evidence of cardiac dysfunction.

Heart failure is an increasingly important chronic syndrome, associated with poor prognosis and poor quality of life for patients, and responsible for high health-care costs.[1,2] Annual mortality in severe heart failure has been reported to be as high as 60%.[3] In the general population, in which all grades of heart failure are represented, 5-year mortality is around 42%,[4] but when the diagnosis is established during a hospital admission 5-year mortality is between 50% and 75%.[5,6]

Prevalence and incidence of heart failure

Early studies of heart failure prevalence used clinical diagnostic criteria known to be inaccurate,[7] particularly early in the disease process.[8,9] More recent studies have included an objective assessment of left ventricular (LV) function, usually echocardiography,[10,11] and indicate a prevalence of left ventricular systolic dysfunction (LVSD) of 2.9% in patients under 75 years[10] and up to 7.5% in 75- to 84-year-olds.[11] However, limitations of these studies include not screening all adult age groups,[10] with data particularly lacking in the elderly in whom heart failure is more common, not examining representative populations, or only examining heart failure due to LV systolic dysfunction.[11]

In the largest recent prospective evaluation of heart failure in the community (ECHOES),[12] LVSD [left ventricular ejection fraction (LVEF) < 40%] was found in 1.8% (95% CI 1.4–2.3) of the population aged over 45 years; borderline LV dysfunction (LVEF 40–50%) was found in a further 3.5%; definite heart failure was found in 2.3% (95% CI 1.9–2.8) of the population (with LVEF < 40% in 41% of cases); and using an LVEF cut-off of < 50% rather than 40%, 3.1% (95% CI 2.6–3.7%) of people aged 45 years or over had heart failure.

Estimates on heart failure incidence are less available and vary from 0.9[13] to 2.2[6] cases per 1000 population per annum in women aged 45–74 years and from 1.6[13] to 4.6[6] cases per 1000 population per annum in men aged 45–74 years. Incidence rises rapidly in the elderly, with 1% of men per year developing heart failure after 75 years and almost 2% per year after 85 years.

Burden of heart failure on patients

Mortality rates in heart failure are high. Annual mortality in the placebo arms of recent trials, with many patients on angiotensin-converting enzyme (ACE) inhibitors, has ranged from 7%[14] in mild heart failure [New York Heart Association (NYHA) class II], to 11%[15] to 13%[12] in moderate cases (NYHA III), to 20%,[5] 23%[16] or 28%[17] in severe heart failure. By comparison, the Framingham cohort showed an overall 1-year heart failure mortality rate of 17%, a 2-year mortality rate of 30% and a 10-year mortality rate of 78%.[18] The National Health and Nutrition Examination Survey (NHANES) study, conducted from 1971–86 in the USA, revealed 10-year mortality rates of 43% in patients who self-reported heart failure and 38% in patients who had heart failure defined by a clinical score.[19]

Mortality data from more recent epidemiological studies provide more reliable case definitions but mainly report on LVSD heart failure only, younger patients only[20] or patients presenting to hospital, usually with incident symptomatic heart failure.[21,22] In these last studies mortality is particularly high with 50% 2-year mortality rates, probably representing late presentations; these rates equate to the prognosis of newly diagnosed colorectal cancer in men or ovarian cancer in women. A more accurate estimate of prognosis of prevalent heart failure, across all ages and stages, is available from follow-up of the ECHOES cohort.[4] The 5-year survival rate of the general population was 93%, compared with 58% in those with a

prevalent diagnosis of LVSD and 58% in those with prevalent definite heart failure. The median survival time of definite heart failure was 7 years 7 months. Those with a diagnosis of heart failure had the lowest survival compared with the general population and survival improved significantly with increasing ejection fraction. However, amongst patients with 'borderline' ejection fraction levels of between 40% and 50%, mortality rates were still over 1.5 times higher than in those with 'normal' ejection fractions over 50%. Those with multiple causes of heart failure had the poorest survival. The ECHOES mortality data provide recent confirmation of the poor prognosis of patients suffering from heart failure across the community, providing a mortality risk estimate of 8–9% per year.[4] Importantly, outcomes in heart failure are improving, which is presumed to be because of better initiation and maintenance of evidence-based therapies.[23]

Morbidity in heart failure is considerable, whether measured by symptom severity, quality of life[24] or need for consultation, treatment or hospital admission. Studies with comparative normative data are few and suggest that heart failure worsens quality of life more than other chronic diseases[25] (although heart failure diagnosis in this study was not determined on the basis of objective tests) and that women may suffer worse impairment.[26] Other studies have shown that heart failure is associated with depressive illness[27] and, further, that this is then linked to a worse prognosis.[28] Those with heart failure had significant impairment of all of the measured aspects of physical and mental health, not only physical functioning. Significantly worse impairment was found in those with more severe heart failure by NYHA class.[24] Patients with asymptomatic LV dysfunction and patients rendered asymptomatic by treatment had similar scores to those of the random population sample. Those with heart failure reported more severe impairment of quality of life than those giving a history of chronic lung disease or arthritis, and a similar level to patients with depression.

Burden of heart failure on health-care systems

Chronic heart failure remains one of the most costly conditions to manage in many health systems. This is principally because the syndrome is common, it frequently results in hospital admission (which is the disproportionate driver of health-care expenditure), admissions are prolonged (averaging 11 days in Europe) and readmission is frequent (nearly 25% of patients are readmitted within 12 weeks of discharge).[29] In the UK, 4.9% of admissions to one hospital were for heart failure, extrapolating to up to 120,000 admissions per year nationally,[30] and these continue to rise.[31,32]

As a consequence, heart failure accounts for at least 2% of total health-care expenditure, namely €26 million per million population in the UK, €37 million per million in Germany, €39 million per million in France and €70 million per million in the USA.[33] The average cost per hospital admission in Europe is €10,000.[33] The burden of heart failure is expected to rise as prevalence rises, which is presumed to be the result of improved survival of patients post myocardial infarction, better treatment of heart failure and an ageing population.[34]

Management of heart failure

Angiotensin-converting enzyme inhibitors improve both morbidity and mortality in all grades of symptomatic heart failure due to LVSD,[35] and they can delay or prevent progression to symptomatic heart failure in patients with asymptomatic LVSD.[36,37] Beta-blocker therapy in heart failure due to LVSD has also been demonstrated to improve prognosis and reduce admission rates,[38] although these agents have to be introduced slowly and may be associated with slight worsening of symptoms initially in a proportion of patients. ACE inhibitors and beta-blockers[35,39] have been shown to improve exercise tolerance and symptoms (as assessed by NYHA functional class) in patients with heart failure due to LVSD, as well as significantly prolonging survival and reducing hospitalisation rates. These drugs have also been shown to improve global quality of life in sufferers,[40,41] as have other interventions producing symptom gains, such as exercise training[42] and intensive nurse-led discharge and outreach programmes.[43] Aldosterone blockers reduce hospitalisation and mortality in severely symptomatic (NYHA grade II and IV) patients[16] or in post-myocardial infarction heart failure or LVSD.[44] Care is needed with these agents in the elderly community as they may be associated with increased mortality if not used carefully in routine practice.[45] Recent data have demonstrated the general utility of angiotensin receptor blockers (ARBs) in patients intolerant of ACE inhibitors or in addition to ACE inhibitors and beta-blockers in those with impaired LV function.[46]

Despite this extensive evidence base for treatments that improve heart failure prognosis and symptoms, heart failure remains suboptimally diagnosed and treated in many countries,[47–49] due at least in part to many patients with suspected heart failure not receiving a formal assessment of LV function.[48,49]

Diagnostic issues in heart failure

Heart failure is a complex syndrome that can result from any structural or functional cardiac disorder which impairs the ability of the heart to function as a pump to support a physiological circulation.[50] The evaluation of a patient with suspected heart failure therefore entails more than determining whether or not the syndrome is present – it also requires an identification of the underlying abnormality of the heart.

The commonest cause of heart failure is LVSD, present in around half of cases, but other causes include valve disease, atrial fibrillation and isolated diastolic dysfunction of the left ventricle. In many patients, particularly the elderly, several cardiac abnormalities may be found concurrently, such as systolic impairment with atrial fibrillation and mild valve disease. The bulk of the evidence base for treating heart failure, summarised above, is derived from randomised controlled trials (RCTs) on people with underlying LVSD.

An essential element for treatment success is the reliable and precise diagnosis of heart failure. The major issue in the diagnosis of the disease relates to the criteria definitions. Guidelines for the evaluation and management of heart failure are established in both the USA [American College of Cardiology (ACC)/American Heart Association (AHA) and consensus recommendations[51]] and Europe [European Society of Cardiology (ESC)[23]]. These state that the diagnosis of heart failure is justified when there are typical signs and symptoms of heart failure and myocardial dysfunction, confirmed by the objective evidence of cardiac dysfunction at rest. In case of diagnostic uncertainty, a clinical response to treatment directed at heart failure is helpful in establishing the diagnosis. Simple and reliable diagnostic procedures are very important for primary care physicians, who are responsible for the early diagnosis of heart failure and the implementation of adequate therapy.

However, current diagnosis of heart failure in primary care is often inaccurate. In one recent UK study,[52] only 34% of patients with an existing clinical label of heart failure in routine general practice records had this diagnosis confirmed following echocardiography and blinded review by a panel of three specialist clinicians. A recent review by the Healthcare Commission[53] on progress towards implementation of the National Service Framework (NSF) for Coronary Heart Disease found that only one in five patients with a diagnosis of heart failure had had an echocardiogram, and that the average wait for this investigation was 67 days.

This picture of general practice diagnosing heart failure on mainly clinical grounds, with only a minority of patients receiving confirmatory tests before the diagnosis is confirmed, is replicated across much of Europe.[48,54] Primary care physicians often have variable or delayed access to tests such as echocardiography. As a consequence, doctors rely on alternatives such as the electrocardiograph (ECG) or chest X-ray (CXR), with both tests perceived as useful and actually used in most cases of heart failure in the IMPROVEMENT study.[54] A normal ECG recording will, in most cases, exclude LVSD;[55,56] however, changes may be subtle and the lack of ECG interpretation skills may still require referral for specialist opinion. Chest X-rays are often cited as useful in diagnosis, but a normal result does not exclude heart failure.[57,58] Furthermore, symptoms and signs may indicate the possibility of heart failure but are not reliable for establishing the diagnosis.[59] It is therefore unsurprising that studies exploring the validity of a clinical diagnosis of heart failure in primary care report high rates of misdiagnosis when patients are assessed against objective criteria (rates of 25–50% accuracy reported in different series).[60–62] Furthermore, underdiagnosis of heart failure is not confined to the primary care physician,[63] with only 31% of patients being offered echocardiography by hospital physicians following referral with possible heart failure in one study.[64]

In this context, the potential role of natriuretic peptides in diagnosing heart failure on the basis of a simple and inexpensive blood test has emerged. Numerous studies have confirmed the stability and feasibility of natriuretic peptide testing, although there are relatively few data testing the peptides in the clinical setting where they would be most used, i.e. in adults presenting with persisting breathlessness in the community. However, current evidence suggests that selecting natriuretic peptide

cut-off values to ensure a high negative predictive value, which is important in a primary care setting, reduces the specificity of the test. For example, both NT-proBNP and BNP assays set at cut-offs to achieve a sensitivity of 100% showed a specificity of 70%, a positive predictive value of 7%, a negative predictive value of 100% and an area under the receiver operating characteristic (ROC) curve (AUC) of 0.92 (95% CI 0.82–1.0) for diagnosing heart failure in the general population.[52] The performance of the assays was similar whatever the cause of heart failure and similar negative predictive values were also shown for diagnosing LVSD.[23]

These data indicate that a normal level of natriuretic peptides virtually guarantees that heart failure is not present, but that confirmatory echocardiography is needed in patients with elevated peptides to confirm the diagnosis. The cost-effectiveness of natriuretic peptides versus standard diagnostic triage is not established. However, they may also have an important role in guiding therapy, at least in specialist and emergency room settings.[65–67]

Current UK guidance

The current National Institute for Health and Clinical Excellence (NICE) guideline[50] recommends that patients with suspected heart failure should have an ECG and/or natriuretic peptide test performed, the latter 'where available'. If both are normal then heart failure is unlikely and an alternative diagnosis to explain the symptoms should be considered. If either one is abnormal then the patient should have a Doppler echocardiogram. This guidance was based on the high sensitivity of BNP and ECG, and the result of a health economic analysis that demonstrated that the cost per life-year gained through echocardiography is dependent upon the proportion of patients referred for echocardiography in whom the diagnosis of heart failure is confirmed.

Clinical experience in the UK suggests that the pretest probability of heart failure being present in patients referred for echocardiography varies markedly, with some centres performing many echocardiograms but with few showing any abnormality. Such inefficient use of the limited resource of echocardiography is problematic, and the NICE committee therefore wished to produce simple guidelines as to which patients should be referred by their GP for further investigation. However, the amount of data available to the committee was limited, and therefore the Health Technology Assessment call that funded this work was timely.

This study will therefore help address important unanswered questions and thus refine the national guideline in a number of areas. What is the optimal decision cut-off point for plasma BNP (or its co-secreted NT-proBNP) in terms of referral for echocardiography? Is performing an ECG and carrying out a BNP test better than carrying out only one of these investigations? What is the diagnostic value added to clinical examination by adding either a BNP test and/or ECG interpretation to the diagnostic process, when there is guidance to the general practitioner as to which clinical features are most important in distinguishing heart failure from other causes of symptoms such as breathlessness?

Current evidence

There have been five recent systematic reviews relevant to the diagnosis of heart failure, four of which have involved the applicants.[50,68–70] Two[50,69] of these reviews covered all symptoms, signs and diagnostic tests, and two[68,70] were specifically concerned with BNP. The fifth is a review of the accuracy of 12-lead ECG.[71] The following points emerge from this evidence base.

Individual symptoms (such as breathlessness, fatigue, exercise intolerance and fluid retention) and signs (such as resting tachycardia, raised jugular venous pressure (JVP), displaced apex beat, third heart sound) are generally weak predictors of heart failure and have poor reliability, with little agreement between clinicians on their presence. A number of clinical scoring systems have been developed to diagnose heart failure, but these are not highly specific.[67,72] However, recent as yet unpublished work led by Hoes in Utrecht suggests that use of a clinical scoring system based on a combination of symptoms and signs may be a reasonable predictor of heart failure (AUC: 0.82) (A Hoes, Utrecht, 2005, personal communication).

Both ECG and BNP have high sensitivity for heart failure and so are good tests for ruling out the diagnosis. UK-based studies restricted to the use of ECG in primary care, however, give a more mixed picture on the value of ECG, with sensitivity in one study[69] as low as 73%. This may relate to

both differences in population characteristics and the skill of the practitioner interpreting the ECG. Although the CXR may show evidence of heart failure (e.g. cardiomegaly, pulmonary vascular congestion), it is not a good independent predictor of the syndrome and is of most value in identifying alternative causes of symptoms.

Echocardiography is the 'gold standard' investigation for LVSD and valve disease. Indirect measures of diastolic dysfunction can be made on echocardiography, but the interpretation of the findings may be difficult, particularly in the elderly and in patients with atrial fibrillation (up to 30% of new cases of heart failure in most series). Most often, 'diastolic' (or 'non-systolic') heart failure is a diagnosis of exclusion, i.e. symptoms and signs for which other causes have been exhaustively excluded and for which there is a response to therapy for heart failure.

Although these reviews are reasonably contemporary, only one has addressed the specific population of patients presenting with suspected heart failure in primary care, and this review was restricted to only UK studies (of which there were four).[69]

Complexities of the evidence base

The complexities of the evidence base that this study therefore seeks to address are discussed in the following sections.

Choice of reference standard

There is no single ideal reference standard for heart failure, as there is no single cardiac disorder that accounts for the syndrome. The underlying cardiac disorders can be classified in different ways. An approach that has utility in the context of this review is to divide heart failure into low ejection fraction and normal ejection fraction heart failure. Echocardiography is a suitable reference standard for low ejection fraction heart failure but not for normal ejection fraction heart failure. The definitive tests to diagnose normal ejection fraction heart failure (cardiac catheterisation with calculation of pressure–volume loops) are often not carried out and so the diagnosis often relies upon clinical judgement and supportive evidence, such as may be obtained from BNP or NT-proBNP, reflecting a potential value of these tests over and above their use as a tool to determine who should undergo echocardiography. In diagnostic test studies, evaluation of such supporting evidence is often carried out formally through the use of an expert panel.

Definition of what is an abnormal ECG

Studies that have tested the value of the ECG in the diagnosis of heart failure have used different criteria with which to define abnormality, and there has been variation in the experience and expertise of those reading the ECGs. Many general practitioners are unable to interpret ECGs accurately.[73] Therefore, it is important to consider both the criteria that are used and who is required to read the ECG. This will have important implications when the costs of different diagnostic strategies are being considered.

Equivalence (or not) of different BNP assays

Combining results from studies evaluating the role of BNP is fraught with difficulty. The accuracy of the assay may depend upon issues such as the length of time after the blood was collected that the assay was performed; storage of the sample; and the assay that was used. These issues may preclude meaningful meta-analysis.

Lack of data in the correct populations

Most of the existing research has been carried out in secondary care populations or in the context of screening studies that identify prevalent cases of heart failure or include patients with existing diagnoses of heart failure. Inclusion of these studies would introduce significant spectrum bias for the question being addressed by this review. Secondary care populations are likely to represent more advanced cases of heart failure, in which the sensitivity of tests is likely to be overestimated and specificity underestimated. Prevalent cases of heart failure will on average reflect milder cases than incident cases, and so studies on these will underestimate sensitivity. Treatment of heart failure influences test performance and so inclusion of patients with existing diagnoses will underestimate the sensitivity of some tests (such as BNP). It is important that this work focuses on patients drawn from primary care populations being investigated for suspected heart failure to avoid these biases.

Impact of pharmacological treatments on test performance

It is recognised that treatments for heart failure such as diuretics and ACE inhibitors may lower serum natriuretic peptide levels.[74] These treatments are not unique to heart failure. People presenting with symptoms suggestive of heart failure may already be receiving them for other indications (e.g. existing coronary disease, diabetes or hypertension), and thus the diagnostic test may perform differently in such patients.

Impact of co-morbidity on test performance

Co-morbidity may influence the performance of the diagnostic tests not only through treatments used (see above) but also through direct influence on the symptoms, signs and test results. This is especially relevant for evaluation of symptoms suggestive of heart failure in conditions such as chronic obstructive pulmonary disease (COPD) and existing ischaemic heart disease (IHD).

Summary

Heart failure is a common disorder, especially in the elderly, with major and increasing significance for patients and health-care systems. There is a need for better identification of patients and more intensive attempts to introduce and maintain the large evidence base for therapies. The most clinically effective and cost-effective diagnostic algorithms are currently not determined.

Chapter 2

Hypotheses tested in the review (research questions)

There were three components to this work: a systematic review, an individual patient data (IPD) analysis and a decision analysis.

The objectives of the systematic review were to assess the accuracy in diagnosing heart failure of:

1. the clinical features – both singly and, if possible, in combination
2. the potential primary care investigations – plasma natriuretic peptides, ECG and CXR (singly and, if possible, in combination).

These reviews aimed to include all studies assessing the diagnostic accuracy of the symptoms, signs and investigations of patients with heart failure, but with a prespecified focus on the accuracy and reliability of clinical features in patients with suspected heart failure presenting in primary care.

The objectives of the IPD analysis were to address the following questions:

1. Can a clinical scoring system based on symptoms and signs usefully predict the presence of heart failure?
2. To rule out heart failure in primary care, what is the optimum decision cut-off point for plasma natriuretic peptides (BNP)?
3. Does the diagnostic performance of plasma natriuretic peptides vary according to patient characteristics (including age, gender, presence of IHD, COPD, diabetes mellitus, obesity and atrial fibrillation, and existing pharmacological therapy at the time of the diagnostic test)?
4. How accurate is the combination of plasma natriuretic peptides with ECG at diagnosing heart failure?

The objective of the decision analysis was to model costs and diagnostic yield for different plausible diagnostic strategies for the diagnosis of heart failure in primary care.

Chapter 3

Systematic review methods

Inclusion and exclusion criteria

Studies were included if they estimated the diagnostic accuracy or reliability of symptoms, signs or investigations for detecting heart failure. Although the main focus of the review was on the diagnostic accuracy for suspected cases of heart failure in primary care, we also included studies from all patient settings, including emergency department, hospital and outpatient settings, as well as population cohort or screening studies and we grouped data by setting. Studies varied in whether they included patients with previously diagnosed heart failure or not; both groups of studies were included in the review. No language restriction was applied.

Studies were eligible if they compared a symptom, sign, ECG, CXR or BNP with an adequate reference standard comprising either a clinical or an echocardiographic diagnosis of heart failure. More specifically, adequate reference standards were considered to be prospective planned evaluation of: (1) a clinical diagnosis, including all information, for example using ESC criteria; (2) echocardiographic criteria for LVSD (such as assessment of LVEF or global assessment of ventricular function); or (3) echocardiographic criteria for heart failure with preserved systolic function. We excluded studies that (1) included children; (2) used an inappropriate index test, for example urinary natriuretic peptides; (3) used a reference standard that was inappropriate for the purposes of this review, such as measures of diastolic function alone or pulmonary capillary wedge pressure; (4) used a retrospective study design (e.g. a reference standard using a hospital discharge diagnosis of heart failure); (5) used a case–control design; or (6) that provided results such that 2×2 data could not be extracted. Although studies that used echocardiographic criteria for LVSD were included in our principle results tables (see Appendix 4), the meta-analysis was restricted to studies that used a diagnosis of heart failure as the reference standard.

Search strategy

MEDLINE and CINAHL were searched from inception to 7 July 2006, including citations in progress. Given that our previous searches on this topic did not find any additional studies in EMBASE, we did not search EMBASE during this review.[75] The search combined terms for the condition of interest (e.g. heart failure; systolic dysfunction) with terms for the index tests of interest. No language restriction or methodological filters were applied as our previous study found that such filters reduced the sensitivity of the search strategy.[75] Details of the search strategy are shown in Appendix 1.

To identify studies missed by the search we checked the reference lists of all primary studies that met the inclusion criteria and any review articles we found in this area. In addition, 'grey literature' databases and conference proceedings of relevant societies (ACC; AHA; ESC; British Cardiac Society; Heart Failure Society of America; Royal College of Physicians; International Academy of Cardiology; International Heart Failure Society; and the Cardiac Society of Australia and New Zealand) were searched. Finally, authors of relevant studies were contacted to clarify any questions regarding overlapping studies or to provide 2×2 data where possible.

Data extraction

For the ECG, CXR and BNP studies, two reviewers screened the titles and abstracts for relevant studies. However, given the size of the search results only one reviewer carried out the initial screening for relevant studies on symptoms and signs. Potentially relevant studies were obtained in hard copy and assessed by two reviewers against the inclusion criteria for the review. When there was disagreement over a study it was discussed with a third reviewer.

Data were extracted by both reviewers on potential sources of bias, demographic details of included subjects, operator and test characteristics (e.g. who assessed the symptoms and signs; who read the ECG; type of BNP assay), reference standard characteristics and test performance results (2×2 tables comparing test with reference standard; test reproducibility data when provided). Quality was assessed using the QUADAS criteria.[76]

Data analysis

The data synthesis was performed using methods recommended by the working group of the Cochrane Collaboration on systematic reviews of diagnostic test accuracy. We grouped the studies by the index test, including the type of assay (BNP and NT-proBNP), and by the type of reference standard (clinical diagnosis of heart failure, echocardiographic criteria of LVSD, echocardiographic criteria of LVSD plus heart failure with preserved systolic function). The studies were then further sorted by the clinical setting (primary care, screening studies, emergency departments, outpatient secondary care settings and inpatients). From the 2×2 tables we calculated sensitivity, specificity, negative and positive predictive values, and likelihood ratios.

The sensitivity and specificity of each of the index tests were plotted in ROC space. The data were then pooled using a bivariate random-effects meta-analysis to calculate summary estimates of the sensitivity, specificity, diagnostic odds ratio (DOR) and positive and negative likelihood ratios for each of the index tests with software codes kindly provided by Roger Harbord.[77] The statistical software package STATA 9 (StataCorp) was used for these analyses. Tests of heterogeneity were not used as such tests may be misleading for systematic reviews of diagnostic test accuracy and are not recommended by the Cochrane diagnostic test accuracy group (Jon Deeks, University of Birmingham, 2007, personal communication).

To understand any influence of setting and prevalence we plotted the predictive values (post-test probabilities) against the prevalence of heart failure (pretest probability).

For studies that contained a direct within-study comparison we pooled the data to compare the diagnostic accuracy of BNP versus NT-proBNP, and BNP (or NT-proBNP) versus ECG. The two tests were compared in a hierarchical summary ROC analysis using software codes kindly provided by Petra Macaskill.[78] This analysis was also used to determine a relative DOR in those studies that directly compared two tests for heart failure.

Chapter 4

Studies included in and excluded from the systematic review

The searches of the electronic databases resulted in the retrieval of 87,389 titles and abstracts. These were screened for inclusion in this review. Based on these searches and checking the reference lists of identified studies and systematic reviews, 335 papers were identified as being potentially eligible for the review and the full text of the articles was retrieved. A total of 95 studies were identified as having 2×2 data comparing symptoms, signs, ECG, CXR or BNP with an appropriate reference standard for the diagnosis of heart failure. In addition, we identified 15 systematic reviews and 11 multivariate analyses. The results of the four search strategies are shown in *Figures 1–4*.

Descriptions of the individual studies included in the review, the quality assessment of the included studies, the data extracted from the primary studies and the details of studies excluded from the review are provided in Appendices 2–5, respectively, of this report.

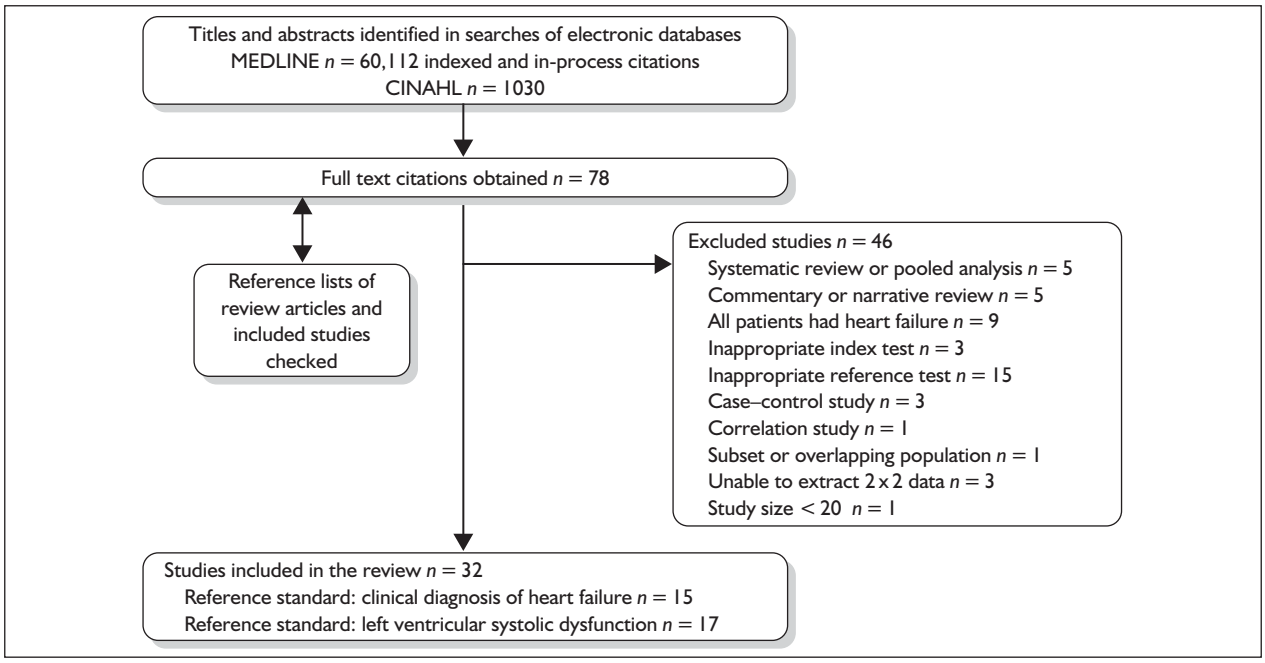

FIGURE 1 *Heart failure AND symptoms and signs of heart failure.*

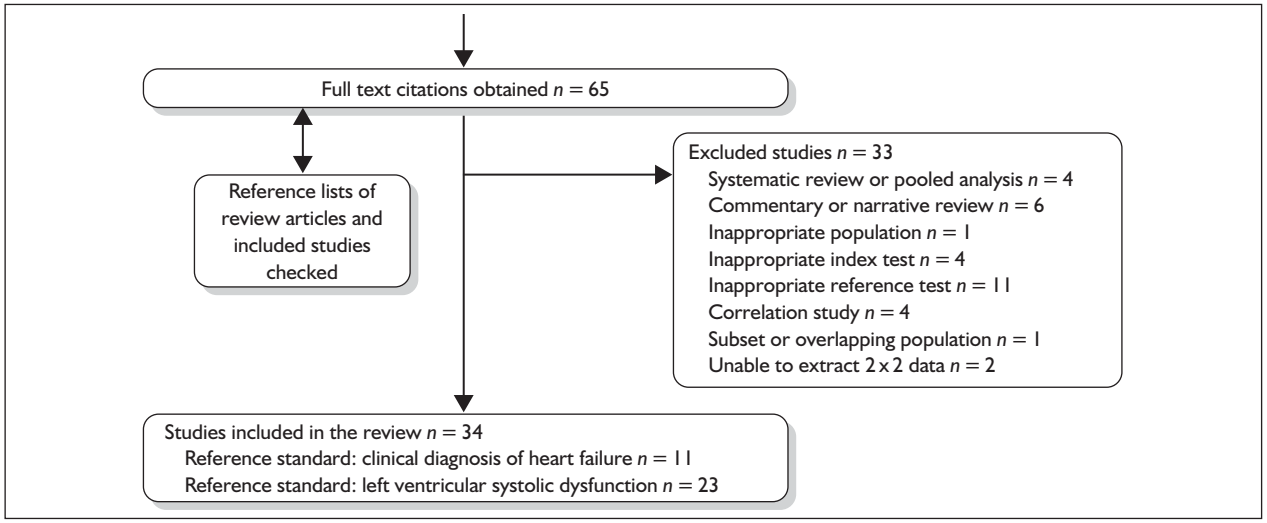

FIGURE 2 *Heart failure AND electrocardiography.*

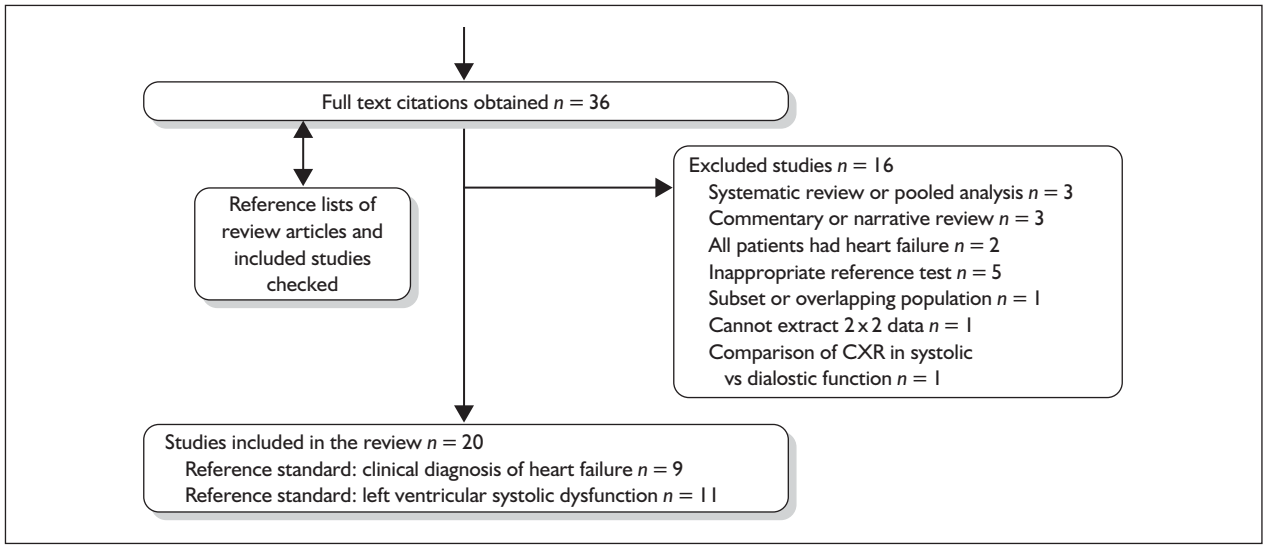

FIGURE 3 *Heart failure AND chest X-ray.*

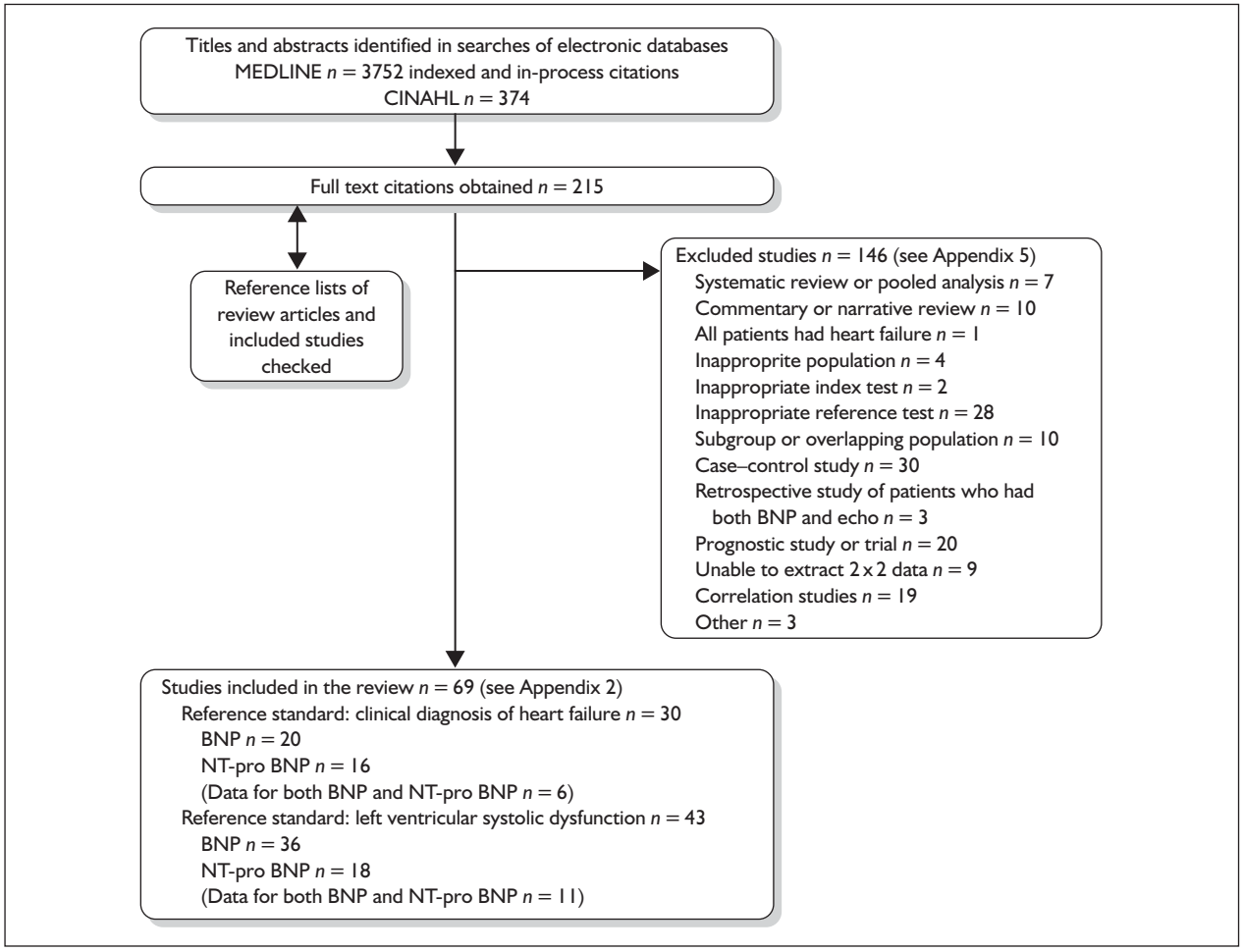

FIGURE 4 *Heart failure AND B-type natriuretic peptides.*

Chapter 5

Results of the systematic review

Symptoms and signs for the diagnosis of clinical heart failure

Fifteen studies – five in general practice, five in patients referred from primary to secondary care, and five in acute care – examined the diagnostic accuracy of symptoms and signs of heart failure compared with an adequate reference standard of a clinically defined diagnosis of heart failure.

Of the general practice studies, the largest single study[79] recruited 5260 patients who attended a practice in Portugal; if patients scored 3 or more on the 'Boston' score they were further assessed by echocardiography. The diagnostic accuracy of symptoms and signs was assessed in these 1058 patients; 200 patients could not be assessed by echocardiography or had uninterpretable echocardiograms (and therefore were classified as not having heart failure). The other four studies were conducted in a random selection of patients from general practice registers: three[80–82] in a random selection of general practice patients and one[83] in patients with COPD not previously known to have heart failure. The ECHOES study by Hobbs *et al*.[82] was divided into substudies of (1) patients with symptoms and signs of heart failure; (2) patients who were over the age of 45 years; (3) patients who were considered at risk of heart failure; (4) patients who had previously been diagnosed with heart failure; and (5) patients who were currently taking diuretics. Unless otherwise stated the data used in the analyses below are from the ECHOES substudy conducted in patients who had symptoms or signs of heart failure as this is the patient group most relevant to this assessment.

Five studies were conducted in general practice patients with suspected heart failure who were referred for further assessment at an open access heart failure clinic or as part of the study design.[84–88] The other five studies were conducted in patients presenting with dyspnoea in accident and emergency departments.[89–93] The studies conducted by Dao *et al*.[94] and Morrison *et al*.[92] involved overlapping cohorts of patients: we have used the Morrison study as it had more participants.

Some of the data in this section were obtained from the study authors as part of this assessment and have not been published previously.[80–88]

Figure 5 shows the numbers of patients with and without heart failure in each of the included studies. The outlier study, with the highest number

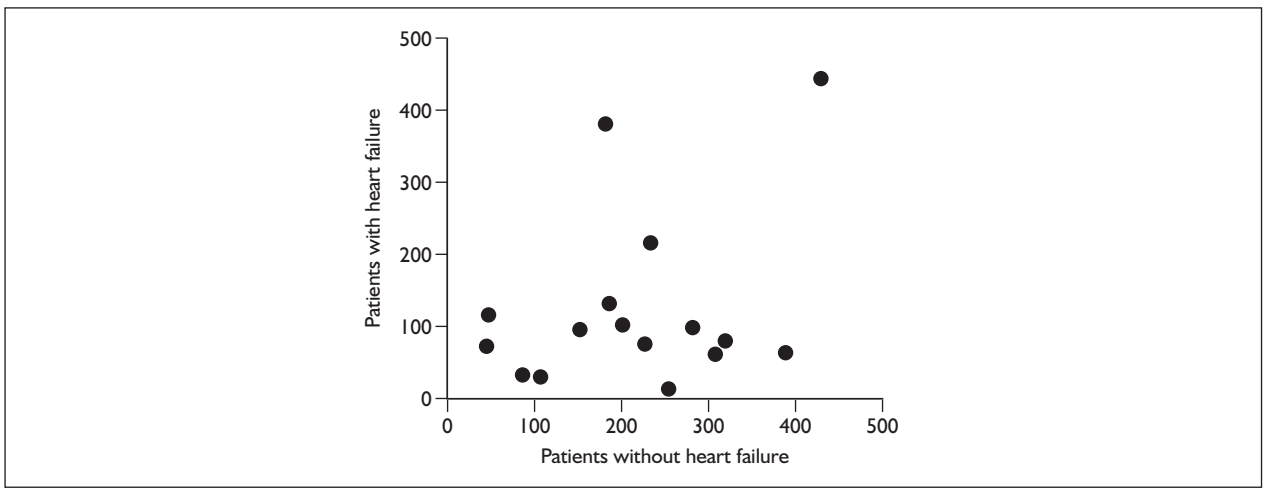

FIGURE 5 *Studies assessing the accuracy of symptoms and signs for the clinical diagnosis of heart failure.*

of patients with heart failure and the highest proportion of patients with heart failure, was the Fonseca study,[79] set in Portugal.

The quality of the included studies is shown in *Tables 37–46* in Appendix 3. The studies were of variable quality, although most of the quality criteria either were met or were unclear from the study report.

Table 1 gives a summary of the overall results for the symptoms and signs assessed in this review. There was considerable variation across the studies, which is illustrated in the figures in the following sections. These differences may be due to differing definitions or elicitation of the symptoms or signs, or to differences in the patient groups studied. In particular, it is likely that those presenting to accident and emergency will be at the more severe end of the heart failure spectrum.

History of myocardial infarction

Ten studies[81–85,87–91] estimated the accuracy of a previous history of myocardial infarction for the clinical diagnosis of heart failure (*Figure 6*). The summary estimates of diagnostic accuracy are:

- sensitivity: 0.26 (95% CI 0.19–0.37)
- specificity: 0.89 (95% CI 0.85–0.91)
- DOR: 2.87 (95% CI 1.71–4.82)
- positive likelihood ratio: 2.37 (95% CI 1.58–3.54)
- negative likelihood ratio: 0.82 (95% CI 0.73–0.93).

Note that these studies used the patient's self-report of the history of myocardial infarction and the diagnosis was not verified. Also, most of these studies were conducted before 2003 and were therefore likely to be using a definition of myocardial infarction that did not include new criteria which include serum troponin elevation.

Dyspnoea for the diagnosis of clinically defined heart failure

Dyspnoea is an important presenting symptom of heart failure. Several of the studies used dyspnoea as an inclusion criterion for the study and therefore it was not possible to estimate the diagnostic accuracy of this symptom from these studies. Five studies[79,80,82,84,92] estimated the diagnostic accuracy of this symptom, with the results showing considerable heterogeneity (*Figure 7*):

- sensitivity: 0.83 (95% CI 0.62–0.94)
- specificity: 0.54 (95% CI 0.40–0.67)
- DOR: 5.71 (95% CI 1.78–18.31)

TABLE 1 *Overall accuracy of clinical features of heart failure*

	Number of patients (studies)	Sensitivity (%)	Specificity (%)	Youden index[a]
History of MI	1769 (10)	26	89	15
Dyspnoea	2187 (5)	87	51	38
Orthopnoea	2901 (6)	44	89	33
Paroxysmal nocturnal dyspnoea	1786 (3)	No summary results		
Oedema	3736 (12)	53	72	25
Tachycardia	1582 (3)	No summary results		
Elevated JVP	3353 (7)	52	70	22
Cardiomegaly	405 (1)	27	85	12
Added heart sounds	2948 (6)	11	99	10
Lung crepitation	4619 (11)	51	81	32
Hepatomegaly	1058 (1)	17	97	14

JVP, jugular venous pressure; MI, acute myocardial infarction.
a Youden index = sensitivity% + specificity% – 100%. This is a measure of the overall diagnostic accuracy of the test, with a maximum score of 100.

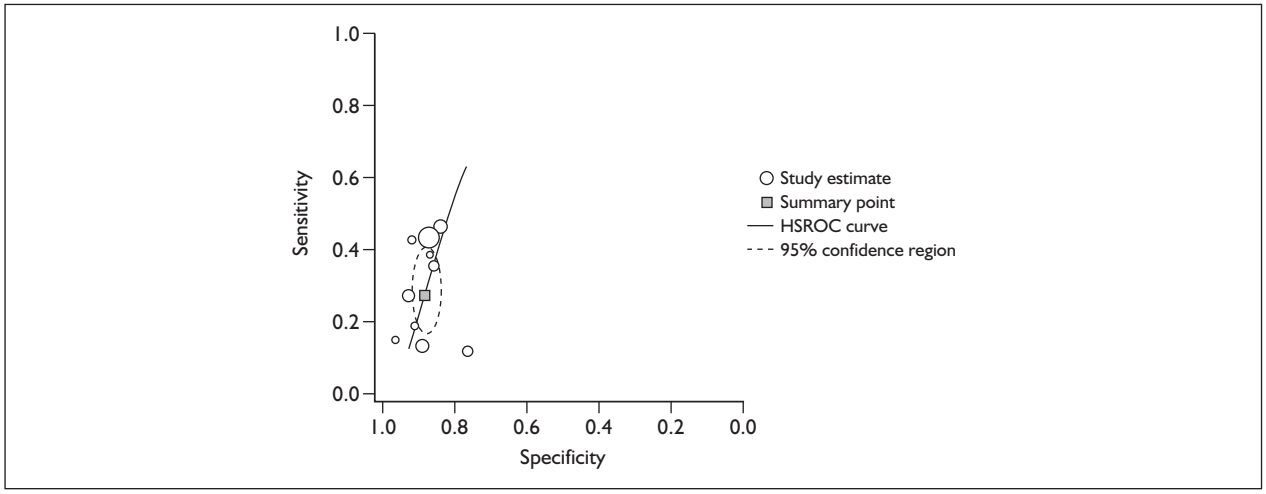

FIGURE 6 *History of myocardial infarction for the diagnosis of clinically defined heart failure: summary receiver operating characteristic (curve) (SROC) plot of studies. Each circle in the above plot represents the estimated sensitivity and specificity from each study plotted in a receiver operating characteristic (ROC) space. The size of each circle is proportional to the size of the study. HSROC, hierarchical summary receiver operating characteristic.*

- positive likelihood ratio: 1.79 (95% CI 1.30–2.47)
- negative likelihood ratio: 0.31 (95% CI 0.12–0.79).

Because this symptom is one of the few symptoms or signs with a relatively high sensitivity, this feature may be a potential method for identifying patients who have heart failure. For this reason, in *Table 2* and *Figure 8* we have included the data from the original studies, including more specific methods for eliciting this symptom as defined in the individual studies. As might be anticipated, the more restrictive definitions of breathlessness (e.g. dyspnoea on exertion) led to higher specificity but lower sensitivity.

The symbols in the ROC plot in *Figure 8* illustrate the considerable heterogeneity in the estimated sensitivity and specificity of dyspnoea for the diagnosis of clinically defined heart failure. The lines between points in the ROC space illustrate where different measures of dyspnoea have been used in the same study. Dyspnoea on exertion

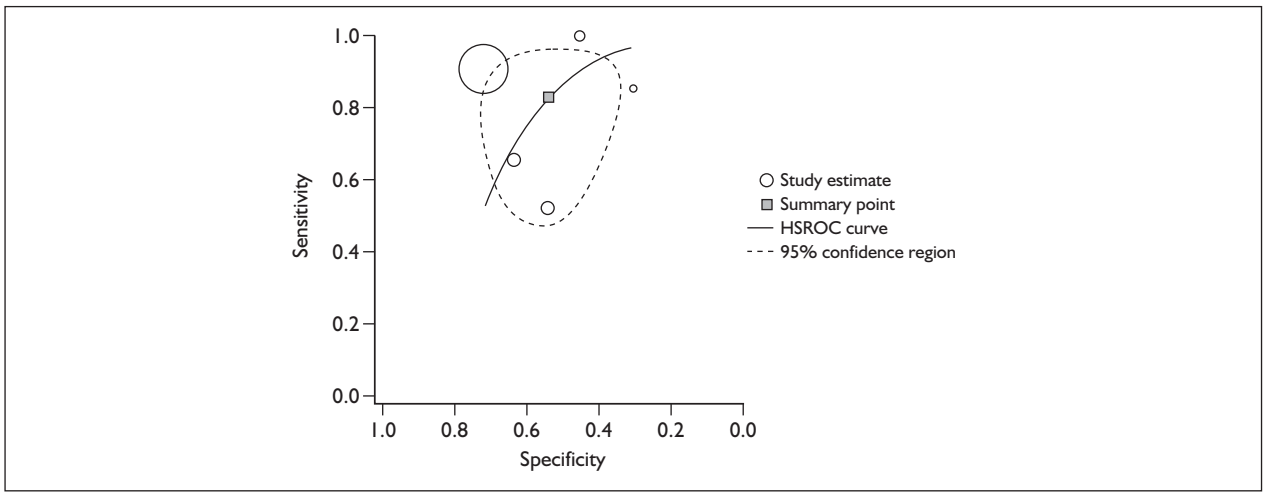

FIGURE 7 *Dyspnoea for the diagnosis of clinically defined heart failure: summary receiver operating characteristic (curve) (SROC) plot of studies. Each circle in the above plot represents the estimated sensitivity and specificity from each study plotted in a receiver operating characteristic (ROC) space. The size of each circle is proportional to the size of the study. HSROC, hierarchical summary receiver operating characteristic.*

TABLE 2 *Diagnostic accuracy of dyspnoea for the diagnosis of clinically defined heart failure*

Study	*n*	Setting	Prevalence of clinically defined heart failure (%)	Symptom	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Fonseca *et al.*, 2004[79]	1058	Patients attending general practice	10	Dyspnoea	91	72	13	99
Hobbs *et al.*, 2004[82]	273	Patients with symptoms and signs of heart failure	6	Dyspnoea	100	45	11	100
	304	Patients aged over 45 years	2	Dyspnoea	100	77	8	100
	124	Patients at high risk of heart failure	4	Dyspnoea	100	61	10	100
	71	Patients taking diuretics	11	Dyspnoea	100	59	24	100
	103	Patients previously diagnosed with heart failure	34	Dyspnoea	97	63	4	56
Alehagen *et al.*, 2003[80]	458	Patients presenting with dyspnoea, fatigue or peripheral oedema	15	Dyspnoea	66	64	24	92
Cowie *et al.*, 1997[84]	122	Patients referred from general practice to an open access heart failure clinic, not previously diagnosed with heart failure	29	Dyspnoea	86	30	33	84
Morrison *et al.*, 2002[92]	276	Patients presenting to an emergency department with acute dyspnoea	49	Dyspnoea	52	54	45	61
Fonseca *et al.*, 2004[79]	1058	Patients attending general practice	10	Dyspnoea at rest	11	99	48	96
Fonseca *et al.*, 2004[79]	1058	Patients attending general practice	10	Dyspnoea on exertion	79	84	18	99
Morrison *et al.*, 2002[92]	276	Patients presenting to an emergency department with acute dyspnoea	49	Dyspnoea on exertion	85	32	47	75
Fonseca *et al.*, 2004[79]	1058	Patients attending general practice	10	Dyspnoea when walking on the flat	36	99	54	97
Fonseca *et al.*, 2004[79]	1058	Patients attending general practice	10	Dyspnoea when walking fast or slightly uphill	77	82	16	99
Fonseca *et al.*, 2004[79]	1058	Patients attending general practice	10	Dyspnoea when walking uphill	88	77	15	99

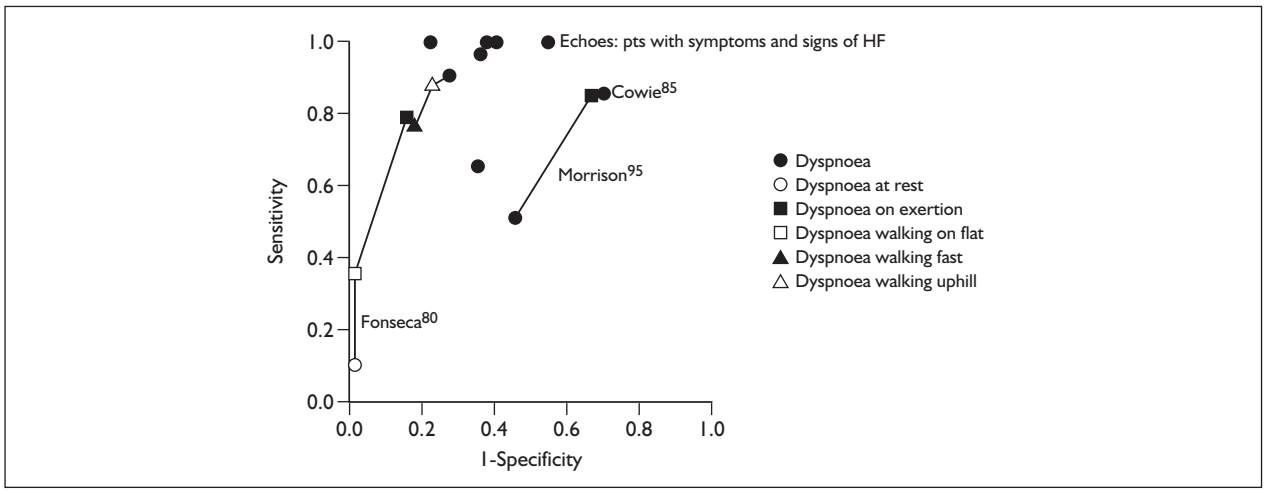

FIGURE 8 *Methods for eliciting the symptom of dyspnoea: receiver operating characteristic (ROC) plot of studies. HF, heart failure.*

has a higher sensitivity but lower specificity than dyspnoea at rest or generally defined dyspnoea. However, there is considerable variation between studies in the estimation of the diagnostic accuracy of dyspnoea.

Orthopnoea and paroxysmal nocturnal dyspnoea for the diagnosis of clinically defined heart failure

Six studies[79,83,89–92] estimated the diagnostic accuracy of orthopnoea for the diagnosis of clinically defined heart failure (*Figure 9*). These showed low sensitivity and varying specificity:

- sensitivity: 0.44 (95% CI 0.33–0.56)
- specificity: 0.89 (95% CI 0.69–0.96)
- DOR: 6.23 (95% CI 2.30–16.92)
- positive likelihood ratio: 3.91 (95% CI 1.51–10.11)
- negative likelihood ratio: 0.63 (95% CI 0.53–0.74).

Paroxysmal nocturnal dyspnoea was evaluated in three studies and showed similar sensitivity and specificity to that of orthopnoea (Fonseca *et al.*[79]: sensitivity 29%, specificity 98%; Morrison *et al.*[92]: sensitivity 34%, specificity 86%; Mueller *et al.*[93]: sensitivity 47%, specificity 73%).

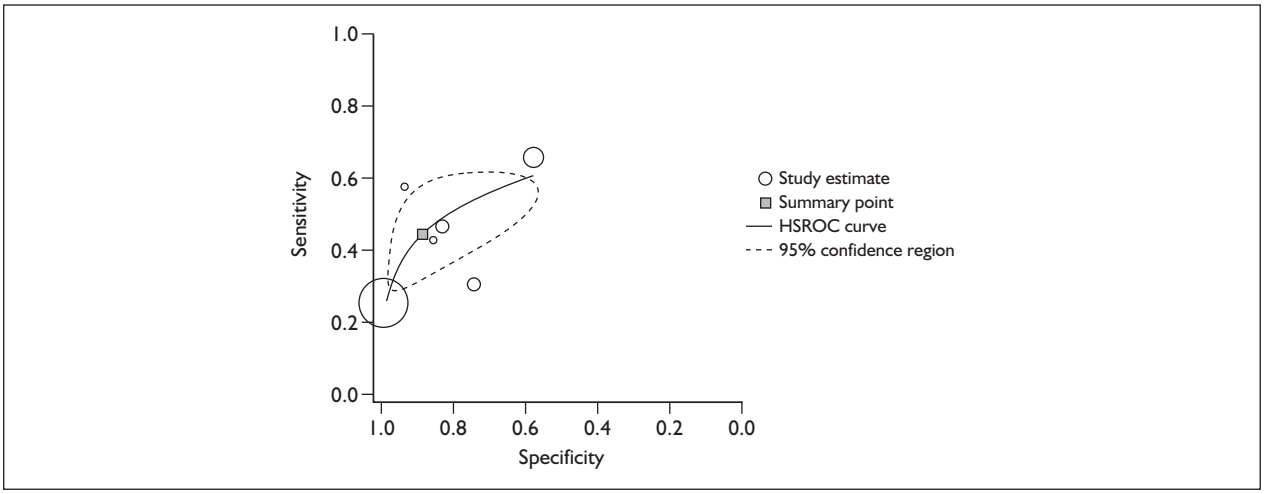

FIGURE 9 *Orthopnoea for the diagnosis of clinically defined heart failure: summary receiver operating characteristic (curve) (SROC) plot of studies. Each circle in the above plot represents the estimated sensitivity and specificity from each study plotted in a receiver operating characteristic (ROC) space. The size of each circle is proportional to the size of the study. HSROC, hierarchical summary receiver operating characteristic.*

Oedema (as a symptom or sign) for the diagnosis of clinically defined heart failure

Twelve studies[79,82–86,88–93] estimated the accuracy of oedema (as either a symptom or a sign) for the diagnosis of clinically defined heart failure. Again, this clinical feature shows low sensitivity and varying specificity (*Figure 10*). In the study by Wright *et al*.,[87] which enrolled patients with either dyspnoea or oedema of recent onset, only 5% of patients who were diagnosed as having heart failure had oedema with no symptoms of dyspnoea:

- sensitivity: 0.53 (95% CI 0.44–0.62)
- specificity: 0.72 (95% CI 0.62–0.80)
- DOR: 2.91 (95% CI 1.89–4.49)
- positive likelihood ratio: 1.89 (95% CI 1.42–2.51)
- negative likelihood ratio: 0.65 (95% CI 0.54–0.78).

Tachycardia for the diagnosis of clinically defined heart failure

Three studies[79,83,89] estimated the accuracy of tachycardia for the diagnosis of clinically defined heart failure. The studies showed poor sensitivity (23%, 24% and 36%) and varying specificity (92%, 82% and 40%).

Elevated jugular venous pressure for the diagnosis of clinically defined heart failure

Seven studies[79,83,89–93] estimated the accuracy of elevated JVP for the diagnosis of clinically defined heart failure. One study[90] defined elevated JVP as JVP > 6 cm; in the other studies, elevated JVP was not further defined. This symptom also showed poor sensitivity with relatively poor specificity (*Figure 11*):

- sensitivity: 0.52 (95% CI 0.41–0.63)
- specificity: 0.70 (95% CI 0.56–0.80)
- DOR: 2.52 (95% CI 1.51–4.22)
- positive likelihood ratio: 1.73 (95% CI 1.23–2.43)
- negative likelihood ratio: 0.68 (95% CI 0.56–0.84).

Cardiomegaly for the diagnosis of clinically defined heart failure

Only one study[83] examined the accuracy of a displaced apex beat for the diagnosis of clinically defined heart failure. This showed a sensitivity of 27% and a specificity of 85%, with a positive predictive value of 31% and a negative predictive value of 82%.

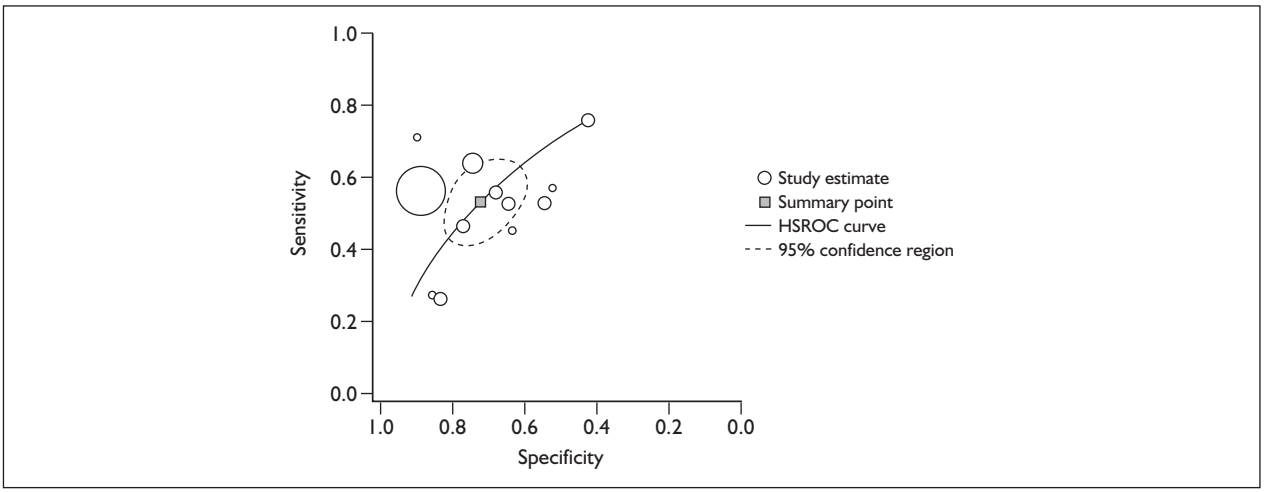

FIGURE 10 *Oedema for the diagnosis of clinically defined heart failure: summary receiver operating characteristic (curve) (SROC) plot of studies. Each circle in the above plot represents the estimated sensitivity and specificity from each study plotted in a receiver operating characteristic (ROC) space. The size of each circle is proportional to the size of the study. HSROC, hierarchical summary receiver operating characteristic.*

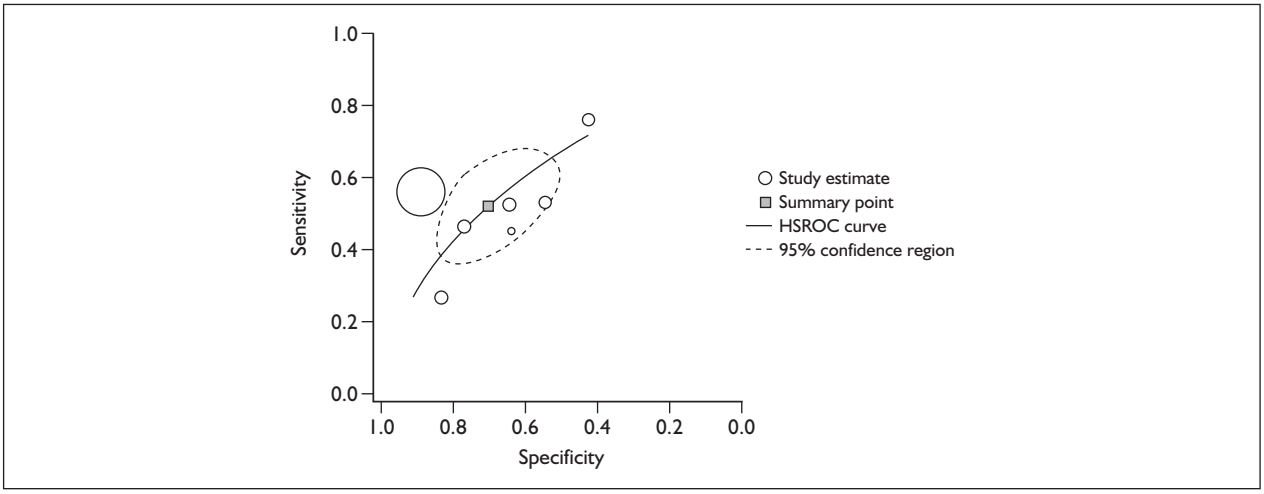

FIGURE 11 *Elevated jugular venous pressure for the diagnosis of clinically defined heart failure: summary receiver operating characteristic (curve) (SROC) plot of studies. Each circle in the above plot represents the estimated sensitivity and specificity from each study plotted in a receiver operating characteristic (ROC) space. The size of each circle is proportional to the size of the study. HSROC, hierarchical summary receiver operating characteristic.*

Added heart sounds for the diagnosis of clinically defined heart failure

Six studies[79,89–93] estimated the accuracy of added heart sounds (third heart sound – S3 or gallop rhythm) for the diagnosis of clinically defined heart failure (*Figure 12*). This sign has very low sensitivity but high specificity:

- sensitivity: 0.11 (95% CI 0.04–0.24)
- specificity: 0.99 (95% CI 0.97–1.00)
- DOR: 13.4 (95% CI 6.58–27.3)
- positive likelihood ratio: 12.1 (95% CI 5.74–25.4)
- negative likelihood ratio: 0.90 (95% CI 0.82–0.99).

This means that if the sign is present it helps to rule the disease in but if absent it does not rule the disease out.

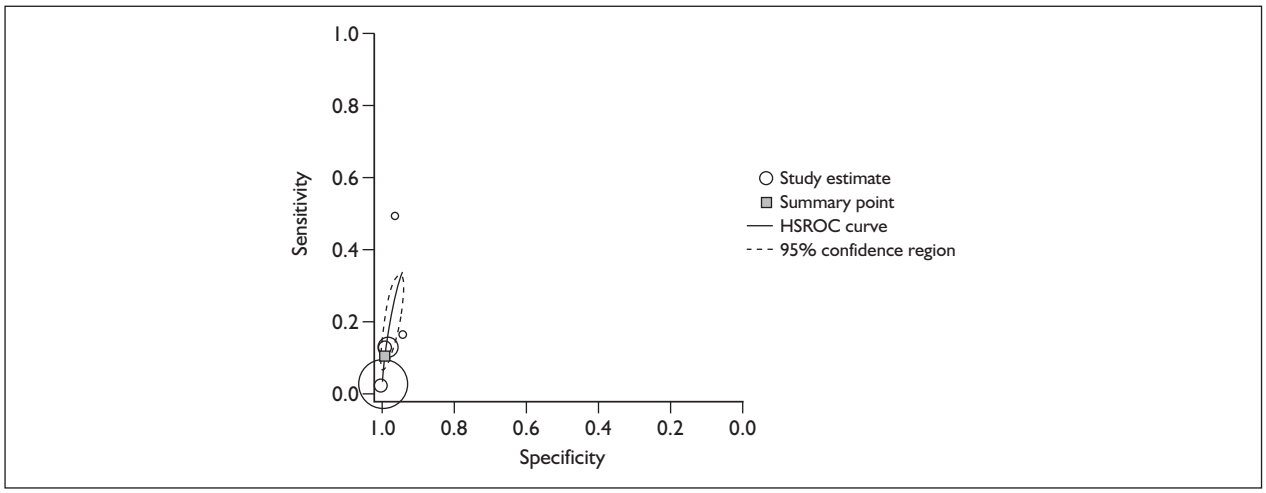

FIGURE 12 *Added heart sounds for the diagnosis of clinically defined heart failure: summary receiver operating characteristic (curve) (SROC) plot of studies. Each circle in the above plot represents the estimated sensitivity and specificity from each study plotted in a receiver operating characteristic (ROC) space. The size of each circle is proportional to the size of the study. HSROC, hierarchical summary receiver operating characteristic.*

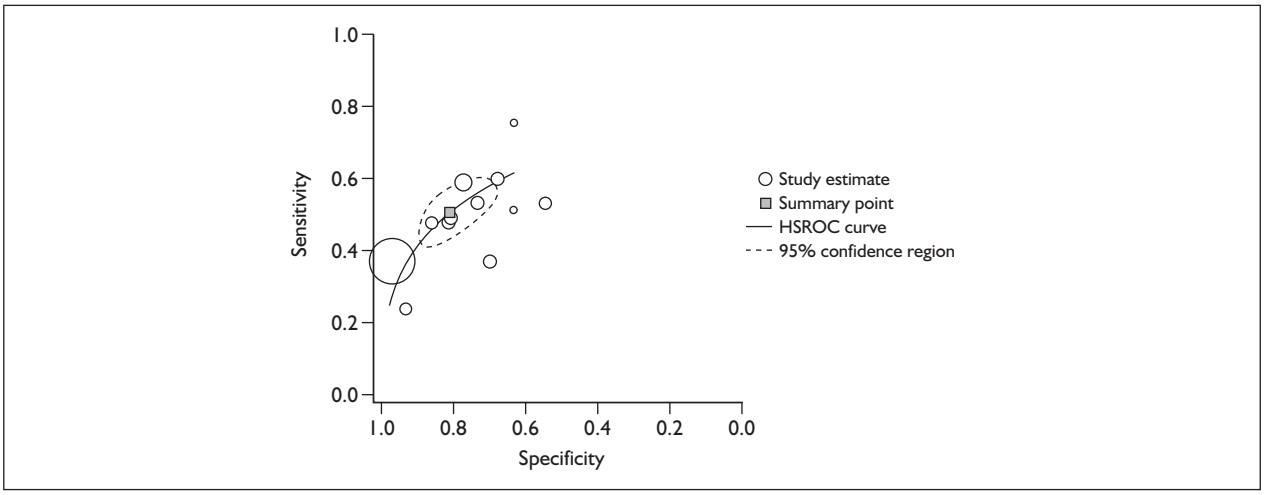

FIGURE 13 *Lung crepitations for the diagnosis of clinically defined heart failure: summary receiver operating characteristic (curve) (SROC) plot of studies. Each circle in the above plot represents the estimated sensitivity and specificity from each study plotted in a receiver operating characteristic (ROC) space. The size of each circle is proportional to the size of the study. HSROC, hierarchical summary receiver operating characteristic.*

Lung crepitations for the diagnosis of clinically defined heart failure

Eleven studies[79,82–85,87,88,90–93] estimated the accuracy of the presence of lung crepitations for the diagnosis of clinically defined heart failure (*Figure 13*). Lung crepitations have poor sensitivity and moderate specificity:

- sensitivity: 0.51 (95% CI 0.44–0.58)
- specificity: 0.81 (95% CI 0.71–0.88)
- DOR: 4.34 (95% CI 2.91–6.47)
- positive likelihood ratio: 2.64 (95% CI 1.86–3.74)
- negative likelihood ratio: 0.61 (95% CI 0.55–0.68).

Hepatomegaly

One study[79] evaluated the sign of hepatomegaly for the diagnosis of clinically defined heart failure and estimated a sensitivity of 17% and a specificity of 97%.

Summary of accuracy of symptoms and signs for the diagnosis of clinical heart failure

The data from these studies show that each of the symptoms and signs of heart failure have varying specificity but their poor sensitivity limits the usefulness of these features in ruling out disease in a general practice setting.

Investigations for the diagnosis of clinically defined heart failure

Electrocardiogram for the diagnosis of clinically defined heart failure

Eleven studies[79–88,90] estimated the accuracy of an abnormal ECG for the diagnosis of clinically defined heart failure.

Figure 14 shows the numbers of patients with and without heart failure in each of the studies that assessed the diagnostic accuracy of ECG for the clinical diagnosis of heart failure. The largest study, which also had a much higher proportion of patients with heart failure than the other studies (the outlier), was the Fonseca study.[79]

In most of the studies the ECG criteria for defining an abnormality used to determine the presence of heart failure were quite broad. For example, in the study by Rutten *et al*.,[83] the criteria used were abnormal Q waves, complete or incomplete left bundle branch block, LV hypertrophy, atrial fibrillation, ST and/or T wave abnormalities and sinus tachycardia. Using broad criteria for ECG abnormality achieves a relatively high sensitivity but only moderate specificity (*Figure 15*):

- sensitivity: 0.89 (95% CI 0.77–0.95)
- specificity: 0.56 (95% CI 0.46–0.66)

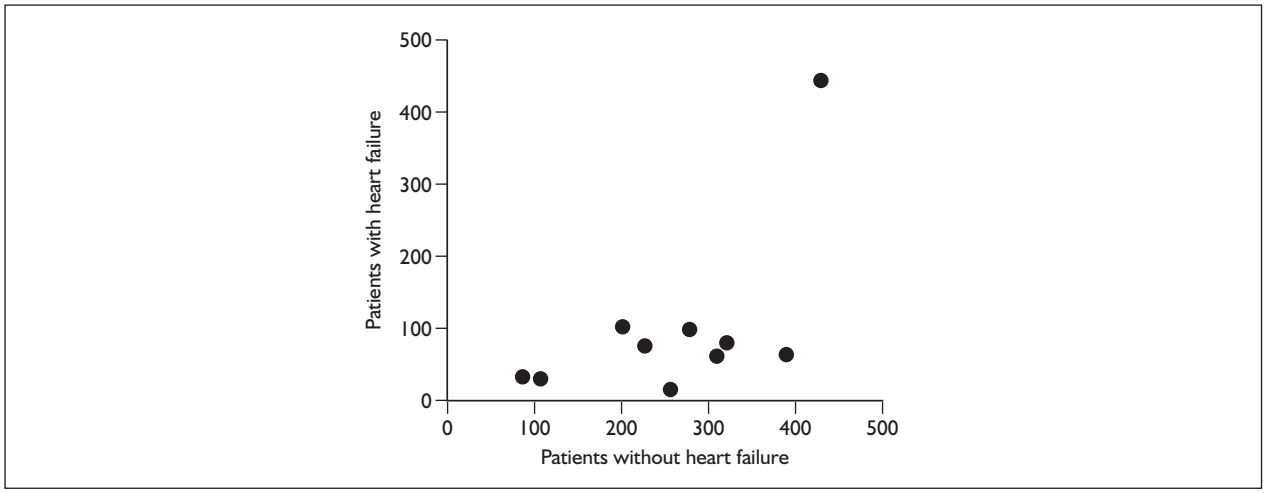

FIGURE 14 *Studies assessing the accuracy of electrocardiography for the clinical diagnosis of heart failure.*

- DOR: 4.80 (95% CI 4.36–25.7)
- positive likelihood ratio: 2.03 (95% CI 1.62–2.53)
- negative likelihood ratio: 0.19 (95% CI 0.09–0.42).

A completely normal ECG can help to rule out the diagnosis of heart failure, but the presence of any abnormality does not help to rule the diagnosis in.

It should also be remembered that in these studies the diagnostic accuracy of the ECG was obtained either from an ECG read by a cardiologist or from the automatic reading of an ECG. In a study comparing the diagnostic accuracy of general practitioners and hospital physicians in detecting heart failure on an ECG the sensitivity and specificity of an ECG read by a general practitioner were 53% and 63%, respectively, and those read by a hospital physician were 95% and 47% respectively.[95] However, the mean sensitivity of 123 Scottish GPs reviewing 180 ECGs was higher at 94%.[96]

The studies of diagnostic accuracy indicate how well a diagnostic test converts the pretest probability of a disease into the probability that a patient has the disease after the test. *Figure 16* shows this graphically for the studies estimating the diagnostic accuracy of ECG for heart failure. The

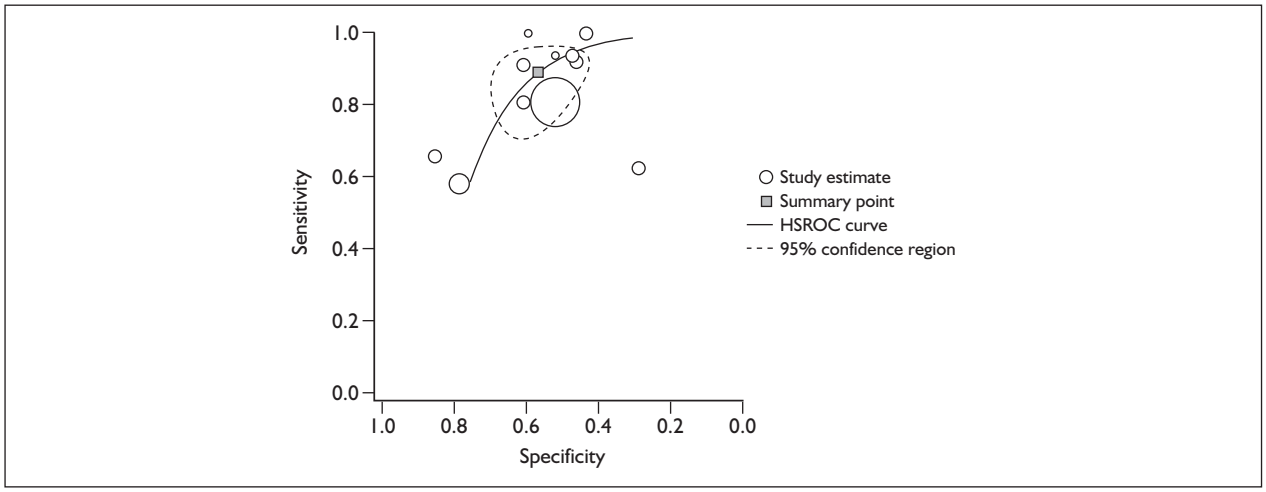

FIGURE 15 *Electrocardiography for the diagnosis of clinically defined heart failure: summary receiver operating characteristic (curve) (SROC) plot of studies. Each circle in the above plot represents the estimated sensitivity and specificity from each study plotted in a receiver operating characteristic (ROC) space. The size of each circle is proportional to the size of the study. HSROC, hierarchical summary receiver operating characteristic.*

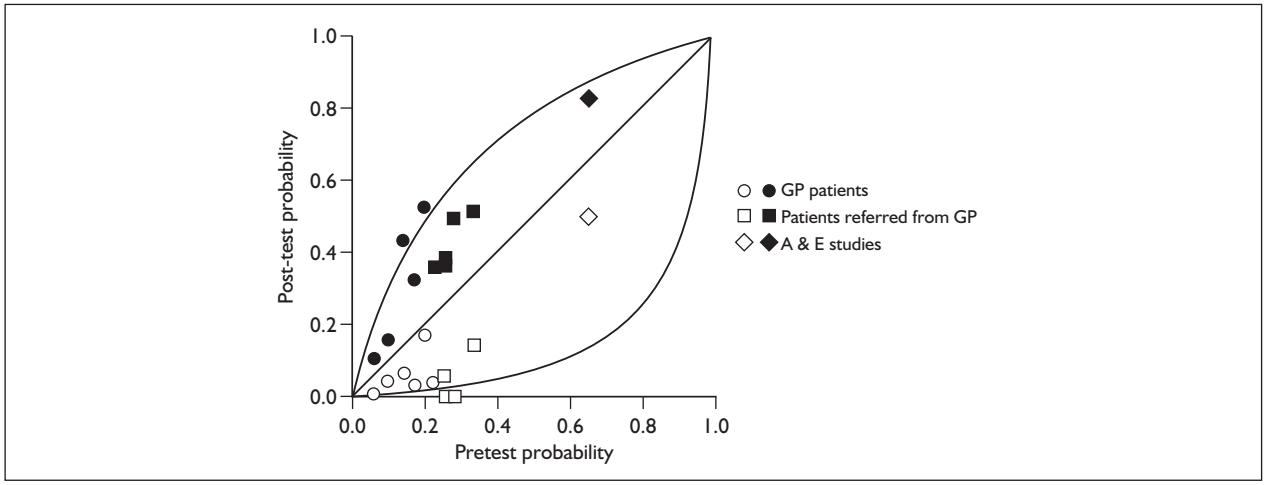

FIGURE 16 *Pretest/post-test graph of electrocardiography for the diagnosis of clinically defined heart failure. Note that the curved lines are back calculated from the overall likelihood ratios and not by a regression fit. Closed symbols represent post-test probability when test result is positive; open symbols represent post-test probability when test result is negative.*

prevalence of heart failure in the patients who were enrolled in the study is shown on the *x*-axis as the pretest probability of disease. The probability that a patient has heart failure after an abnormal ECG is shown by the closed symbols, and the probability that a patient has heart failure after a normal ECG is shown by the open symbols. The summary estimates of how well the test is able to rule in or rule out the disease (as calculated by the positive and negative likelihood ratios) are shown by the curved lines. The further that these lines are from the line at 45° to the *x*-axis, the better the test is able to discriminate between those who have the disease and those who do not have the disease.

Chest X-ray for the diagnosis of clinically defined heart failure

Nine studies[79,80,84,85,87,89–92] measured the accuracy of either any abnormality seen on CXR or an increase in the cardiothoracic ratio.

Five studies[79,80,84,85,87] estimated the accuracy of any sign of heart failure on CXR to detect the diagnosis of clinically defined heart failure (*Figures 17, 18* and *19*). The estimates for the diagnostic accuracy of this test varied greatly:

- sensitivity: 0.68 (95% CI 0.40–0.88)
- specificity: 0.83 (95% CI 0.66–0.93)

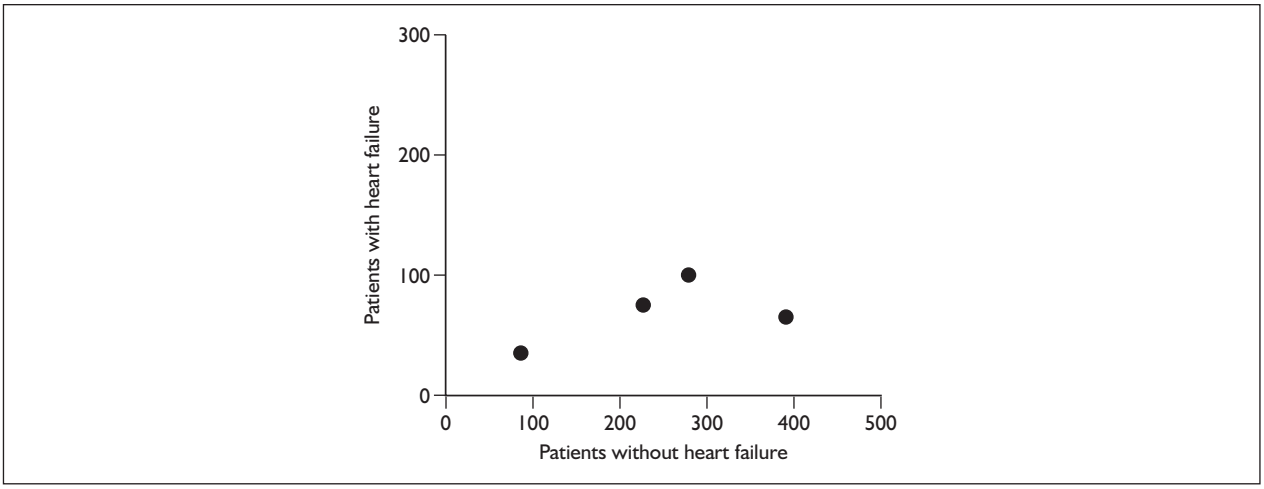

FIGURE 17 *Studies assessing the accuracy of chest X-ray for the clinical diagnosis of heart failure.*

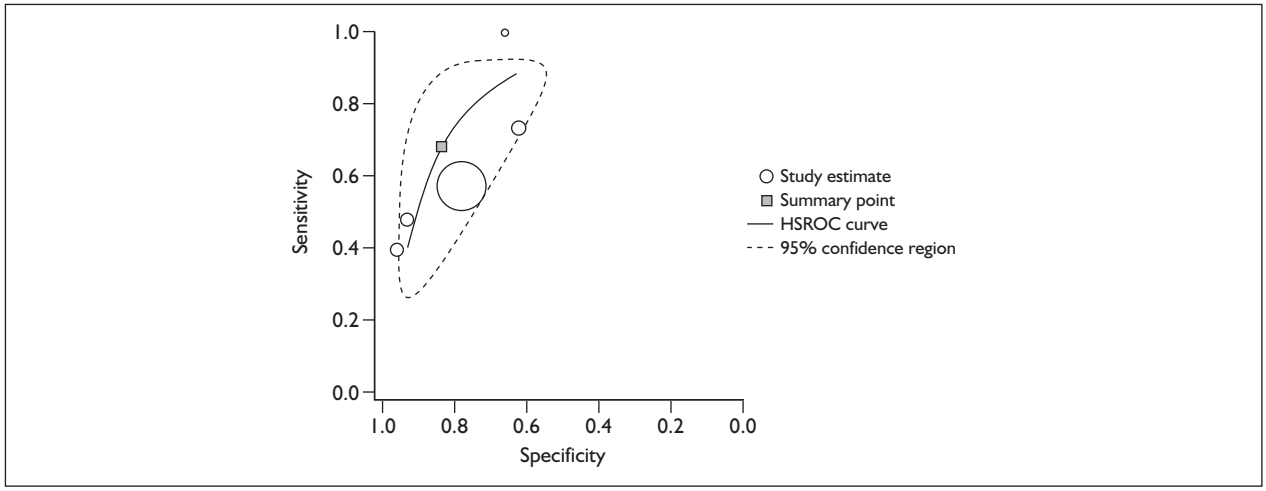

FIGURE 18 *Chest X-ray for the diagnosis of clinically defined heart failure: summary receiver operating characteristic (curve) (SROC) plot of studies. Each circle in the above plot represents the estimated sensitivity and specificity from each study plotted in a receiver operating characteristic (ROC) space. The size of each circle is proportional to the size of the study. HSROC, hierarchical summary receiver operating characteristic.*

- DOR: 10.7 (95% CI 4.45–25.5)
- positive likelihood ratio: 4.07 (95% CI 2.25–7.39)
- negative likelihood ratio: 0.38 (95% CI 0.18–0.78).

An abnormal CXR is moderately helpful for ruling the diagnosis in, but a normal CXR is not able to rule out the diagnosis.

Six studies[79,87,89–92] estimated the diagnostic accuracy of increased cardiothoracic ratio on CXR:

- sensitivity: 0.67 (95% CI 0.53–0.78)
- specificity: 0.76 (95% CI 0.65–0.84)
- DOR: 6.25 (95% CI 3.60–10.8)
- positive likelihood ratio: 2.73 (95% CI 1.94–3.86)
- negative likelihood ratio: 0.44 (95% CI 0.31–0.61).

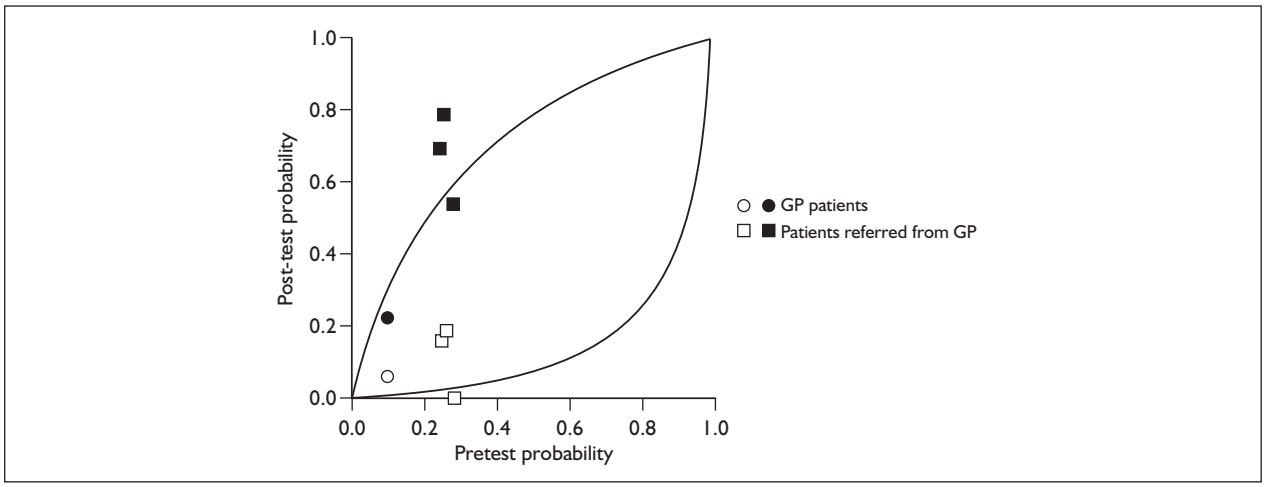

FIGURE 19 *Pretest/post-test graph of chest X-ray for the diagnosis of clinically defined heart failure. Note that the curved lines are back calculated from the overall likelihood ratios and not by a regression fit. Closed symbols represent post-test probability when test result is positive; open symbols represent post-test probability when test result is negative.*

B-type natriuretic peptides for the diagnosis of clinically defined heart failure

Twenty studies[82,84,88,91–93,97–110] examined the accuracy of BNP for a diagnosis of clinically defined heart failure (*Figure 20*). The largest single study was the Breathing Not Properly Study[104] (the outlier in *Figure 20*), which recruited 1586 patients in 11 emergency departments in the USA and Europe.

The results of the studies show a consistently high sensitivity but varying specificity for the diagnosis of heart failure (*Figures 21* and *22*). An elevated BNP does not confirm the diagnosis of clinically defined heart failure but a normal level rules the diagnosis out:

- sensitivity: 0.93 (95% CI 0.91–0.95)
- specificity: 0.74 (95% CI 0.63–0.83)
- DOR: 39.5 (95% CI 21.44–72.6)
- positive likelihood ratio: 3.57 (95% CI 2.44–5.21)
- negative likelihood ratio: 0.09 (95% CI 0.06–0.13).

Four studies[82,84,88,97] estimated the diagnostic accuracy of BNP for the diagnosis of clinical heart failure in patients in general practice or patients referred from general practice (*Figure 23*). The studies in general practice showed slightly lower sensitivity than, but similar specificity to, the studies overall:

- sensitivity: 0.84 (95% CI 0.72–0.92)
- specificity: 0.73 (95% CI 0.65–0.80)

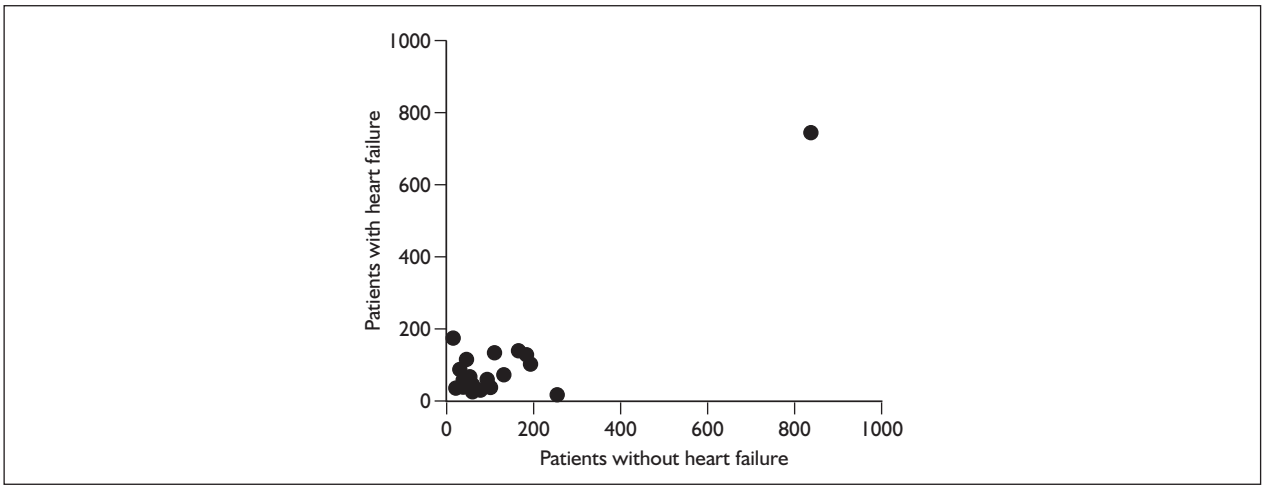

FIGURE 20 *Studies assessing the accuracy of BNP for the clinical diagnosis of heart failure.*

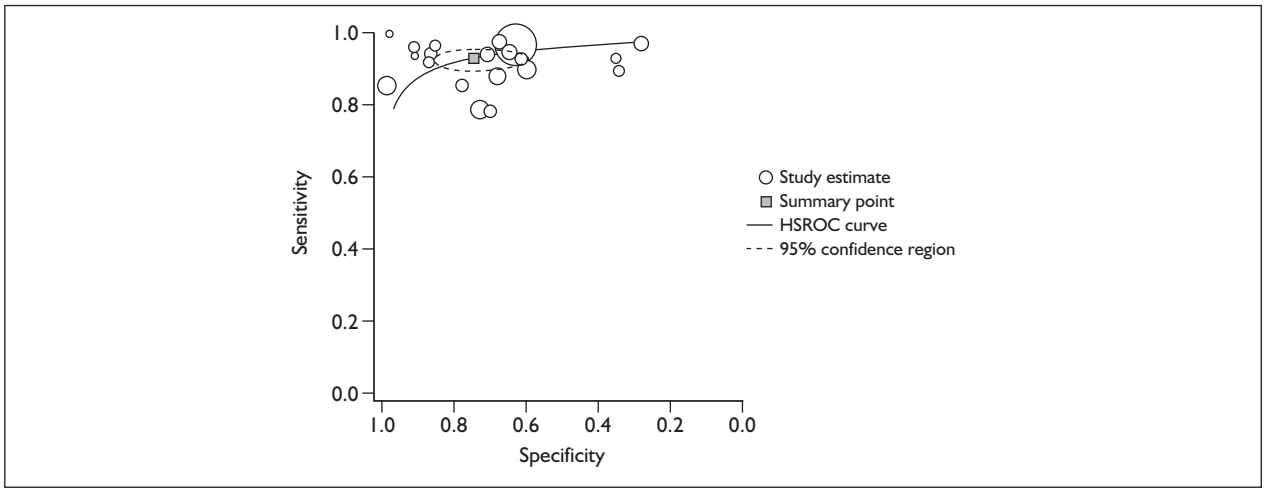

FIGURE 21 *BNP for the diagnosis of clinically defined heart failure: summary receiver operating characteristic (curve) (SROC) plot of studies. Each circle in the above plot represents the estimated sensitivity and specificity from each study plotted in a receiver operating characteristic (ROC) space. The size of each circle is proportional to the size of the study. HSROC, hierarchical summary receiver operating characteristic.*

- DOR: 14.3 (95% CI 5.45–37.8)
- positive likelihood ratio: 3.12 (95% CI 2.22–4.39)
- negative likelihood ratio: 0.22 (95% CI 0.11–0.42).

N-terminal pro-B-type natriuretic peptides for the diagnosis of clinically defined heart failure

Sixteen studies[80–83,86–89,93,109,102,104,111–114] examined the accuracy of NT-proBNP for the diagnosis of clinically defined heart failure (*Figure 24*).

The results for NT-proBNP again show generally high sensitivity but varying specificity, with a somewhat lower specificity than for BNP (*Figures 25* and *26*):

- sensitivity: 0.93 (95% CI 0.88–0.96)
- specificity: 0.65 (95% CI 0.56–0.74)
- DOR: 24.6 (95% CI 14.4–42.2)
- positive likelihood ratio: 2.70 (95% CI 2.12–3.43)
- negative likelihood ratio: 0.11 (95% CI 0.07–0.18).

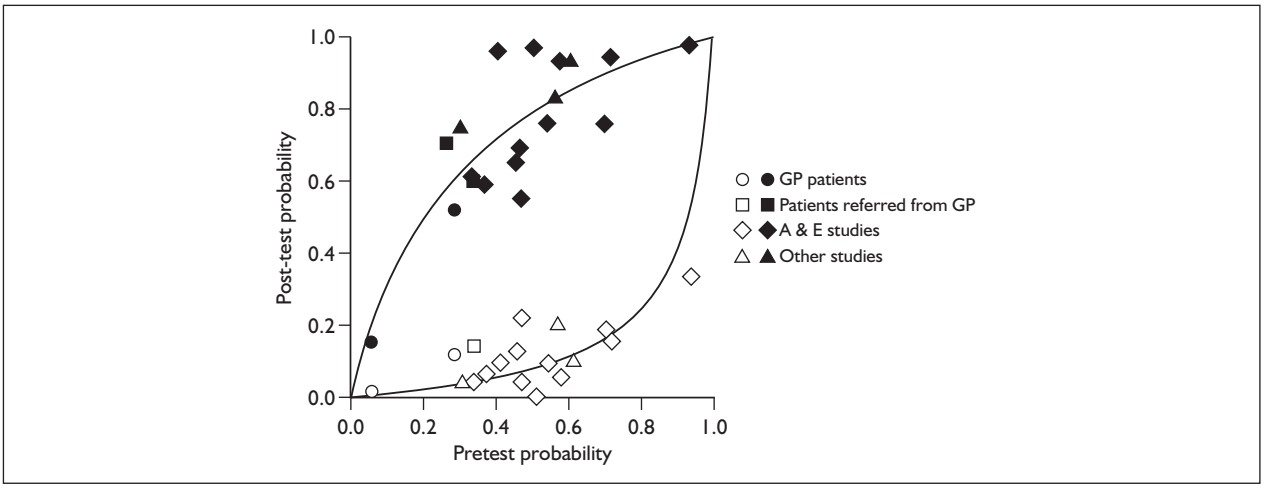

FIGURE 22 *Pretest/post-test graph of BNP for the diagnosis of clinically defined heart failure. Note that the curved lines are back calculated from the overall likelihood ratios and not by a regression fit. Closed symbols represent post-test probability when test result is positive; open symbols represent post-test probability when test result is negative.*

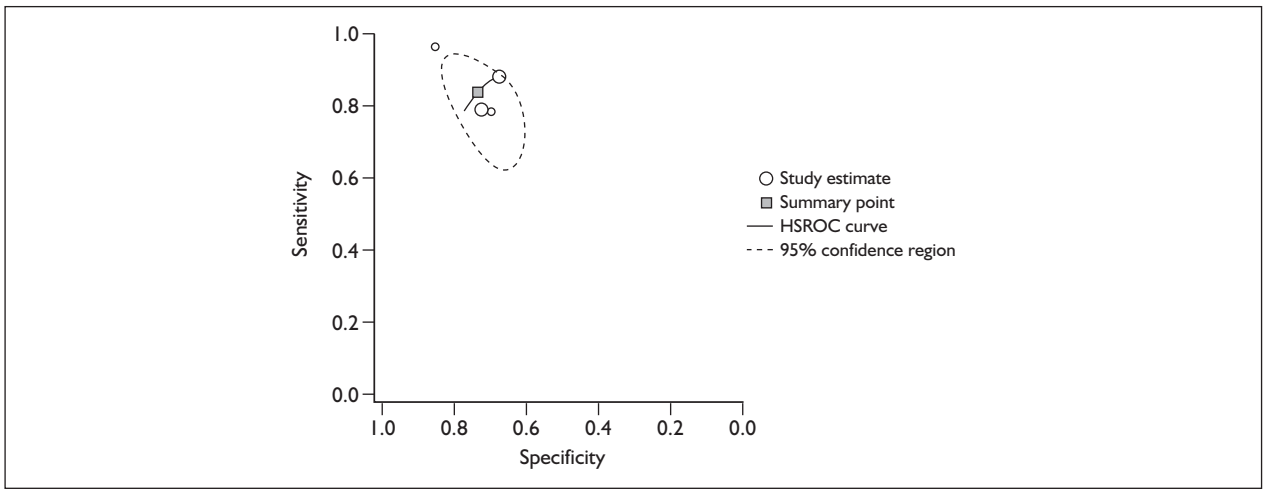

FIGURE 23 *BNP for the diagnosis of clinically defined heart failure: summary receiver operating characteristic (curve) (SROC) plot of studies set in general practice. Each circle in the above plot represents the estimated sensitivity and specificity from each study plotted in a receiver operating characteristic (ROC) space. The size of each circle is proportional to the size of the study. HSROC, hierarchical summary receiver operating characteristic.*

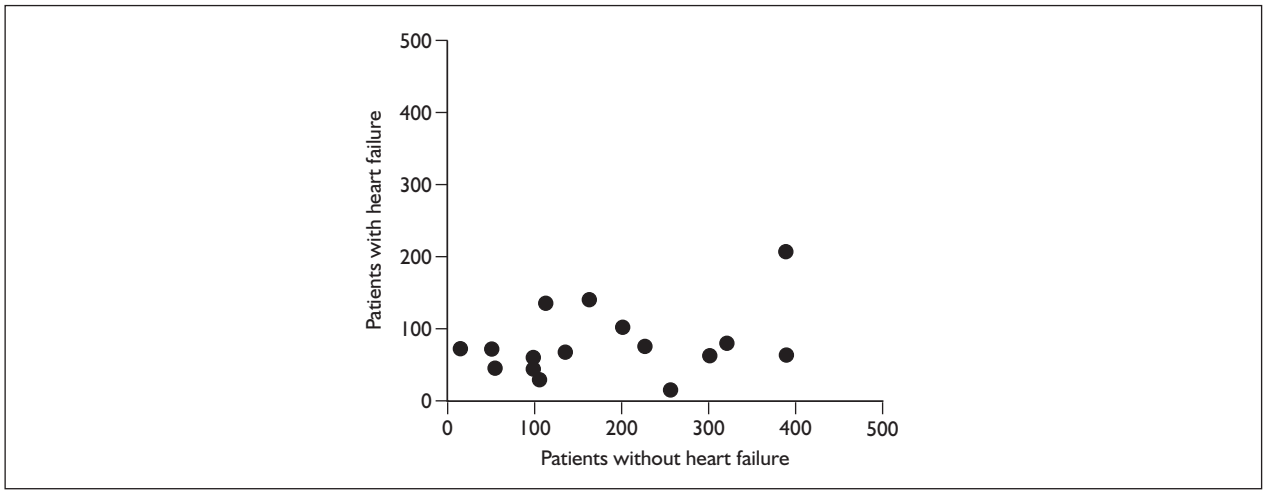

FIGURE 24 *Studies assessing the accuracy of NT-proBNP for the clinical diagnosis of heart failure.*

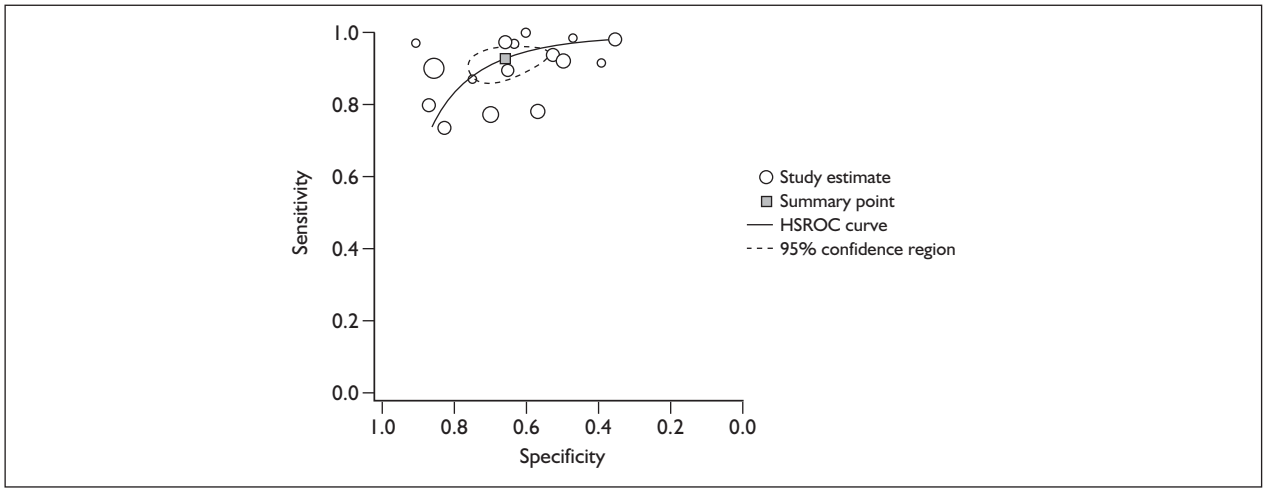

FIGURE 25 *NT-proBNP for the diagnosis of clinically defined heart failure: summary receiver operating characteristic (curve) (SROC) plot of studies. Each circle in the above plot represents the estimated sensitivity and specificity from each study plotted in a receiver operating characteristic (ROC) space. The size of each circle is proportional to the size of the study. HSROC, hierarchical summary receiver operating characteristic.*

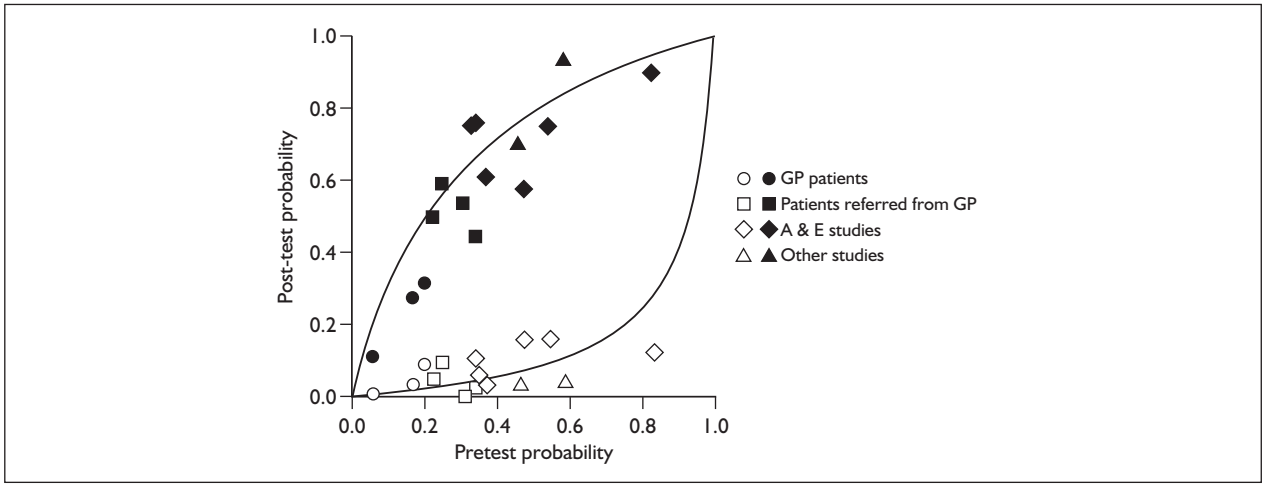

FIGURE 26 *Pretest/post-test graph of NT-proBNP for the diagnosis of clinically defined heart failure. Note that the curved lines are back calculated from the overall likelihood ratios and not by a regression fit. Closed symbols represent post-test probability when test result is positive; open symbols represent post-test probability when test result is negative.*

Eight of the studies[80–83,86–88,111] that examined the accuracy of NT-proBNP for the diagnosis of clinically defined heart failure were conducted in general practice patients or patients referred from general practice. Results for the studies conducted in general practice patients were similar to the overall results for NT-proBNP, with slightly lower specificity than for the overall results (*Figure 27*):

- sensitivity: 0.90 (95% CI 0.81–0.96)
- specificity: 0.60 (95% CI 0.50–0.70)
- DOR: 14.3 (95% CI 7.73–26.5)
- positive likelihood ratio: 2.28 (95% CI 1.82–2.86)
- negative likelihood ratio: 0.16 (95% CI 0.09–0.30).

Comparison of BNP versus NTpro-BNP for the diagnosis of clinically defined heart failure

Six studies[82,88,93,100,102,104] ($n = 1623$) compared the diagnostic accuracy of BNP with that of NT-proBNP for the clinical diagnosis of heart failure. There was no statistical difference in the diagnostic accuracy between the two tests, with a relative DOR of NT-proBNP/BNP of 1.20 (95% CI 0.30–4.80) ($p = 0.77$).

The performance of the individual assays is shown in *Figure 28*. There is no clear evidence of the superiority of one assay over another. In some studies an individual assay performs better than the

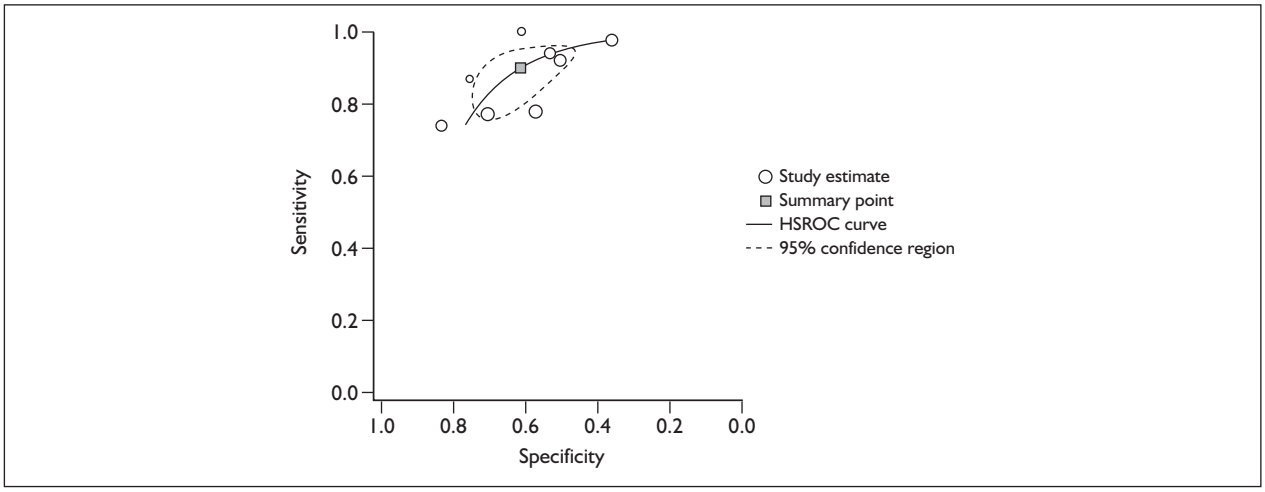

FIGURE 27 *NT-proBNP for the diagnosis of clinically defined heart failure in general practice: summary receiver operating characteristic (curve) (SROC) plot of studies. Each circle in the above plot represents the estimated sensitivity and specificity from each study plotted in a receiver operating characteristic (ROC) space. The size of each circle is proportional to the size of the study. HSROC, hierarchical summary receiver operating characteristic.*

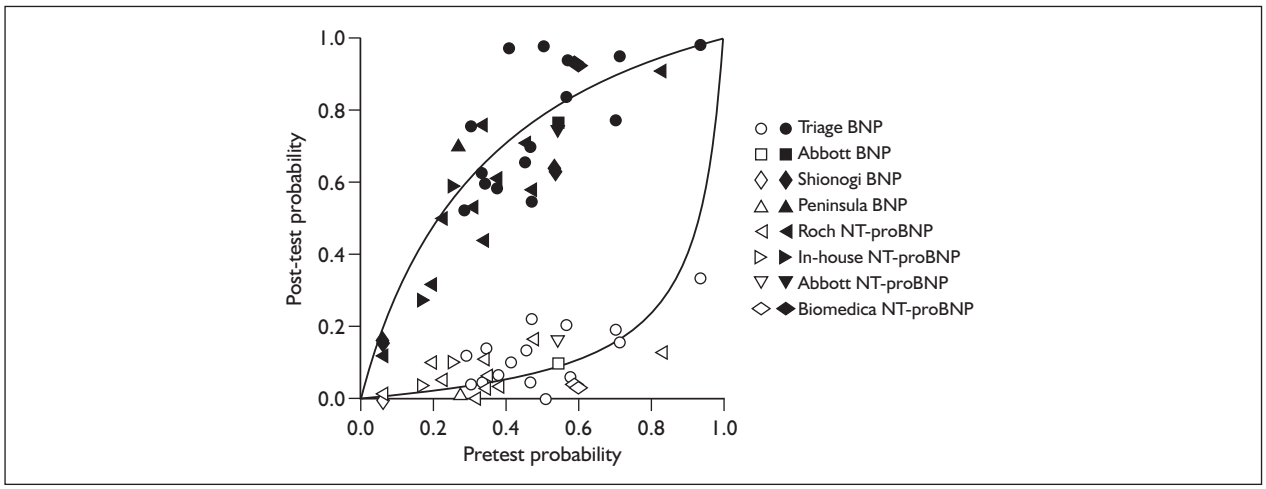

FIGURE 28 *Pretest/post-test graph of BNP and NT-proBNP by assay type for the diagnosis of clinically defined heart failure. Note that the curved lines are back calculated from the overall likelihood ratios and not by a regression fit. Closed symbols represent post-test probability when test result is positive; open symbols represent post-test probability when test result is negative.*

TABLE 3 *Overall accuracy of investigations for heart failure*

	Number of patients (studies)	Sensitivity (%)	Specificity (%)	Youden index[a]
ECG	4702 (11)	89	56	45
CXR: any abnormality	2323 (5)	68	83	51
CXR: increased cardiothoracic ratio	2797 (6)	67	76	43
BNP	4744 (20)	93	74	67
NT-proBNP	4229 (16)	93	65	58

a Youden index = sensitivity% + specificity% – 100%. This is a measure of the overall diagnostic accuracy of the test.

overall group (i.e. the point representing the study falls outside the curves); however, the same assay performs worse than the overall group in other studies.

Comparison of natriuretic peptides versus electrocardiogram for the diagnosis of clinically defined heart failure

Four studies[82,84,88,90] ($n = 1889$) examined the diagnostic accuracy of BNP and ECG for the diagnosis of heart failure in the same patient populations. BNP was shown to have a greater diagnostic accuracy than ECG, with a relative DOR of ECG/BNP of 0.32 (95% CI 0.12–0.87) ($p = 0.03$).

Seven studies[80–83,86–88] ($n = 2574$) examined the diagnostic accuracy of NT-proBNP versus ECG for the diagnosis of heart failure in the same patient populations. There was no difference in the diagnostic accuracy between NT-proBNP and ECG in these studies, with a relative DOR of ECG/NT-proBNP of 0.43 (95% CI 0.59–3.15) ($p = 0.38$).

Summary of accuracy of investigations for the diagnosis of clinically defined heart failure

A summary of the test accuracy of the investigations used for heart failure is shown in *Table 3*. BNP and ECG have relatively high sensitivity and so are useful for ruling out heart failure. CXR has the highest specificity and so is of some value in making a positive diagnosis of heart failure.

Chapter 6

Introduction to the individual patient data analysis

The systematic review identified the diagnostic value of individual symptoms and signs and investigations for the diagnosis of heart failure. However, in clinical practice these are not interpreted in isolation of each other but rather as a whole.

There are many well-developed heart failure prognostic tools in the literature that combine the results of different symptoms/signs and tests.[72] Mosterd *et al*.[72] applied criteria from six established heart failure scores including Framingham, Walma and Boston to a sample of 54 participants in the Rotterdam study. Most showed high sensitivity to detect definite heart failure with AUC ranging between 0.89 and 0.96. One of these, the Walma study, was designed to assess heart failure in elderly patients on diuretic therapy in general practice, whereas all other scores were developed for use in large epidemiological studies. However, use of these would be impractical in primary care because of the substantial number of variables in several of the scores, and also because many of the clinical signs have considerable interobserver variation even amongst specialists (raised JVP, third heart sound, hepatojugular reflux).[115,116] Furthermore, four of the scores include specific CXR parameters, which would be difficult to apply in general practice.

Two unpublished studies have attempted to address these difficulties. The first study by Barksfield[117] developed several simple models from the UKNP[88] study data ($n = 297$). The models included clinical features (age, gender, previous myocardial infarction, ankle oedema, breathlessness, crepitations) and BNP. External validation of the models was demonstrated on the Hillingdon data set[84] using AUC and Hosmer–Lemeshow tests. A second study by Cost[97] developed and compared several heart failure models as part of a PhD thesis. The research compared prognostic models developed from participants of the Rotterdam study ($n = 149$) and suggested that natriuretic peptides, in addition to clinical signs/symptoms (age, gender, orthopnoea, history of myocardial infarction, history of COPD, crepitations), could replace the use of ECG to detect the presence of heart failure in patients suspected of heart failure in primary care.

Given therefore that clinical scoring systems relevant to general practice were already available, we decided that the most efficient strategy for determining whether a clinical scoring system based on symptoms and signs could usefully predict the presence of heart failure would be to develop and test one of these. We decided to develop the Barksfield models as opposed to the Cost models as the former were based on a larger sample size and had been successfully validated on an external data set.

Chapter 7

Methods of the individual patient data analysis

For a clinical decision rule to be acceptable for use in practice, it requires validation across at least one, and preferably several, populations beyond the original population in which it was developed.[118] IPD analysis involves the collection and reanalysis of 'raw' data from all studies worldwide that have addressed a given research question, with data obtained from those responsible for the original studies.[119] Hence, obtaining raw data from other studies of patients with symptoms of heart failure allows us to test out our clinical prediction rule on data sets with varying characteristics and therefore assess its transferability and generalisability.

Studies included in the individual patient data analysis

Studies from the systematic review were deemed suitable for inclusion in the IPD analysis if they (1) were based in primary care and (2) had a minimum of 100 recently symptomatic patients. This limit on sample size was made to both reduce publication bias and limit the inclusion of smaller studies of lower methodological quality.

Description of collaborating studies

Eleven studies were identified from the systematic review as meeting the criteria for inclusion in the IPD analysis. Authors of the following nine studies gave us permission to use their data; data from two studies[111,120] were not available.

- Zaphiriou *et al.*[88] – UKNP, 2005
- Cowie *et al.*[84] – Hillingdon, 1997
- Hobbs *et al.*[82] – ECHOES, 2004
- Cost[97] – Rotterdam, 2000
- Fox *et al.*[85] – Bromley, 2000
- Wright *et al.*[87] – New Zealand, 2003
- Alehagen *et al.*[80] – Sweden, 2003
- Lim and Senior[86] – Northwick Park, 2006
- Galasko *et al.*[81] – Northwick Park, 2005.

Six[80,84–88] of these studies were of patients referred to a cardiologist for assessment following presentation in primary care with symptoms of heart failure. The symptoms of heart failure were not described by four[84–86,88] of these published studies. Wright *et al.*[87] identified the symptoms of heart failure as dyspnoea and/or oedema and Alehagen *et al.*[80] as shortness of breath and/or bilateral peripheral oedema and/or tiredness. The remaining three data sets were from population screening studies[81,82,97] in which subsamples of patients with heart failure symptoms were extracted. The Hobbs *et al.*[82] symptoms included shortness of breath, tiredness, ankle swelling or prescribed diuretics; the Galasko *et al.*[81] symptoms included shortness of breath on level or worse, shortness of breath on hill, shortness of breath plus ankle swelling or prescribed loop diuretics;[81] and Cost[97] included a subset of the Rotterdam study participants who were referred by a GP if they scored 3 or more points on the Rotterdam heart failure score or if heart failure was suspected for other reasons.

Validating databases

Rigorous checking of each data set was performed by comparison of key fields with published data. The data providers were contacted when discrepancies or coding problems were identified. Several variables of interest were manipulated in an attempt to ensure consistency across data sets. Blood natriuretic peptides that were measured in pmol/l were converted to pg/ml. Definite heart failure was defined by ESC criteria – namely, appropriate symptoms (NYHA II or worse) plus objective evidence of cardiac dysfunction. For data in which this was not explicitly recorded, heart failure was identified as symptomatic patients (NYHA > 1) with an ejection fraction < 40%, atrial fibrillation or valve disease.[80,81,86] Current medications in the Galasko data set were available as text fields; these were categorised and coded as ACE inhibitor, beta-blocker, diuretic or ARB.[81]

Model development

Model derivation using Zaphiriou (UKNP) data

Logistic regression models were constructed using backward elimination: the full model was fitted and variables were then removed one at a time until all those remaining contributed significantly ($p < 0.05$) to the model. Variables entered into the original model are listed in *Table 4*. Prespecified two-way interactions were also included: age by gender; BNP (or NT-proBNP) by age, gender, diabetes, IHD, COPD and current medication.

Sample size

To allow a direct comparison of models, 299 (98%) patients with complete data were included in the model building for BNP, and 300 patients were included in the development of a clinical rule for NT-proBNP.

Model assumptions

As 95% of the Zaphiriou derivation sample was found to have shortness of breath, it was recognised that this symptom would have little discriminatory power. Therefore, it was dropped from all analyses.

The linearity assumption for age was tested by creating a categorical variable with four levels using three cut-points based on the quartiles of the age distribution.[121] The model was then refitted with the categorical variable for age replacing the continuous variable. A plot of the estimated coefficients versus the mid-points of the groups indicated a non-linear relationship. Various parametric forms including quadratic and cubic splines were then chosen and compared with the linear model using likelihood ratio tests. No significant improvement was found between the models and the simplest model with the linear term for age, which was therefore adopted. The distribution of BNP was positively skewed and transformed using natural logs to improve the fit of the model.

Adjusting for pretest probabilities using Albert's method

The post-test probabilities estimated by conventional logistic analysis do not allow for different pretest probabilities. By including the log of the pretest odds of heart failure as an 'offset' term,[122] the resulting logistic model estimates likelihood ratios, which can then be applied to different pretest probabilities using Bayes' theorem.[123]

Model validation

Seven nested models with Albert's adjustment were identified as potential clinical prediction rules. These were then externally validated on the three data sets[82,84,98] that contained all of the required variables. Models with more limited variable requirements were further validated with additional datasets.[85,87] Validation included the calculation of the AUC and calibration plots. The AUC is a measure of the model's ability to discriminate between those persons with heart failure and those without; values range between 0 and 1, with a value of 0.5 or less representing a useless test.

To measure each model's goodness of fit, calibration plots were used. Data were divided into five groups according to the predicted probability of heart failure (0 to < 0.2, 0.2 to < 0.4, 0.4 to

TABLE 4 *Variables entered in the logistic regression model*

Demographics	**Age, gender**
Social history	Smoking status, alcohol consumption
Symptoms	Breathlessness, fatigue, ankle oedema
Past medical history	Angina, myocardial infarction, CABG, PTCA, hypertension, diabetes, stroke, peripheral vascular disease, dyslipidaemia, COPD
Physical examination	Obesity (> 30 kg/m^2), systolic blood pressure, diastolic blood pressure, crepitations
Current medication	Diuretic, ACE inhibitor, angiotensin receptor blocker, beta-blocker
Investigations	Abnormal ECG, BNP, NT-proBNP

ACE, angiotensin-converting enzyme; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; PTCA, percutaneous transluminal coronary angioplasty.

< 0.6, 0.6 to < 0.8, 0.8–1). Within each group the observed prevalence of heart failure was calculated with its corresponding 95% confidence interval. These were then plotted against the average predicted probability. A well-calibrated model will have all points lying on the diagonal.

Parsimonious model

The seven models were then compared with each other using likelihood ratio tests. Here, reductions in deviance (–2 log likelihood value) were used to assess whether extra variables resulted in a significant improvement in model fit.

Simple clinical prediction rule

The model identified as the most parsimonious was then simplified into a nomogram designed for use in general practice. Validation of the nomogram was then performed using the AUC across all data sets for which sufficient data were available.

Effect modifiers

The development of the clinical rules was based on models derived from the Zaphiriou data set. To provide further evidence that the performance of BNP and NT-proBNP does not vary with co-morbidity or pharmacological treatment, the data from all studies were initially pooled and tests of heterogeneity were performed. Pooling the data would give more power to detect any significant interactions. However, there was evidence of significant heterogeneity between the data sets in terms of patient selection and the relationship between heart failure and BNP [$\chi^2(3) = 14.9$, $p = 0.002$]. Therefore, pooling was inappropriate and no pooled results are presented. Data-dependent logistic regression models were therefore evaluated. All potential effect modifiers (age, gender, obesity, IHD, atrial fibrillation, COPD, diabetes, use of diuretics, use of beta-blockers) were examined by their inclusion as interactions with BNP (and NT-proBNP) adjusted for clinical score. Statistical analyses were performed using SAS (version 9.1) and SPSS (version 14.0).

Chapter 8

Results of the individual patient data analysis

The characteristics of the data sets utilised in the model derivation and validation are shown in *Table 5*. The mean age of subjects ranged from 66 years[84] to 76 years.[97] The majority of patients studied were female (53–65%). The derivation data set had the highest prevalence of heart failure (34%) and that of Hobbs *et al.*[82] the lowest (13%). The proportion of participants with breathlessness ranged from 24% to 95%. The distribution of patients in NYHA class III or IV ranged from 24%[82] to 49%;[84] NYHA class was unavailable for Cost[97] and Wright *et al*.[87]

Table 6 presents the results of logistic models predicting heart failure from BNP alone, clinical features alone, ECG alone, and combinations of all three. No significant interactions were found between age and gender, or between BNP and the prespecified list of patient characteristics. Age and ankle oedema were not significant in all models but have remained to allow comparison between nested models. The results show that the odds of heart failure increase threefold for every unit on the log of BNP, the odds are double for men compared with women, and the odds for past medical history of myocardial infarction, ankle oedema and crepitations are 5.2, 2.5 and 4.8 times, respectively, those of patients without these conditions. The odds of a person with an abnormal ECG are six times greater than the odds of someone with a normal ECG. These prognostic clinical and ECG effects are greatly reduced when used in combination with BNP.

TABLE 5 *Characteristics of data sets utilised in the model validation*

Variable	Zaphiriou et al., 2005[88]	Cowie et al., 1997[84]	Hobbs et al., 2004[82]	Cost, 2000[97]	Fox et al., 2000[85]	Wright et al., 2003[87]
	UKNP, *n* = 299	Hillingdon, *n* = 105	ECHOES, *n* = 392	Rotterdam, *n* = 143	Bromley, *n* = 380	New Zealand, *n* = 297
Demographics						
Heart failure	103 (34)	29 (28)	52 (13)	42 (29)	101 (27)	75 (25)
Age (years), mean (SD)	71.5 (11.5)	66.4 (12.0)	68.0 (10.9)	76.5 (7.2)	73.9 (9.6)	72.0 (11.8)
Gender male	123 (41)	49 (47)	177 (45)	58 (41)	165 (43)	103 (35)
Symptoms and signs						
Shortness of breath	283 (95)	80 (76)	235 (60)	35 (24)	279 (73)	136 (46)
Ankle oedema	192 (64)	55 (52)	183 (47)	73 (51)	208 (55)	196 (66)[a]
Previous MI	42 (14)	7 (7)	70 (18)	16 (11)	43 (11)	43 (14)
Crepitations	84 (28)	16 (15)	49 (13)	58 (41)	109 (29)	68 (23)
Investigations						
Abnormal ECG	159 (53)	63 (60)	247 (63)	52 (37)	260 (68)	189 (64)
BNP (pg/ml), median (IQR)	86.8 (31.0–224.0)	59.2 (37.8–143.4)	74.2 (13.7–134.5)	52.0 (36.0–86.0)		
NT-proBNP (pg/ml), median (IQR)	381.5 (135.5–1200.5)		412.6 (160.1–1037.8)			442.0 (195.5–1071.0)

IQR, interquartile range; MI, myocardial infarction.
a Peripheral oedema.
Figures given are number (%) unless stated otherwise.

TABLE 6 *Models to predict heart failure in individuals presenting with symptoms suggestive of heart failure, derived from the Zaphiriou et al.[88] (UKNP) data set*

Model	Beta coefficient	SE of beta	*p*-value	OR (95% CI)
1. BNP model				
Log(BNP+1)	1.19	0.14	< 0.0001	3.29 (2.47–4.37)
Constant	–5.66	0.73	< 0.0001	
2. Clinical model				
Age	0.004	0.01	0.74	1.00 (0.98–1.03)
Gender	0.66	0.29	0.02	1.94 (1.11–3.40)
Past medical history MI	1.67	0.39	< 0.0001	5.30 (2.49–11.26)
Ankle oedema	0.93	0.31	0.003	2.55 (1.38–4.70)
Crepitations	1.58	0.30	< 0.0001	4.84 (2.67–8.79)
Constant	–1.99	0.97	0.04	
3. ECG model				
ECG	1.80	0.29	< 0.0001	6.03 (3.45–10.55)
Constant	–1.07	0.24	< 0.0001	
4. BNP + clinical model				
Log(BNP+1)	1.24	0.17	< 0.0001	3.46 (2.46–4.87)
Age	–0.05	0.02	0.008	0.95 (0.92–0.99)
Gender	0.90	0.35	0.01	2.47 (1.25–4.89)
Past medical history MI	1.25	0.46	0.006	3.50 (1.42–8.61)
Ankle oedema	0.62	0.37	0.10	1.85 (0.89–3.85)
Crepitations	1.35	0.36	0.0002	3.86 (1.92–7.79)
Constant	–3.81	1.23	0.002	
5. BNP + ECG model				
Log(BNP+1)	1.07	0.15	< 0.0001	2.91 (2.16–3.92)
ECG	0.75	0.34	0.03	2.11 (1.09–4.10)
Constant	–5.54	0.73	< 0.0001	
6. Clinical + ECG model				
Age	–0.01	0.01	0.52	0.99 (0.96–1.02)
Gender	0.66	0.30	0.04	1.85 (1.02–3.35)
Past medical history MI	1.56	0.41	0.0002	4.74 (2.10–10.68)
Ankle oedema	0.96	0.33	0.004	2.61 (1.36–5.01)
Crepitations	1.57	0.33	< 0.0001	4.83 (2.55–9.16)
ECG	1.69	0.32	< 0.0001	5.42 (2.90–10.11)
Constant	–2.01	1.04	0.05	
7. BNP + clinical + ECG model				
Log(BNP+1)	1.12	0.19	< 0.0001	3.08 (2.14–4.43)
Age	–0.05	0.02	0.01	0.95 (0.92–0.99)
Gender	0.81	0.35	0.02	2.26 (1.13–4.50)
Past medical history MI	1.21	0.46	0.009	3.34 (1.35–8.28)
Ankle oedema	0.60	0.38	0.11	1.83 (0.88–3.82)
Crepitations	1.35	0.36	0.0002	3.86 (1.90–7.86)
ECG	0.60	0.38	0.11	1.83 (0.87–3.83)
Constant	–3.59	1.22	0.004	

MI, myocardial infarction; OR, odds ratio.
All models included log of pretest odds of heart failure as an additional intercept term (Albert's method).

Validation: area under the curve

Tables 7 and *8* present the results of the internal and external validation. BNP – both alone and in combination – showed excellent discrimination in the derivation and external data sets with the AUC ranging between 0.83 and 0.96. The clinical model and ECG models provided 'acceptable' discrimination with AUCs from 0.66–0.83 (*Table 7*). Similar results were found for models that included NT-proBNP, in which AUC ranged from 0.82 to 0.91 (*Table 8*).

Validation: calibration

Figure 29 shows the calibration plots for the derivation data set. The post-test probabilities fall reasonably close to the diagonal line for all models indicating that the models are well calibrated. *Figures 30* and *31* show calibration plots for the Cowie *et al*.[84] and Hobbs *et al*.[82] data sets respectively. The Hobbs data were closer to the line than the Cowie data with wide confidence intervals reflecting the low prevalence. All models are well calibrated at the low end of the probability scale. The BNP and BNP + clinical models underestimate the top end, whereas the other models overestimate the top end. *Figure 32* shows calibration plots for the Cost[97] data. The ECG and clinical + ECG models are well-calibrated models. The clinical alone model overestimates the top end whereas all other models underestimate across the range of probabilities. The clinical + ECG model is the best calibrated model of the Fox *et al*.[85] data (*Figure 33*) whereas the clinical model is the best calibrated model from the Wright *et al*.[87] data (*Figure 34*). Calibration plots of the corresponding NT-proBNP models show similar goodness of fit and are provided in *Figures 35* and *36*.

Parsimonious model

Table 9 shows the deviances calculated for each logistic model developed from the derivation data set. The BNP model improved by adding either clinical features (model 1 versus model 4: $\chi^2(5) = 27.9$, $p < 0.0001$) or ECG (model 1 versus model 5: $\chi^2(1) = 4.9$, $p = 0.03$). However, there was no gain by the addition of ECG to BNP + clinical (model 4 versus model 7: $\chi^2(1) = 2.5$, $p = 0.11$), whereas BNP + ECG did improve when clinical features were added (model 5 versus model 7: $\chi^2(5) = 35.5$, $p < 0.0001$). Hence, BNP + clinical was identified as the parsimonious model.

These model comparisons were also undertaken with NT-proBNP substituted for BNP. Similar results were found, with NT-proBNP + clinical shown to be the most parsimonious model (*Table 10*).

Simplifying the heart failure prediction model

For the BNP + clinical model to be used in practice it was advantageous to simplify it further by splitting the model into a two-stage process:

1. clinical
2. nomogram of clinical score with BNP.

Those with a high probability of heart failure from the clinical score alone could then be referred directly for echocardiography; the remainder would undergo a BNP test and then use a nomogram that would give a probability estimate of heart failure dependent on BNP result and clinical score.

As the age term in the clinical model alone (see *Table 6*) was not significant, this was removed from further analyses. The model was then rerun for the clinical part only, with the resultant model being:

$$\text{Log}(p/1-p) = -2.27 + 0.59 \times \text{gender} + 1.72 \times \text{myocardial infarction} + 0.84 \times \text{ankle} + 1.55 \times \text{crepitations}$$

where p = probability of heart failure.

The coefficients for this model are different from those shown in *Table 6* because of the omission of age. This model was then simplified further into a scoring system by creating new weights that were related to the parameter estimates in the model. The following weights were assigned (the four features can be remembered as MICE: *m*ale *i*nfarction *c*repitations o*e*dema):

- male: 2 points
- history of myocardial infarction: 6 points
- crepitations: 5 points
- ankle oedema: 3 points

Thus, any individual presenting with symptoms of heart failure could be given a clinical score between 0 (female with no history of myocardial infarction,

TABLE 7 *Area under the curve (AUC) for BNP models to predict heart failure in individuals presenting with symptoms suggestive of heart failure derived from the Zaphiriou et al.[88] data set*

	Derivation	Validation				
	Zaphiriou *et al.*, 2005[88]	Cowie *et al.*, 1997[84]	Hobbs *et al.*, 2004[82]	Cost, 2000[97]	Fox *et al.*, 2000[85]	Wright *et al.*, 2003[87]
	HF prevalence = 103/299 (34.4%)	HF prevalence = 29/105 (27.6%)	HF prevalence = 52/392 (13.3%)	HF prevalence = 42/143 (29.4%)	HF prevalence = 101/380 (26.6%)	HF prevalence = 75/297 (25.3%)
Model	**AUC (95% CI)**	**AUC (95% CI)**	**AUC (95% CI)**	**AUC (95% CI)**	**AUC (95% CI)**	**AUC (95% CI)**
1. BNP only	0.84 (0.79–0.89)	0.96 (0.92–0.99)	0.84 (0.79–0.89)	0.84 (0.77–0.91)		
2. Clinical only	0.77 (0.72–0.83)	0.70 (0.57–0.82)	0.73 (0.66–0.80)	0.73 (0.64–0.83)	0.66 (0.60–0.72)	0.79 (0.73–0.86)
3. ECG only	0.70 (0.64–0.76)	0.78 (0.69–0.86)	0.69 (0.63–0.75)	0.68 (0.58–0.78)	0.72 (0.67–0.77)	0.69 (0.63–0.75)
4. BNP + clinical	0.88 (0.84–0.92)	0.93 (0.87–0.98)	0.86 (0.82–0.91)	0.83 (0.76–0.90)		
5. BNP + ECG	0.85 (0.80–0.89)	0.96 (0.93–0.99)	0.86 (0.82–0.91)	0.86 (0.79–0.93)		
6. Clinical + ECG	0.83 (0.78–0.88)	0.83 (0.76–0.91)	0.78 (0.72–0.84)	0.76 (0.67–0.85)	0.78 (0.73–0.83)	0.83 (0.77–0.88)
7. BNP + clinical + ECG	0.89 (0.85–0.93)	0.94 (0.90–0.98)	0.87 (0.83–0.92)	0.85 (0.78–0.91)		

HF, heart failure.

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TABLE 8 *Area under the curve (AUC) for NT-proBNP models to predict heart failure in individuals presenting with symptoms suggestive of heart failure derived from the Zaphiriou et al.[88] data set*

	Derivation	**Validation**				
	Zaphiriou et *al.*, 2005[88]	**Hobbs et *al.*, 2004[82]**	**Wright et *al.*, 2003[87]**	**Alehagen et *al.*, 2003[80]**	**Lim and Senior, 2006[86]**	**Galasko et *al.*, 2005[81]**
	HF prevalence = 103/300 (34.3%)	**HF prevalence = 52/391 (13.3%)**	**HF prevalence = 75/297 (25.3%)**	**HF prevalence = 67/458 (14.6%)**	**HF prevalence = 31/137 (22.6%)**	**HF prevalence = 64/366 (17.5%)**
Model	**AUC (95% CI)**	**AUC (95% CI)**	**AUC (95% CI)**	**AUC (95% CI)**	**AUC (95% CI)**	**AUC (95% CI)**
1. NT-proBNP only	0.85 (0.81–0.90)	0.89 (0.84–0.93)	0.87 (0.82–0.92)	0.82 (0.76–0.87)	0.87 (0.78–0.96)	0.86 (0.81–0.91)
4. NT-proBNP + clinical	0.90 (0.86–0.93)	0.91 (0.87–0.94)	0.90 (0.86–0.95)			
5. NT-proBNP + ECG	0.86 (0.81–0.90)	0.89 (0.85–0.94)	0.88 (0.84–0.93)	0.85 (0.80–0.90)	0.88 (0.79–0.97)	0.87 (0.82–0.92)
7. NT-proBNP + clinical + ECG	0.90 (0.86–0.93)	0.91 (0.87–0.94)	0.91 (0.86–0.95)			

HF, heart failure.
Models 2, 3 and 6 are not shown here as they did not involve an NT-proBNP test.

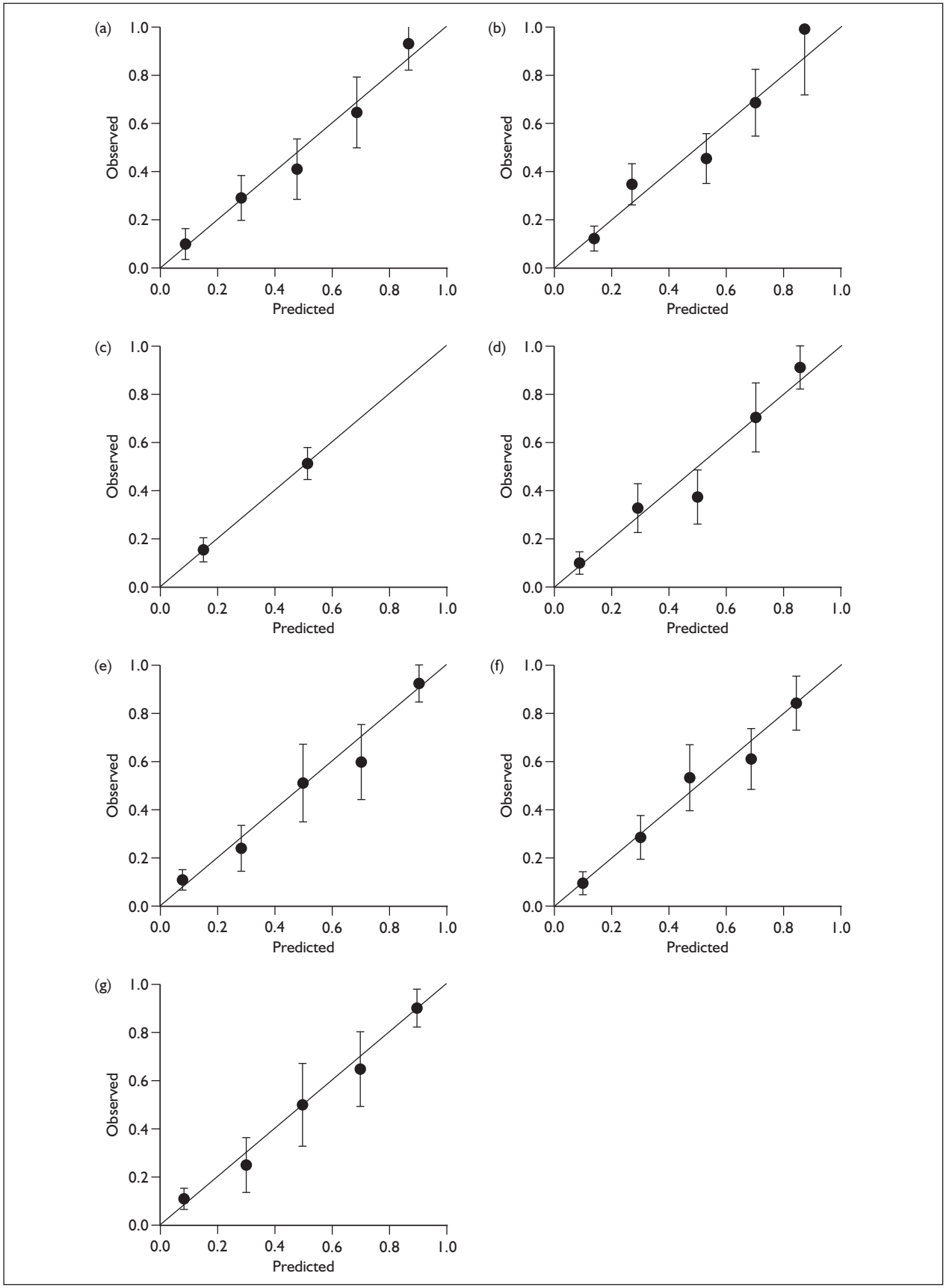

FIGURE 29 *Calibration plots using Zaphiriou[88] data set-derived models. The circles represent the observed proportion in the data set that had heart failure, and the vertical lines the 95% confidence interval around this proportion. (a) Model 1: BNP only. (b) Model 2: clinical only. (c) Model 3: ECG only. (d) Model 4: BNP + clinical. (e) BNP + ECG. (f) Model 6: clinical + ECG. (g) Model 7: BNP + clinical + ECG.*

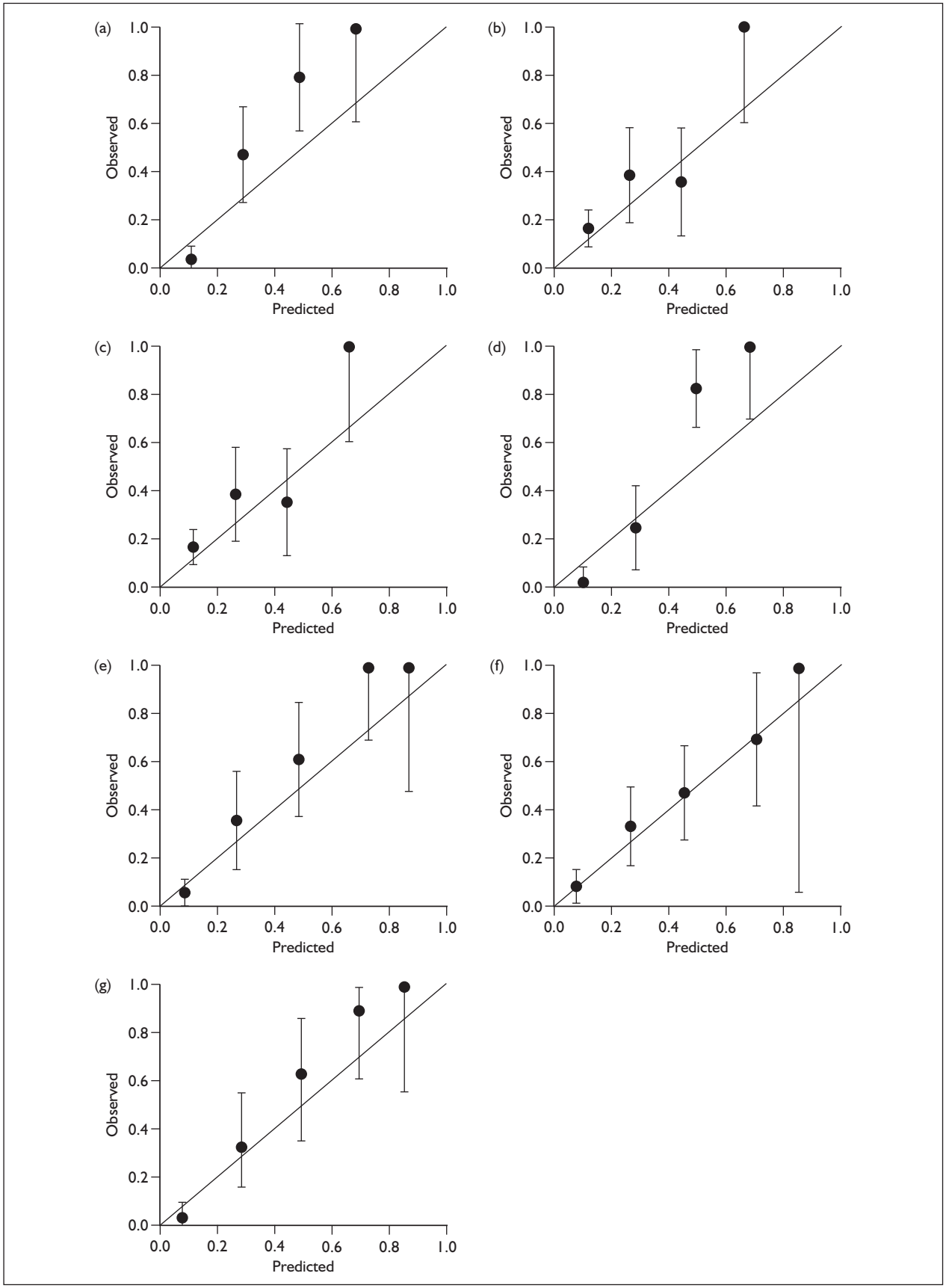

FIGURE 30 *Calibration plots of Zaphiriou-derived[88] models applied to Cowie[84] data. The circles represent the observed proportion in the data set that had heart failure, and the vertical lines the 95% confidence interval around this proportion. (a) Model 1: BNP only. (b) Model 2: clinical only. (c) Model 3: ECG only. (d) Model 4: BNP + clinical. (e) Model 5: BNP + ECG. (f) Model 6: clinical + ECG. (g) Model 7: BNP + clinical + ECG.*

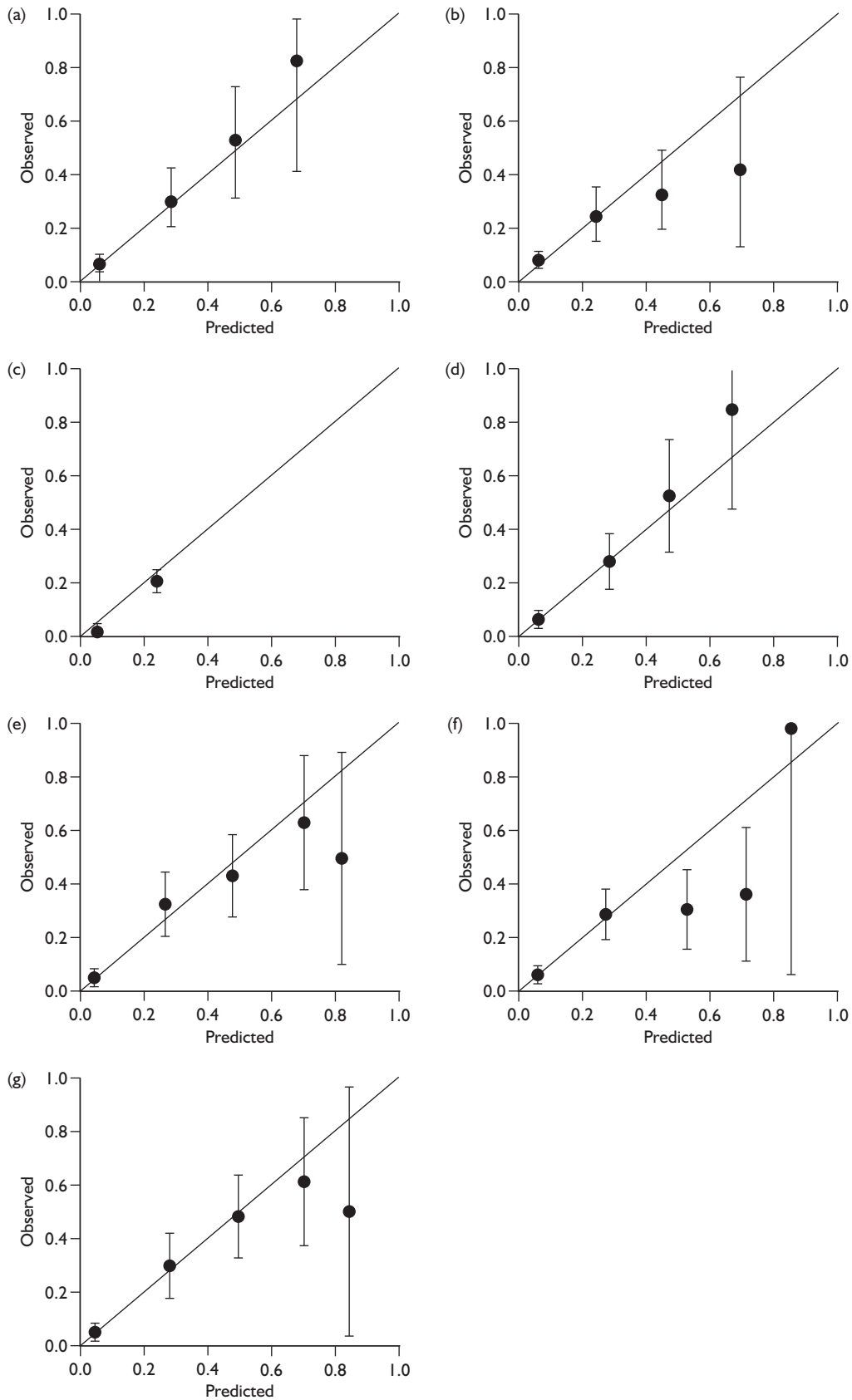

FIGURE 31 *Calibration plots of Zaphiriou-derived[88] models applied to Hobbs[82] data. The circles represent the observed proportion in the data set that had heart failure, and the vertical lines the 95% confidence interval around this proportion. (a) Model 1: BNP only. (b) Model 2: clinical only. (c) Model 3: ECG only. (d) Model 4: BNP + clinical. (e) Model 5: BNP + ECG. (f) Model 6: clinical + ECG. (g) BNP + clinical + ECG.*

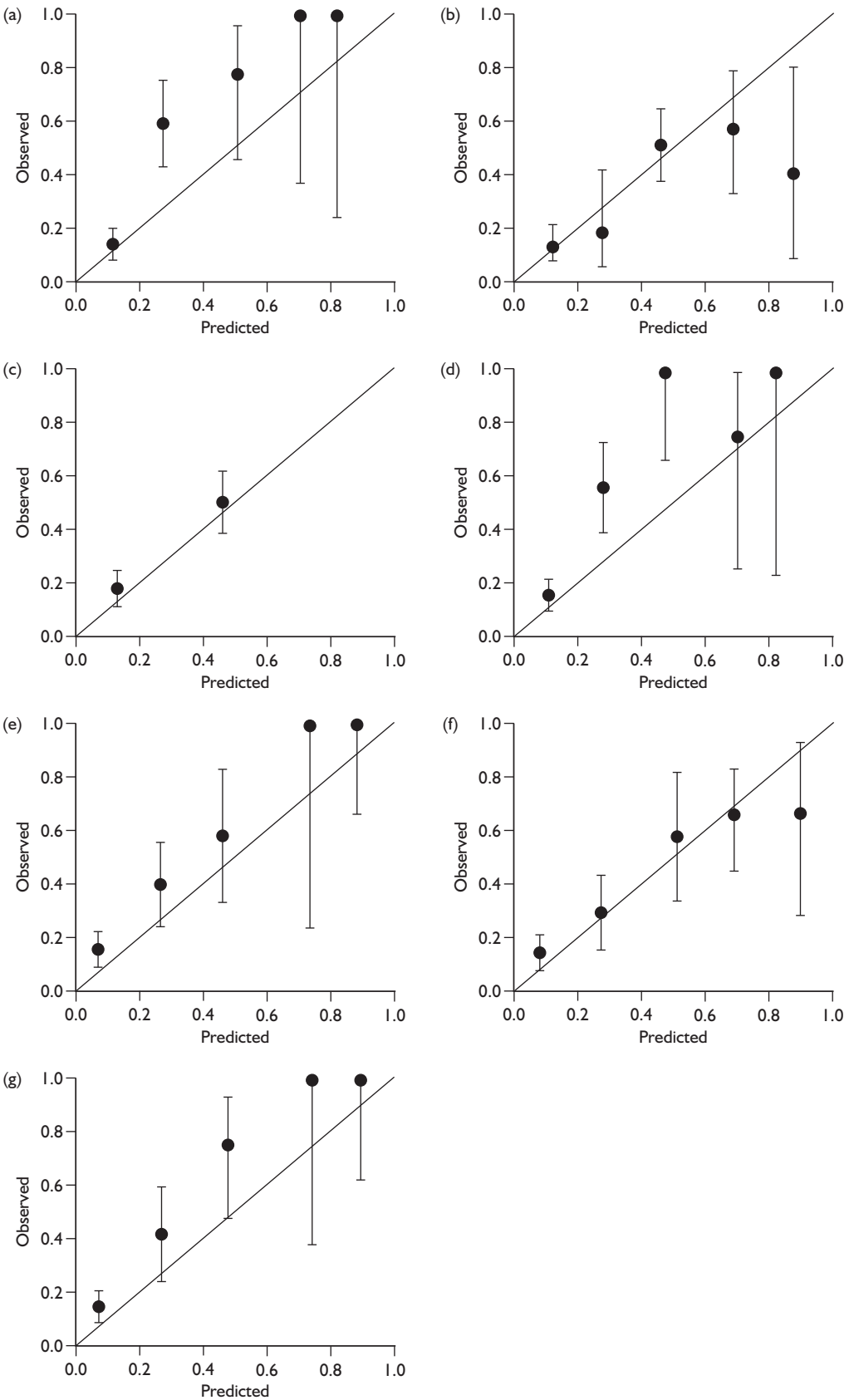

FIGURE 32 *Calibration plots of Zaphiriou-derived[88] models applied to Cost[97] data. The circles represent the observed proportion in the data set that had heart failure, and the vertical lines the 95% confidence interval around this proportion. (a) Model 1: BNP only. (b) Model 2: clinical only. (c) Model 3: ECG only. (d) Model 4: BNP + clinical. (e) Model 5: BNP + ECG. (f) Model 6: clinical + ECG. (g) BNP + clinical + ECG.*

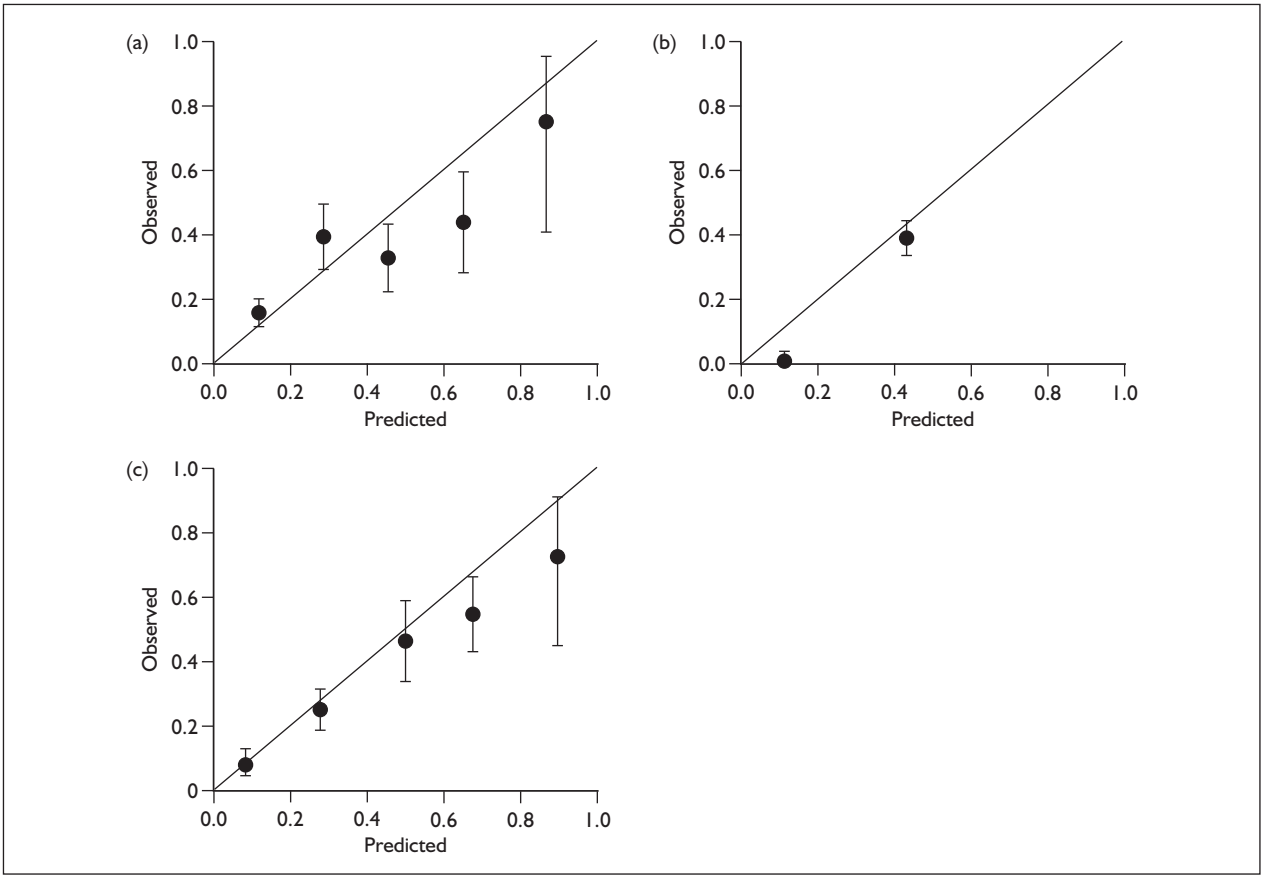

FIGURE 33 *Calibration plots of Zaphiriou-derived[88] models applied to Fox[85] data. The circles represent the observed proportion in the data set that had heart failure, and the vertical lines the 95% confidence interval around this proportion. (a) Model 2: clinical only. (b) model 3: ECG only. (c) Model 6: clinical + ECG.*

no ankle oedema, no basal crepitations) and 16 (all features present).

Impact of adding breathlessness to the model

Given that breathlessness had been identified in the systematic review as a useful symptom in discriminating between heart failure and no heart failure, the impact of adding breathlessness was explored.

Table 11 shows the odds ratios for heart failure if shortness of breath is present once adjustment has already been made for presence of other clinical features (the MICE score) and BNP or NT-proBNP score. In two data sets[82,88] the additional effect of breathlessness appeared to be significant, but the estimates of the post-test odds for both of these studies were unreliable as they depended on only one case of heart failure who did not have shortness of breath. The post-test odds for the data sets in which there were sufficient numbers of cases of heart failure without breathlessness varied between 0.75 and 1.6, but none was significantly > 1. Thus, addition of breathlessness was not found to add diagnostic value in these data sets.

Performance characteristics of the simple clinical rule

Table 12 gives the performance characteristics of the simple clinical rule, likelihood ratios of a positive test and post-test probability of heart failure associated with a pretest probability of 30%. A plot of the ROC curve demonstrated that the optimal cut-point on performance characteristics would be 5 (*Figure 37*).

This suggested the simple clinical rule shown in *Box 1*.

The interpretation of the BNP result would depend upon the clinical score, as shown in the nomogram (*Figure 38*). For example, to obtain the post-test probability estimate of heart failure for

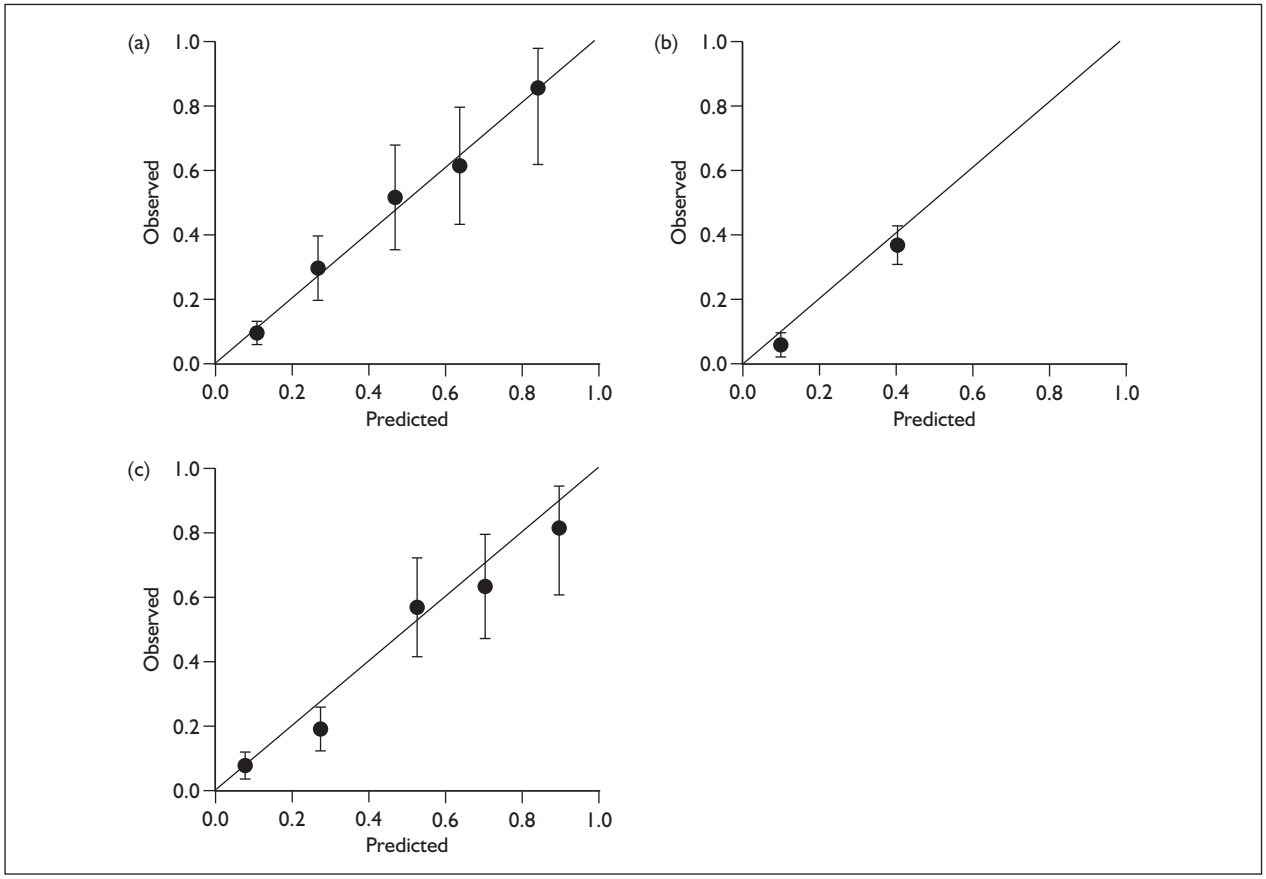

FIGURE 34 *Calibration plots of Zaphiriou-derived[88] models applied to Wright[87] data. The circles represent the observed proportion in the data set that had heart failure, and the vertical lines the 95% confidence interval around this proportion. (a) Model 2: clinical only. (b) model 3: ECG only. (c) Model 6: clinical + ECG.*

BOX 1 *Simple clinical rule*

In a patient presenting with symptoms such as breathlessness in whom heart failure is suspected, if the patient has any one of:

- a history of myocardial infarction
- basal crepitations
- is a male with ankle oedema

then refer straight for echocardiography

Otherwise, carry out a BNP (or NT-proBNP) test and refer to echocardiography depending on the results of the BNP or NT-proBNP test

a female with no clinical features (score of zero) with a BNP of 100 pg/ml, the clinician would draw a perpendicular line from the BNP value on the *x*-axis up to the appropriate curve and read the corresponding probability off the *y*-axis (10%). The nomogram for NT-proBNP and clinical features is presented in *Figure 39*.

Validation of nomograms

AUCs were calculated for both nomograms for data sets in which items were available (*Table 13*). The AUCs for both nomograms were very similar to the AUCs for previous unsimplified models: BNP + simple clinical, 0.84–0.94; NT-proBNP + simple clinical, 0.88–0.90. This indicates

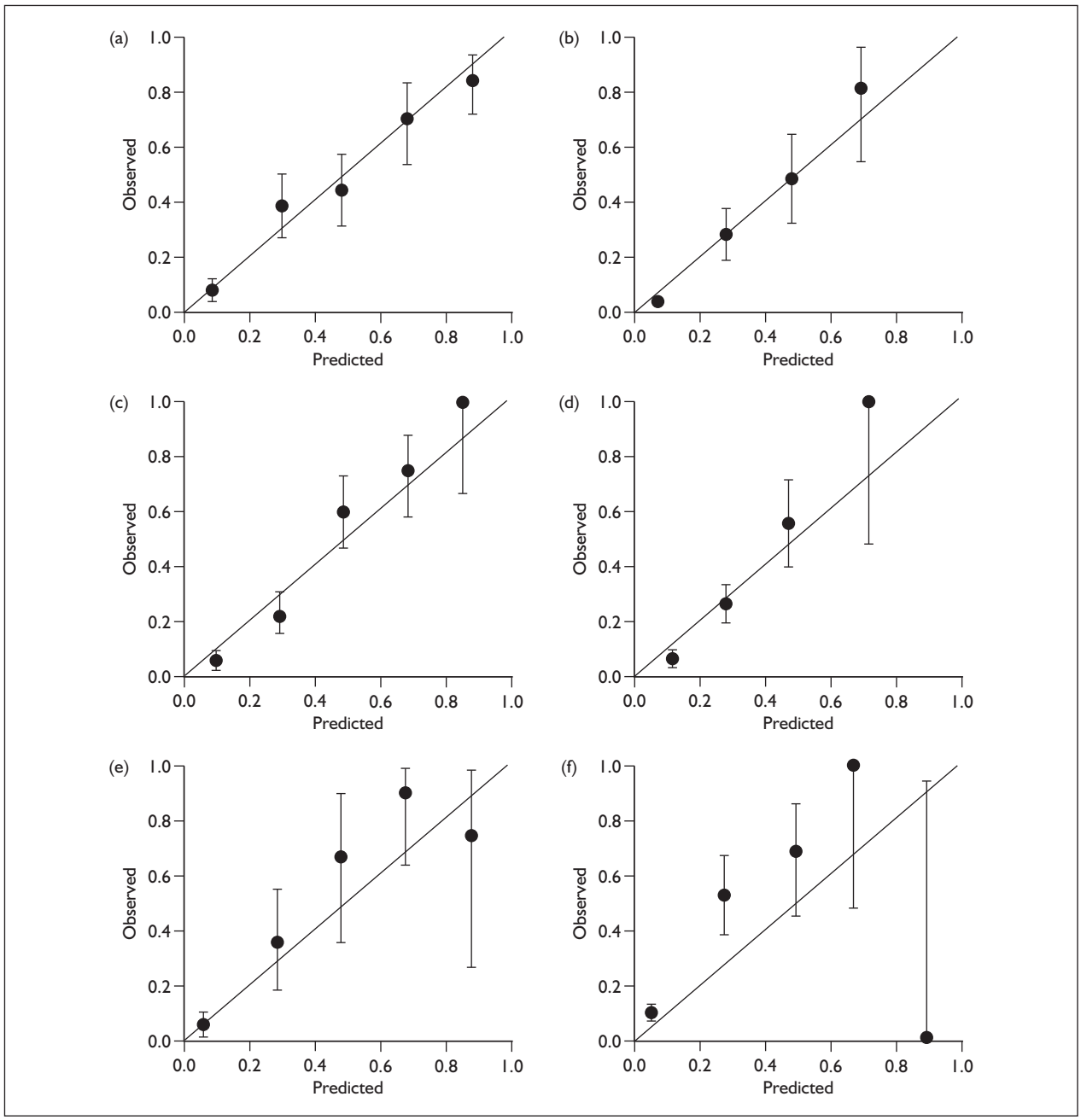

FIGURE 35 *Calibration plots of model 1 (NT- proBNP only) by data set. The circles represent the observed proportion in the data set that had heart failure, and the vertical lines the 95% confidence interval around this proportion. (a) Zaphiriou[88] data. (b) Hobbs[82] data. (c) Wright[87] data. (d) Alehagen[80] data. (e) Lim[86] data. (f) Galasko[81] data.*

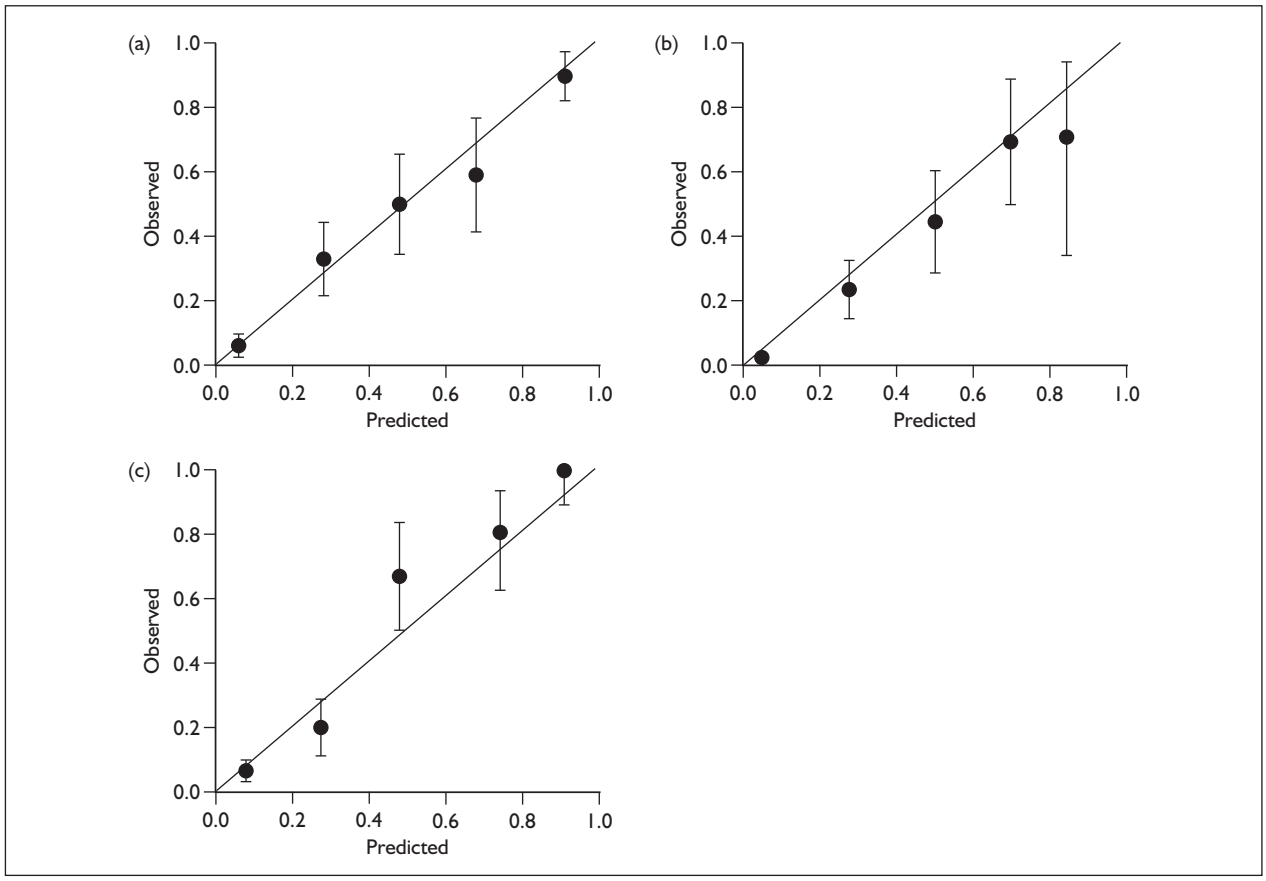

FIGURE 36 *Calibration plots of model 5 (NT-proBNP + clinical) by data set. The circles represent the observed proportion in the data set that had heart failure, and the vertical lines the 95% confidence interval around this proportion. (a) Zaphiriou[88] data. (b) Hobbs[82] data. (c) Wright[87] data.*

TABLE 9 *Deviances obtained by logistic regression modelling of the ability of BNP, clinical features and electrocardiography to predict heart failure in individuals presenting with symptoms*

Model	Deviance
Null model (intercept only)	385.1
1. BNP only	274.5
2. Clinical only	317.1
3. ECG only	338.6
4. BNP + clinical	236.6
5. BNP + ECG	269.6
6. Clinical + ECG	285.4
7. BNP + clinical + ECG	234.1
All models based on sample size of 299.	

TABLE 10 *Deviances obtained by logistic regression modelling of the ability of NT-proBNP, clinical features and electrocardiography to predict heart failure in individuals presenting with symptoms*

Model	Deviance
Null model (intercept only)	385.9
1. NT-proBNP only	264.7
2. Clinical only	317.8
3. ECG only	337.8
4. NT-proBNP + clinical	227.6
5. NT-proBNP + ECG	262.8
6. Clinical + ECG	283.6
7. NT-proBNP + clinical + ECG	226.8
All models based on sample size of 300.	

TABLE 11 *Logistic regression modelling to test predictive value of shortness of breath in diagnosis of heart failure adjusted for prior probability of heart failure obtained from MICE and natriuretic peptide rules*

	Odds ratio (95% CI)				
	Zaphiriou et *al.*, 2005[88]	**Cowie et *al.*, 1997[84]**	**Hobbs et *al.*, 2004[82]**	**Cost, 2000[97]**	**Wright et *al.*, 2003[87]**
Post-test odds (MICE and BNP rules)	21.831[a] (2.24–212.6)	1.6 (0.30–8.62)	155.41[a] (15.9 to > 999.9)	1.39 (0.38–5.08)	0.75 (0.33–1.67)
Post-test odds (MICE and NT-proBNP rules)	15.871[a] (1.67–150.6)		130.6 (13.8 to > 999.9)		0.75 (0.33–1.67)

MICE, male infarction crepitations oedema.
a Unreliable estimates because of sparsity of data.
Models included log of post-test odds of heart failure as an additional intercept term (Albert's method).

TABLE 12 *Performance characteristics of the simple clinical rule to predict heart failure in individuals presenting with symptoms suggestive of heart failure*

Cut-point ≥	Sensitivity (%)	Specificity (%)	LR+	Pretest probability	Post-test probability
0	100	0	1	30	30
2	96.2	19.8	1.20	30	34
3	92.3	32.7	1.37	30	37
5	79.8	62.9	2.15	30	48
6	60.6	76.7	2.60	30	53
7	59.6	76.7	2.56	30	52
8	53.8	80.7	2.79	30	54
9	35.6	91.1	4.00	30	63
10	30.8	94.1	5.22	30	69
11	19.2	98.5	12.8	30	85
13	8.7	100	> 20	30	> 90
14	6.7	100	> 20	30	> 90
16	2.9	100	> 20	30	> 90

LR+, likelihood ratio of a positive test.
Note: Because of division by zero, calculations cannot be made for the last three rows.

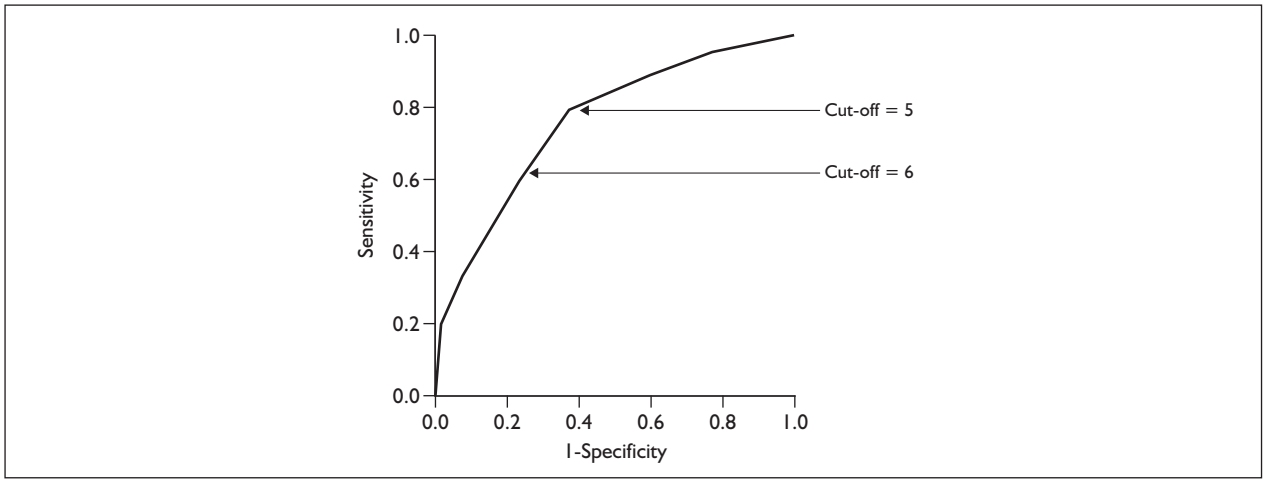

FIGURE 37 *Receiver operating characteristic curve of the simple clinical rule predicting heart failure among patients with symptoms suggestive of heart failure. Diagonal segments are produced by ties.*

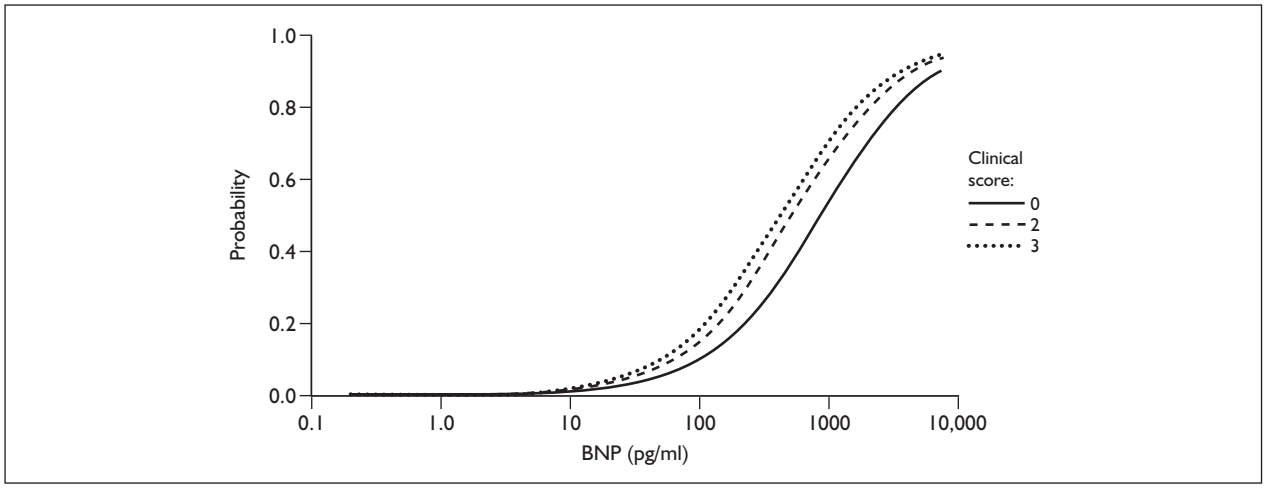

FIGURE 38 *Nomogram estimating the probability of heart failure in patients with symptoms using the clinical score and BNP.*

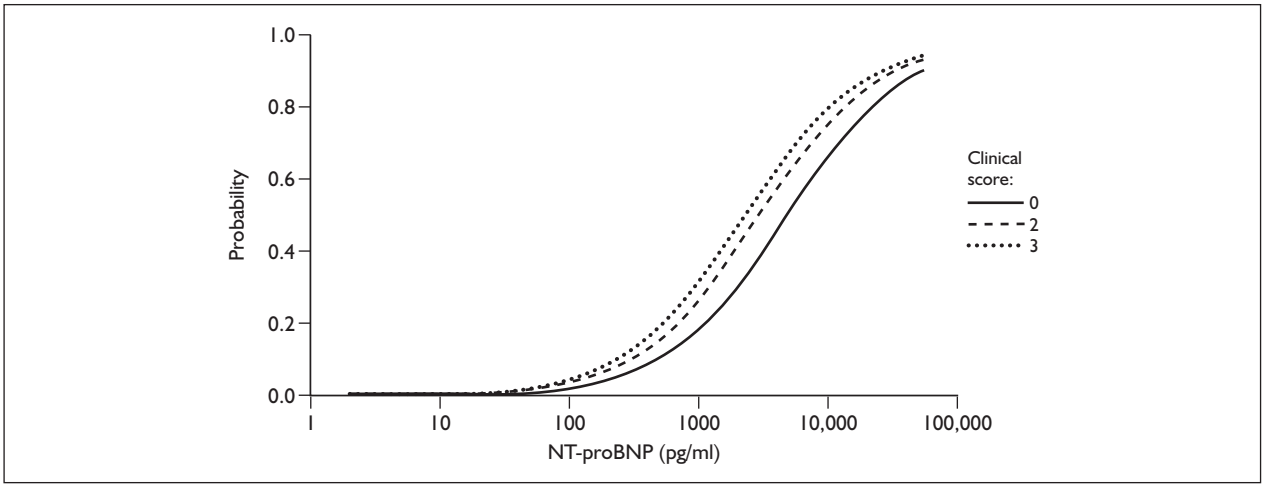

FIGURE 39 *Nomogram estimating the probability of heart failure in patients with symptoms using the clinical score and NT-proBNP.*

TABLE 13 *Area under the curve (AUC) for nomograms*

	Nomogram clinical score + BNP	Nomogram clinical score + NT-proBNP
Data set	**AUC (95% CI)**	**AUC (95% CI)**
Zaphiriou *et al.*, 2005[88]	0.87 (0.83–0.91)	0.88 (0.85–0.92)
Cowie *et al.*, 1997[84]	0.94 (0.89–0.98)	
Hobbs *et al.*, 2004[82]	0.86 (0.81–0.91)	0.89 (0.85–0.93)
Cost, 2000[97]	0.84 (0.77–0.91)	
Wright *et al.*, 2003[87]		0.90 (0.85–0.94)

that the nomograms show excellent discrimination between those persons with and those without heart failure.

Effect modifiers

Further evaluation of interactions between the plasma concentration of natriuretic peptides and patient characteristics in the prediction of heart failure was performed on all available data. A breakdown of patient characteristics by data set is presented in *Table 14*. Results of the logistic models, adjusting for clinical score, are given in *Table 15*.

There was no evidence that age, atrial fibrillation, diabetes or COPD had an effect on the performance of BNP or NT-proBNP. A marginal effect of obesity on BNP[88] and diuretics on NT-proBNP[87] was found, although this effect was not seen in the remaining data sets. The relationship between BNP and the risk of heart failure varied with gender of the individual for the Cost[97] data only ($p = 0.03$). Several significant interactions were found for the Hobbs *et al.*[82] data; the relationship between NT-proBNP and risk of heart failure varied according to whether patients had IHD

TABLE 14 *Characteristics of data available for analyses of interaction effects*

Characteristic	Zaphiriou *et al.*, 2005[88] *n* = 305	Cowie *et al.*, 1997[84] *n* = 105	Hobbs *et al.*, 2004[82] *n* = 392	Cost, 2000[97] *n* = 143	Wright *et al.*, 2003[87] *n* = 297
Obese	123 (42)	27 (26)	97 (25)	36 (25)	117 (39)
IHD	91 (30)	13 (12)	136 (35)		43 (14)
COPD	58 (19)	10 (10)	22 (6)	46 (32)	42 (14)
Diabetes	58 (19)	4 (4)	51 (13)	17 (12)	42 (14)
Diuretic	192 (63)	53 (51)	182 (46)		70 (24)[a]
ACE inhibitor	71 (23)	3 (11)[b]	93 (24)		78 (26)
Beta-blocker	70 (23)		58 (15)		72 (24)
ARB			10 (3)		

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; IHD, ischaemic heart disease.
a Furosemide recorded only.
b Based on 28 cases with available data.
Figures are *n* (%) unless stated otherwise; denominators vary slightly with completion of each characteristic.

TABLE 15 *Interaction tests between patient characteristic and blood natriuretic peptide by data set*

	p-value				
Interaction	**Zaphiriou et *al.*, 2005[88]**	**Cowie et *al.*, 1997[84]**	**Hobbs et *al.*, 2004[82]**	**Cost, 2000[97]**	**Wright et *al.*, 2003[87]**
Age and BNP	0.16	0.39	0.58	0.69	
Age and NT-proBNP	0.06		0.32		0.29
Gender and BNP	0.64	0.30	0.50	0.03	
Gender and NT-proBNP	0.35		0.14		0.53
Obesity and BNP	0.08	0.08	0.81	0.20	
Obesity and NT-proBNP	0.05		0.77		0.28
IHD and BNP	0.49	0.51	0.09		
IHD and NT-proBNP	0.86		0.04		0.21
AF and BNP	0.71	0.88	0.24		
AF and NT-proBNP	0.80		0.44		0.27
Diabetes and BNP	0.36		0.79	0.32	
Diabetes and NT-proBNP	0.09		0.77		0.36
COPD and BNP	0.15	0.20	0.93	0.25	
COPD and NT-proBNP	0.64		0.70		0.76
Diuretic and BNP	0.55	0.69	0.51		
Diuretic and NT-proBNP	0.56		0.45		0.05
ACE inhibitor and BNP	0.73		0.004		
ACE inhibitor and NT-proBNP	0.56		0.003		0.24
Beta-blocker and BNP	0.35		0.09		
Beta-blocker and NT-proBNP	0.64		0.03		0.85

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; IHD, ischaemic heart disease.

($p = 0.04$) or were on beta-blockers ($p = 0.03$) or ACE inhibitors ($p = 0.003$). Similarly there was evidence from these data that ACE inhibitors had a modifying effect on BNP ($p = 0.004$); however, these effects were not replicated in the other data sets.

Summary of results of individual patient data analysis in terms of the objectives

1. Can a clinical scoring system based on symptoms and signs usefully predict the presence of heart failure? We found that a simple clinical scoring system based on previous myocardial infarction, basal crepitations and ankle oedema did usefully predict the presence of heart failure in terms of determining whether or not an individual should be referred immediately for echocardiography or should have a BNP test, with the decision to proceed to echocardiography depending upon the results of that test.
2. To rule out heart failure in primary care, what is the optimum decision cut-off point for plasma natriuretic peptides (BNP)? *Figures 38* and *39* show the post-test probability of heart failure for a given BNP result and a given clinical score. The determination of the optimum decision cut-point depends upon the

value placed upon making a correct diagnosis of heart failure. This is explored further in the decision modelling.

3. Does the diagnostic performance of plasma natriuretic peptides vary according to patient characteristics (including age, gender, presence of IHD, presence of COPD, diabetes mellitus, obesity, atrial fibrillation, existing pharmacological therapy at time of diagnostic test)? We found no consistent evidence of any significant interactions between the performance of plasma natriuretic peptides and patient characteristics.
4. How accurate is the combination of plasma natriuretic peptides and ECG at diagnosing heart failure? We found that adding ECG to clinical features + BNP did not result in improved accuracy of diagnosis.

Chapter 9

Modelling the impact of different plausible strategies for diagnosis of heart failure in primary care

The IPD analysis developed and validated a simple clinical rule to determine whether to refer a patient in whom heart failure is suspected in primary care directly for echocardiography or whether to perform a BNP test first. The cut-point at which to refer straight to echocardiography was determined purely on the basis of the performance of the clinical rule and not on any estimation of the costs of unnecessary investigations or of missed diagnoses of heart failure. Furthermore, on clinical grounds alone, it is difficult to determine the optimum threshold of BNP score at which to refer for echocardiography, as, again, this requires some estimation of how important it is to avoid missing a diagnosis.

The purpose of the decision analysis model is therefore to take account of the potential costs of missed diagnoses (patients not referred who have heart failure) and the costs of echocardiography when the result is normal so that decision cut-points can be recommended on the grounds of cost-effectiveness.

Approach taken for the decision analysis

The approach we took needed to take into account the fact that BNP is a continuous variable, with no predefined positive or negative value. Therefore we needed to compare a large number of possible strategies, corresponding to the many possible BNP cut-points. To do this we first needed to define how much it would be worth spending to diagnose a case of heart failure – we refer to this as 'willingness to pay' (WTP). Once we had established a WTP, we could calculate what would be an appropriate cut-point for BNP. This cut-point will vary according to the pretest probability (which is given by the MICE score) and the test performance of BNP (which we have reported in the IPD analysis). Having done this we could reduce the decision analysis to a manageable number of alternatives: do nothing; perform BNP and echocardiography depending upon the result of the BNP test; or proceed straight to echocardiography. Therefore a key first step was to calculate plausible extremes for the WTP. This is described in the following section.

Estimating the value of diagnosing heart failure

To inform our estimation of the cost of a missed diagnosis we updated the systematic reviews carried out by NICE for the 2003 guideline on diagnosis and management of heart failure.[50] This updated review is shown in Appendix 6.

There is good evidence that treatment of heart failure with beta-blockers [124] and ACE inhibitors [125] can reduce mortality and the risk of hospital admission from heart failure. Therefore, once a diagnosis has been made, it can be assumed that the diagnosis will precipitate treatment that will reduce the risk of death and the risk of hospital admission. Conversely, it can be assumed that if a diagnosis is not made then the condition will worsen and result in an acute admission to hospital (when a diagnosis will be made), sudden death or worsening symptoms such that the diagnosis is reviewed and the correct diagnosis made. For the purposes of the calculations below we have assumed that the diagnosis will be delayed by 6 months (unless there is a hospital admission or the patient dies) in patients with genuine heart failure if they are not referred for echocardiography. The potential costs of missed diagnoses are avoidable hospital admissions and reduced life expectancy and quality of life. The size of these costs will depend upon the proportion of people who would be treated with beta-blockers and ACE inhibitors once a diagnosis has been made, as these are the two treatments for heart failure that have been shown to improve outcome and are considered indicated for the vast majority of patients with heart failure.

How many patients with a new diagnosis of heart failure will be treated with beta-blockers or ACE inhibitors?

In a follow-up of new cases of heart failure identified in Hillingdon during 1995–6,[126] 65% of patients were prescribed ACE inhibitors. An ongoing analysis of a large GP database (the THIN database, 315 practices, total population 2.97 million; Ronan Ryan, University of Birmingham, 2008, personal communication) identified 16,000 incident cases of heart failure between 1995 and 2005 and found that 69% of people with a definite diagnosis of heart failure were on ACE inhibitors within 2 years of diagnosis. A proportion of people who were not on ACE inhibitors will have been on ARBs instead. These drugs appear to have similar effects on mortality as ACE inhibitors.[127] In the THIN database this represented an additional 16% of cases. The same database found that 34% of patients with definite heart failure were on beta-blockers. These data are consistent with the findings of a survey carried out for the Healthcare Commission, [128] which found that 85% of patients registered on GP systems with a diagnosis of LV dysfunction and coronary heart disease are being treated with an ACE inhibitor or an ARB and that 33% of people discharged from hospital with a diagnosis of heart failure are on beta-blockers.

Therefore, for the purposes of our model we will assume that 85% of new cases of heart failure are started on an ACE inhibitor/ARB and 34% on beta-blockers, and that the 34% of people on beta-blockers are also taking an ACE inhibitor/ARB.

What is the likely survival and QALY gain from early detection of heart failure?

The 1-year survival rate from diagnosis of heart failure in patients in the Framingham Heart Study[18] was 57% for men and 64% for women. The mean age of these patients was 70 years and there was no temporal change in survival over the 40 years that patients with heart failure were identified (1948–88). As ACE inhibitors were not available for most of that period, and beta-blockers were not used to treat heart failure, the Framingham survival data can be taken to be the prognosis in the minimally treated population, i.e. symptomatic treatment with diuretics alone, without use of drugs known to improve the prognosis.

Systematic reviews of the beta-blocker and ACE inhibitor trials[124,125] suggest that the relative risk of death is reduced by 33% and 20%, respectively, by these agents. From the data available from these systematic reviews and the Framingham study[18] it is possible to generate survival curves (untreated) for men and women separately and odds ratios for mortality for those taking ACE inhibitors alone (0.8) and ACE inhibitors combined with beta-blockers (0.5). If we assume that these odds ratios are stable over time and applicable separately to men and women, it is possible to calculate survival probabilities as shown in *Table 16*.

We then used these data to generate survival curves by linear interpolation. A patient with a 6-month delay to diagnosis is assumed to have the same probability of survival as someone who is

TABLE 16 *Estimated survival probabilities for people with heart failure treated with angiotensin-converting enzyme inhibitors and beta-blockers and on no therapy*

	Men			Women		
Time (year)	Untreated	ACEI only	ACEI + BB	Untreated	ACEI only	ACEI + BB
0.25	0.73	0.77	0.84	0.72	0.76	0.84
1	0.57	0.62	0.73	0.64	0.69	0.78
2	0.46	0.52	0.63	0.56	0.61	0.72
5	0.25	0.29	0.40	0.38	0.43	0.55
10	0.11	0.13	0.20	0.21	0.25	0.35

ACEI, angiotensin-converting enzyme inhibitor; BB, beta-blocker.

untreated for that 6-month period. After 6 months it is assumed that their probability of survival is the same as someone who is on treatment. For example, the estimated survival curves for men diagnosed early (and therefore treated early), diagnosed late (and therefore treated late) and untreated are shown in *Figure 40*. In this illustrative example the treatment entails ACE inhibitors. Similar curves could be drawn for the effect of the combination of ACE inhibitors and beta-blockers, and for women.

The survival benefit due to early treatment is the area between the upper and middle curves. The longer the time horizon used to estimate the quality-adjusted life-year (QALY) gain from early diagnosis, the greater the benefit. *Table 17*, derived from *Figure 40* (and similar graphs not shown), reports the estimated survival gain up to a time horizon of 3, 5 or 10 years for men and women separately treated either with an ACE inhibitor alone or with an ACE inhibitor plus beta-blocker. Assuming equal numbers of men and women, the average increase in life expectancy for a person diagnosed early is the mean of the increases in life expectancy given in *Table 17* weighted for the proportions of people in each treatment category (51% treatment with ACE inhibitors alone; 34% ACE inhibitors plus beta-blockers; 15% no treatment). This gives an overall estimated survival gain of 0.163–0.390 years depending upon the time horizon (*Table 17*).

In terms of QALY gain, a patient with significant heart failure (NYHA class III or IV) has a mean EuroQol 5 dimensions (EQ-5D) score of 0.6.[129] Patients with all categories of heart failure are likely to have a higher overall mean EQ-5D score, for example 0.65. Using this estimate of 0.65, the overall life-years gained shown in *Table 17* can be

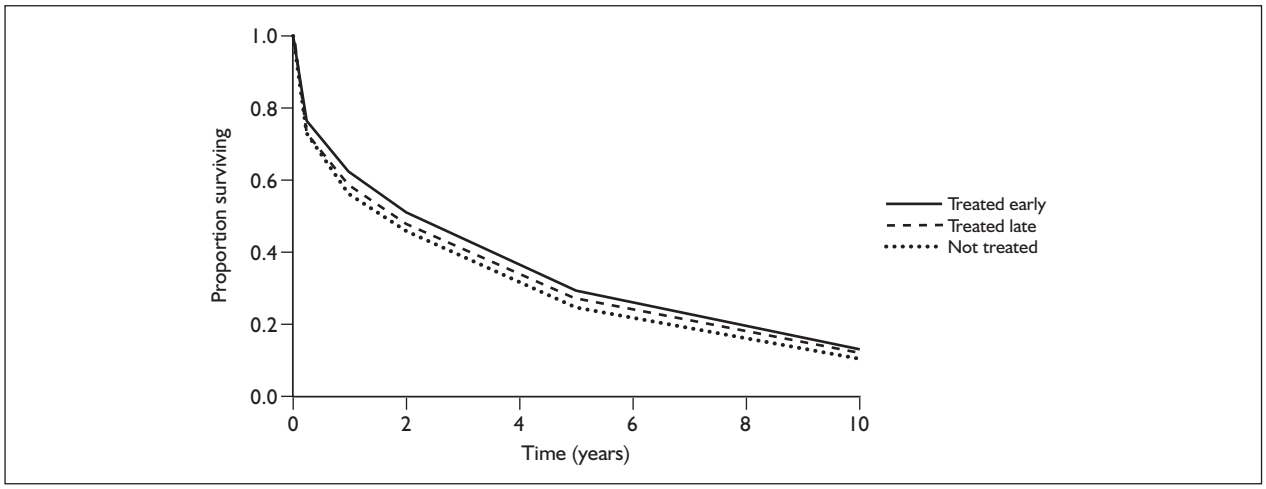

FIGURE 40 *Estimated survival from earlier diagnosis of heart failure if treated with angiotensin-converting enzyme inhibitors.*

TABLE 17 *Estimated increases in survival and quality-adjusted life-years (QALYs) as a result of early diagnosis of heart failure by treatment*

Time horizon (years)	Life-years gained (years)					QALY gain
	Men		Women			
	ACEI	ACEI + BB	ACEI	ACEI + BB	Overall	Overall
3	0.104	0.307	0.113	0.326	0.163	0.106
5	0.150	0.459	0.174	0.511	0.247	0.161
10	0.218	0.697	0.278	0.854	0.390	0.254

ACEI, angiotensin-converting enzyme inhibitor; BB, beta-blocker.

converted to estimates of overall QALY gain: 0.106, 0.161 and 0.254 for the 3-, 5- and 10-year time horizons respectively.

What is the likely reduction in hospitalisation as a result of early detection of heart failure?

From a heart failure incidence study in Bromley,[130] 59% of people with a new diagnosis of heart failure (mean age 75 years) had a subsequent hospital admission over the following 19 months. This is a population who will have received treatment and so the admission rate in the untreated population will be higher. Both beta-blockers and ACE inhibitors reduce admissions by 33%.[124,125]

If we assume that the 'hospital-free survival' curve follows the same pattern (constant odds ratio) as the survival curve for untreated men (*Figure 40*), the chance of going to 19 months without admission to hospital is 0.506 (odds 1.02 in favour of no admission) and to 6 months is 0.677 (odds 2.09). Given that the Bromley data hospital-free survival at 19 months is 0.41 (odds 0.695), this gives an estimated odds at 6 months of $0.695 \times 2.09/1.02 = 1.42$, which gives a probability of 0.587, hence a probability of admission if treated of 0.413. Treatment is estimated to give a relative risk of admission of 0.64[125] and so the estimated rate of admission within 6 months if untreated is $0.413/0.64 = 0.645$.

What are the drug costs from early diagnosis?

Offset against the additional hospitalisation costs from late diagnosis must be the additional drug costs for early diagnosis. These are as follows (source *British National Formulary* (BNF); www.bnf.org, accessed 18 September 2007):

- beta-blocker (carvedilol): £12.30 per month for 34% of patients = £25 per patient
- ACE inhibitor (lisinopril): £2.41 per month for 69% of patients = £10 per patient
- ARB (losartan): £18.09 per month for 16% of patients = £17 per patient.

These combine to give an approximate cost of £50 per patient for early diagnosis if we assume that it results in an additional 6 months of treatment.

How much is it worth paying to detect a case of heart failure?

The WTP per case detected is made up of three consequences of early diagnosis:

- reduced service costs because of reduced risk of hospital admission
- extra drug costs incurred as a result of treatment
- value of 'QALY gain' for early detection.

Reduced service costs because of hospitalisation are estimated on the basis that 23% extra cases (64%–41%) will be admitted within 6 months if untreated (see section above, What is the likely reduction in hospitalisation as a result of early detection of heart failure?). The reference cost for heart failure is £1400 (source NHS reference costs: www.dh.gov.uk, accessed 18 September 2007). This gives a 'per patient' cost of $0.23 \times £1400 = £320$.

Offset against this is the £50 drug cost per patient not incurred.

For the purposes of the model we have used two WTP figures. The first takes into account the cost to the NHS in terms of hospital admissions and drug costs. This gives a WTP of £320–£50 = £270. In other words, each diagnosis of heart failure made will generate £270 of cost savings through reduced admissions taking into account the increased drug costs. Therefore, it is cost neutral to the NHS to spend £270 on diagnosing each new case of heart failure.

We have estimated that the average QALY gain per patient is between 0.106 and 0.254 depending upon the time horizon used (see *Table 17*). Using the lower NICE threshold that a QALY is worth £20,000, this would be valued at between £2100 and £5100 per patient (*Table 18*). Taking into account the cost savings from reduced admissions this gives revised WTP values as shown in *Table 18*.

Methods for heart failure modelling

The cost-effectiveness modelling is based on the decision tree shown in *Figure 41*. Three strategies are compared: 'do nothing', in which no further investigation is made; 'BNP', in which patients are given a BNP test and those whose

TABLE 18 *Willingness to pay (WTP) thresholds incorporating quality-adjusted life-year (QALY) gain from improved life expectancy*

Time horizon (years)	QALY gain	Value of QALY gain	WTP to detect a case[a]
3	0.106	£2100	£2370
5	0.161	£3200	£3470
10	0.254	£5100	£5370

a Value of QALY gain + £270 (savings from reduced admissions less drug costs).

BNP score exceeds a given threshold are then sent on for echocardiography; and 'echo all', in which all patients are referred immediately for echocardiography. The model is run for a patient group defined by a clinical score (the MICE score – see Chapter 8, Simplifying the heart failure prediction model), to produce a preferred option for that score. Running the model for a range of clinical scores then gives a policy of a minimum score for immediate referral for echocardiography, and possibly a minimum score below which BNP testing is not cost-effective.

The outputs of the model are in terms of investigation costs and cases detected. For convenience these are calculated per 1000 patients with any particular clinical score. This produces an incremental cost-effectiveness ratio (ICER) between any two strategies, which is the additional cost per additional case detected in comparing the more effective strategy with the less effective. The ICER is then compared against a threshold that represents the WTP for each additional case found. The WTP is estimated from two viewpoints. In the principal analysis only the NHS costs averted by early detection are considered (including hospital admissions), whereas a sensitivity analysis also includes valuation of the estimated QALYs gained from early detection.

Definition of thresholds for BNP and NT-proBNP

As BNP is a continuous variable, it is necessary to define a BNP threshold above which a particular patient should be referred for echocardiography. By definition, the cost-effective BNP threshold will be the one at which the cost of the echocardiography matches the WTP. If we take the WTP to diagnose a case of heart failure to be £270 (see How much is it worth paying to detect a case of heart failure?), it follows that we would be willing to perform echocardiography up to a cost of £270 to diagnose a case of heart failure. If the cost of an echocardiogram is £100 then we would be willing to accept a probability of heart failure of 100/270 for each case referred, i.e. a post-BNP probability of 0.37. Thus, the BNP cut-off will vary according

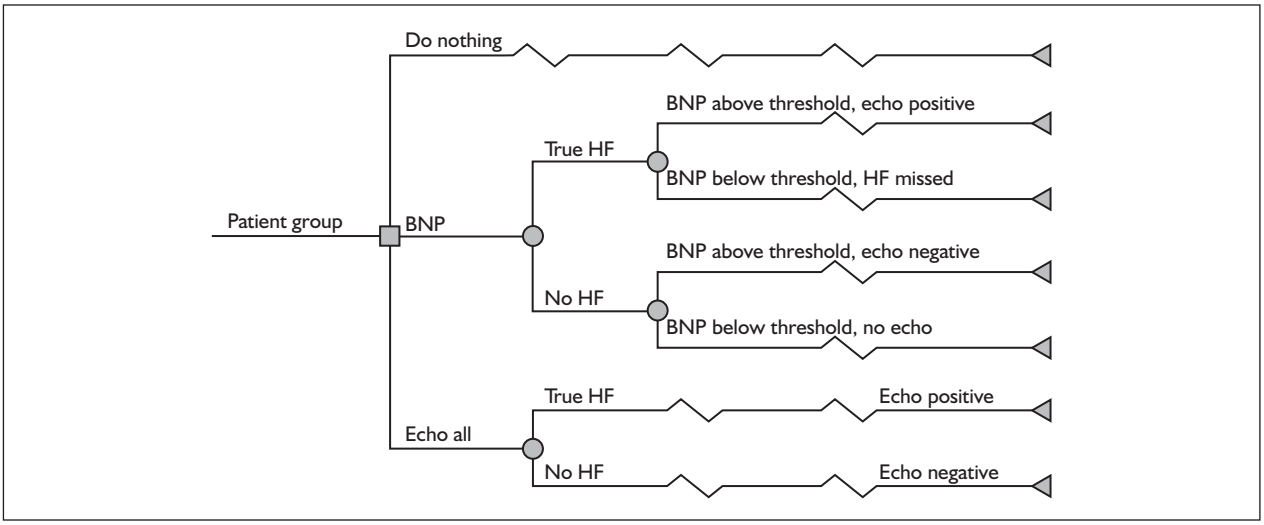

FIGURE 41 *Decision tree for heart failure diagnosis.*

to the pretest probability (i.e. the MICE score) and will be that which will give a post-test probability of 0.37 for a given MICE score. This is the equivalent of post-test odds of 0.588 [0.37/(1–0.37)]. The appropriate cut-off for BNP can be derived from the following formula (which is the equation for the graph shown in *Figure 38*):

$$\text{Ln(odds)} = -6.4855 + 0.242 \times \text{clinscore} + 1.019 \times \ln(\text{BNP}+1)$$

Similarly, the appropriate cut-off for NT-proBNP can be derived from the following formula, which is the equation for the graph shown in *Figure 39*:

$$\text{Ln(odds)} = -7.9412 + 0.2389 \times \text{clinscore} + 0.9367 \times \ln(\text{NTproBNP}+1)$$

This gives the cut-offs for BNP and NT-proBNP by MICE score shown in *Table 19*. These cut-offs are based upon a WTP of £270 per case of heart failure detected. For a different WTP there will be a different optimal post-test probability and therefore different cut-off points (see sensitivity analysis).

Costs of testing for heart failure

For the baseline analysis we took the cost of echocardiography to be £100 per investigation, and the cost of BNP (or NT-proBNP) testing to be £15 per test.

Base-case analysis and sensitivity analyses

For the base-case analysis we used the following inputs:

- cost of echocardiography: £100
- cost of BNP testing: £15
- WTP: £270 per case of heart failure detected
- blood test used: BNP.

Methods of sensitivity analysis

The parameters that go into the model are as follows:

- cost of investigation (namely echocardiography and BNP testing)
- WTP
- test performance of the BNP test
- pretest probability of heart failure.

A probabilistic sensitivity analysis cannot be performed here as the analysis is dependent upon a quantitative variable, BNP, whose cut-off in turn depends upon model parameters. In effect, the true decision problem has a very large number of options, and methods of probabilistic sensitivity analysis are not readily applicable to such problems. Therefore, we have used the approach below to explore the effect of varying all of the model parameters.

The pretest probability of heart failure is already varied in the base-case analysis through the use of the MICE score.

For cost of investigation sensitivity analysis we used an 'extreme case' approach, looking at the extremes in cost that would be most favourable to echocardiography (namely low-cost echocardiography and expensive BNP) and least favourable to echocardiography (high-cost echocardiography and cheap BNP).

With regard to WTP, the base-case analysis used a low value in that it ignored potential benefits in terms of increased life expectancy and quality of life and only took into account potential benefits in terms of reduced hospitalisation. Therefore, the sensitivity analysis explored the impact of increasing this WTP, taking into account increased

TABLE 19 *Cut-off points for BNP and NT-proBNP by MICE score*

	MICE score				
	0	**2**	**3**	**5**	**6**
BNP	490	305	240	149	117
NT-proBNP	1439	900	712	445	352

BNP and NT-proBNP units are pg/ml.

life expectancy due to earlier treatment. We did not take into account improved quality of life as a result of symptom improvement as we felt that this effect would be relatively minor over the short time scale (maximum of 6 months) that we anticipated that treatment could be delayed relative to the effects of emergency admissions avoided and improved survival.

We varied test performance by repeating the analysis using the test performance characteristics for NT-proBNP, which is the principal alternative to BNP that is available.

The actual parameters that we changed were as follows:

- cost of echocardiography: £50–150
- cost of BNP testing: £10–20
- WTP to detect a case of heart failure: up to £5370 per case detected
- blood test used: NT-proBNP.

Results of heart failure modelling

Base-case results ignoring impact on QALYs

As described earlier (see Methods for heart failure modelling), the aim is to compare two possible strategies (performing a BNP test and then performing echocardiography depending upon the result of the BNP test, and performing echocardiography without carrying out a BNP test) with doing nothing. *Table 20* shows the results of the base-case analysis, comparing these different strategies for 1000 patients stratified by MICE score. The sensitivity and specificity data show the test performance for BNP for the given cut-off, and the pre-BNP probability data the pretest probability that corresponds to the MICE score. The next four rows give the additional investigation costs and cases found for the two strategies compared with doing nothing. The next two rows give the incremental costs and benefits (in terms of additional cases found) of moving from a strategy of performing BNP first in all patients to a strategy of performing an echocardiogram on everyone without carrying out a BNP test. The bottom section of the table provides the incremental cost-effectiveness analysis. Thus, for a MICE score of 0, performing a BNP test and then echocardiography only if the BNP score is greater than 490 will result in 32 cases of heart failure detected at a cost of £21,470, i.e. a cost of £669 per case detected. This is more cost-effective than proceeding straight to echocardiography, which costs £1111 per case detected, and the ICER for moving from the strategy of doing BNP first to performing an echocardiograph on everyone is £1356. However, the cost of any of these strategies exceeds the conservative WTP threshold of £270. Therefore, in this case the optimal decision for a MICE score of 0 would be not to investigate the patient (hence decision = no test in bottom row). A similar conclusion is drawn for a MICE score of 2 or 3. However, for a MICE score of 5–8, the ICER for moving from a strategy of doing nothing to a strategy of performing a BNP test first (with echocardiography if the BNP test is 'positive') is below the WTP threshold (hence decision = BNP). For MICE scores above 8, the ICER for moving from a strategy of performing a BNP test first to performing an echocardiogram straight away is below the WTP threshold and so the optimal decision is to proceed straight to echocardiography.

This conservative baseline analysis, which ignores the impact of the early diagnosis of heart failure on improved survival, suggests that use of the MICE score would enable triage of patients with suspected heart failure into three groups:

1. MICE score 0–3 (i.e. men without ankle oedema, basal crepitations or history of myocardial infarction; women without basal crepitations or history of myocardial infarction) – optimal strategy is no investigation unless clinical picture changes.
2. MICE score 5–8 – optimal strategy is to perform a BNP test and refer for echocardiography if the BNP (rounded to two figures) exceeds the following thresholds:
   i. MICE score 5 – refer if BNP > 150 pg/ml
   ii. MICE score 6 – refer if BNP > 120 pg/ml
   iii. MICE score 7 – refer if BNP > 90 pg/ml
   iv. MICE score 8 – refer if BNP > 70 pg/ml.
3. MICE score 9–11 – optimal strategy is to refer straight for echocardiography.

This first analysis used a conservative estimate of WTP that took into account the cost to the NHS (in terms of costs saved through admissions averted and costs spent on investigations) but did not take into account benefits to patients in terms of QALY gain. However, a strategy that is cost neutral is not synonymous with the most cost-effective strategy, as this does need to take into account likely benefits in terms of improvements in survival. Therefore, our next step was to incorporate these benefits into the modelling.

TABLE 20 *Comparison of different heart failure diagnostic strategies by MICE score (base-case decision analysis ignoring impact on quality-adjusted life-years)*

	MICE score									
	0	**2**	**3**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
BNP cut-off (pg/ml)	490	305	240	149	117	92	72	57	45	35
Sensitivity	0.356	0.503	0.583	0.715	0.772	0.821	0.861	0.894	0.919	0.939
Specificity	0.964	0.929	0.897	0.819	0.759	0.689	0.607	0.520	0.431	0.346
Pre-BNP probability	0.09	0.15	0.20	0.31	0.37	0.45	0.52	0.59	0.66	0.72
Strategy 1: BNP test and then echocardiography if BNP +ve										
Additional cost per 1000 patients	£21,470	£28,552	£34,937	£49,663	£58,730	£69,075	£78,635	£87,418	£95,007	£100,902
Additional cases found per 1000 patients	32	76	117	222	286	369	448	527	607	676
Strategy 2: Perform echocardiography on all										
Additional cost per 1000 patients	£100,000	£100,000	£100,000	£100,000	£100,000	£100,000	£100,000	£100,000	£100,000	£100,000
Additional cases found per 1000 patients	90	150	200	310	370	450	520	590	660	720
Consequences of moving from strategy 1 to strategy 2										
Additional cost per 1000 patients	£78,530	£71,448	£65,063	£50,337	£41,270	£30,925	£21,365	£12,582	£4993	–£902
Additional cases found per 1000 patients	58	74	83	88	84	81	72	63	53	44
Incremental cost-effectiveness analysis										
ICER (echo vs BNP)	£1356	£959	£780	£570	£490	£384	£296	£200	£94	Echo[a]
ICER (echo vs nothing)	£1111	£667	£500	£323	£270	£222	£192	£169	£152	£139
ICER (BNP vs nothing)	£669	£378	£300	£224	£206	£187	£176	£166	£157	£149
Decision	No test	No test	No test	BNP	BNP	BNP	BNP	Echo	Echo	Echo

Echo, echocardiography; ICER, incremental cost-effectiveness ratio.

a In this case echocardiography dominates BNP. This is because so many patients would be referred for echocardiography that the cost of BNP tests for all exceeds the cost of the small number of echocardiograms avoided.

TABLE 21 *Sensitivity analysis incorporating the impact of quality-adjusted life-year gain on decision analysis (willingness to pay £2370, time horizon 3 years)*

	MICE score				
	0	**2**	**3**	**5**	**6**
BNP cut-off (pg/ml)	38	23	18	11	8
Sensitivity	0.934	0.963	0.972	0.985	0.988
Specificity	0.370	0.223	0.168	0.090	0.067
Pre-BNP probability	0.09	0.15	0.2	0.31	0.37
Strategy 1: BNP test and then echocardiography if BNP +ve					
Additional cost per 1000 patients	£80,742	£95,458	£101,029	£108,311	£110,316
Additional cases found per 1000 patients	84	144	194	305	366
Strategy 2: Perform echocardiography on all					
Additional cost per 1000 patients	£100,000	£100,000	£100,000	£100,000	£100,000
Additional cases found per 1000 patients	90	150	200	310	370
Consequences of moving from strategy 1 to strategy 2					
Additional cost per 1000 patients	£19,258	£4542	–£1029	–£8311	–£10,316
Additional cases found per 1000 patients	6	6	6	5	4
Incremental cost-effectiveness analysis					
ICER (echo vs BNP)	£3227	£810	Echo[a]	Echo[a]	Echo[a]
ICER (echo vs nothing)	£1111	£667	£500	£323	£270
ICER (BNP vs nothing)	£961	£661	£520	£355	£302
Decision	BNP	Echo	Echo	Echo	Echo

Echo, echocardiography; ICER, incremental cost-effectiveness ratio.
a In this case, echocardiography dominates BNP. This is because so many patients would be referred for echocardiography that the cost of BNP tests for all exceeds the cost of the small number of echocardiograms avoided.

Impact of incorporating estimate of QALY gain on results of model

For our base-case WTP calculation incorporating QALY gain we used a 3-year time horizon (i.e. the length of time following diagnosis that we took into account the estimated QALY gain). With this conservative time horizon of 3 years, the strategy of performing an echocardiography on all patients came out as the preferred option for all MICE scores greater than 0 (*Table 21*).

It can be seen that, even with this conservative estimate of QALY gain, the BNP cut-off values are low and so in the 'BNP first' strategy the majority of patients would be referred for echocardiography. Indeed, for MICE scores of 3 or more, echocardiography dominates the 'BNP first' strategy, being both less expensive and more effective. For a MICE score of 0, the ICER of £3227 is above the threshold for WTP of £2950 and so this low pretest probability of heart failure is the only circumstance in which BNP before echocardiography is the preferred option.

Chapter 10

Analysis of the robustness of the model results (sensitivity analyses)

Impact of changing the costs of investigation

In the baseline analysis the cost of echocardiography was set at £100 and BNP testing at £15. We conducted sensitivity analyses looking at the impact of changing these costs. Two cases are considered: one most favourable to echocardiography, in which the echocardiography cost is lowered and the BNP cost raised; and the other least favourable to echocardiography, in which the echocardiography cost is raised and the BNP cost lowered.

Most favourable to echocardiography ignoring impact on QALYs

In this case the cost of echocardiography is set at £50 and the cost of BNP at £20. The results are shown in *Table 22*. The optimal BNP cut-offs are lower because of the lower costs of echocardiography. As a result, many more patients are referred for echocardiography. In the case of MICE scores of 5 or more it is now both less expensive and more effective to refer everyone straight to echocardiography because the cost

TABLE 22 *Sensitivity analysis most favourable to echocardiography ignoring impact on quality-adjusted life-years*

	MICE score				
	0	**2**	**3**	**5**	**6**
BNP cut-off (pg/ml)	192	119	94	58	45
Sensitivity	0.645	0.769	0.818	0.892	0.918
Specificity	0.869	0.764	0.694	0.526	0.437
Pre-BNP probability	0.09	0.15	0.20	0.31	0.37
Strategy 1: BNP test and then echocardiography if BNP +ve					
Additional cost per 1000 patients	£28,869	£35,783	£40,418	£50,175	£54,703
Additional cases found per 1000 patients	58	115	164	276	339
Strategy 2: Perform echocardiography on all					
Additional cost per 1000 patients	£50,000	£50,000	£50,000	£50,000	£50,000
Additional cases found per 1000 patients	90	150	200	310	370
Consequences of moving from strategy 1 to strategy 2					
Additional cost per 1000 patients	£21,131	£14,217	£9582	–£175	–£4703
Additional cases found per 1000 patients	32	35	36	34	31
Incremental cost-effectiveness analysis					
ICER (echo vs BNP)	£661	£410	£263	Echo[a]	Echo[a]
ICER (echo vs nothing)	£556	£333	£250	£161	£135
ICER (BNP vs nothing)	£498	£310	£247	£182	£161
Decision	No test	No test	Echo	Echo	Echo

Echo, echocardiography; ICER, incremental cost-effectiveness ratio.
a In this case, the strategy of performing echocardiography on all is less expensive and identifies more cases of heart failure. Echocardiography therefore dominates BNP.

of all the BNP tests exceeds the cost of the small number of echocardiograms avoided. For a MICE score of 3, the ICER for proceeding straight to echocardiography falls below the WTP threshold. For a MICE score of 0 and 2, no investigation remains the preferred option.

Least favourable to echocardiography ignoring impact on QALYs

Here the cost of echocardiography is set at £150 and the cost of BNP at £10. The results are shown in *Table 23*. The BNP cut-offs are now higher because of the increased cost of echocardiography. In this case the results up to a MICE score of 8 are the same as in the base case (apart from the higher BNP cut-offs), i.e. no investigation for a MICE score of 3 or less; BNP and then echocardiogram if BNP positive at higher MICE values. However, BNP first is now favoured up to and including a MICE score of 11, with echocardiography first favoured only for MICE scores of 13, 14 or 16. Therefore, the table has been extended to show higher MICE scores.

Impact of changing time horizon (i.e. changing QALY gain)

For the base-case analysis that incorporated QALY gain, referral for echocardiography was the preferred strategy for all patients except those with a MICE score of 0. As the time horizon extends, these benefits of echocardiography become greater.

We tested the robustness of this conclusion by repeating the sensitivity analysis on costs but this time using the WTP derived from incorporating QALYs. Because echocardiography came out as the preferred option for all MICE scores other than 0 in the base-case analysis incorporating QALYs, we have not reported the impact of lowering the cost of echocardiography as this would inevitably reach the same conclusion. When raising the cost of echocardiography and lowering the cost of BNP has led to a change in the conclusion, we have also looked at the longer time horizons. The results of this analysis are shown in *Table 24*.

The conclusion that echocardiography is the preferred initial investigation if the impact of early diagnosis on QALYs is taken into account is robust to increasing the cost of echocardiography (and lowering the cost of BNP) at all MICE scores except 0, 2 and 3. At a score of 0, BNP first is the preferred strategy regardless of the time horizon used, whereas the optimal decision changes back to echocardiography at a score of 3 if a 5-year or longer time horizon is used, and at a score of 2 if a 10-year time horizon is used.

Impact of using NT-proBNP

Finally, we repeated all of the analyses using test performance data for NT-proBNP rather than for BNP. The results were the same as for BNP.

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TABLE 23 *Sensitivity analysis least favourable to echocardiography ignoring impact on quality-adjusted life-years*

MICE score	0	2	3	5	6	7	8	9	10	11	13	14	16
BNP cut-off (pg/ml)	1029	639	504	313	247	194	153	120	95	75	46	36	22
Sensitivity	0.178	0.283	0.348	0.495	0.575	0.642	0.708	0.766	0.816	0.857	0.917	0.937	0.964
Specificity	0.988	0.976	0.966	0.932	0.900	0.871	0.825	0.767	0.697	0.617	0.441	0.356	0.213
Pre-BNP probability	0.09	0.15	0.20	0.31	0.37	0.45	0.52	0.59	0.66	0.72	0.83	0.86	0.92
Strategy 1: BNP test and then echocardiography if BNP +ve													
Additional cost per 1000 patients	£14,048	£19,476	£24,577	£40,089	£51,341	£63,986	£77,828	£92,125	£106,205	£118,641	£138,361	£144,394	£152,546
Additional cases found per 1000 patients	16	42	70	154	213	289	368	452	539	617	761	806	887
Strategy 2: Perform echocardiography on all													
Additional cost per 1000 patients	£150,000	£150,000	£150,000	£150,000	£150,000	£150,000	£150,000	£150,000	£150,000	£150,000	£150,000	£150,000	£150,000
Additional cases found per 1000 patients	90	150	200	310	370	450	520	590	660	720	830	860	920
Consequences of moving from strategy 1 to strategy 2													
Additional cost per 1000 patients	£135,952	£130,524	£125,423	£109,911	£98,659	£86,014	£72,172	£57,875	£43,795	£31,359	£11,639	£5606	–£2546
Additional cases found per 1000 patients	74	108	130	156	157	161	152	138	121	103	69	54	33
Incremental cost-effectiveness analysis													
ICER (echo vs BNP)	£1837	£1214	£962	£702	£627	£533	£475	£420	£361	£305	£168	£103	Echo[a]
ICER (echo vs nothing)	£1667	£1000	£750	£484	£405	£333	£288	£254	£227	£208	£181	£174	£163
ICER (BNP vs nothing)	£878	£458	£353	£261	£241	£222	£211	£204	£197	£192	£182	£179	£172
Decision	No test	No test	No test	BNP	BNP	BNP	BNP	BNP	BNP	BNP	Echo	Echo	Echo

Echo, echocardiography; ICER, incremental cost-effectiveness ratio.

a In this case, echocardiography dominates BNP. This is because so many patients would be referred for echocardiography that the cost of BNP tests for all exceeds the cost of the small number of echocardiograms avoided.

TABLE 24 *Sensitivity analysis incorporating quality-adjusted life-year gain and using costs least favourable to echocardiography*

	MICE score				
	0	**2**	**3**	**5**	**6**
Time horizon 3 years, WTP £2370					
BNP cut-off (pg/ml)	58	36	28	17	13
Incremental cost-effectiveness analysis					
ICER (echo vs BNP)	£6488	£3882	£2605	£915	£273
ICER (echo vs nothing)	£1667	£1000	£750	£484	£405
ICER (BNP vs nothing)	£1083	£809	£659	£472	£408
Decision	BNP	BNP	BNP	Echo[a]	Echo[a]
Time horizon 5 years, WTP £3470					
BNP cut-off (pg/ml)	39	24	18		
Incremental cost-effectiveness analysis					
ICER (echo vs BNP)	£6934	£3491	£2017		
ICER (echo vs nothing)	£1667	£1000	£750		
ICER (BNP vs nothing)	£1281	£900	£712		
Decision	BNP	BNP	Echo[a]		
Time horizon 10 years, WTP £5370					
BNP cut-off (pg/ml)	24	15			
Incremental cost-effectiveness analysis					
ICER (echo vs BNP)	£6409	£2231			
ICER (echo vs nothing)	£1667	£1000			
ICER (BNP vs nothing)	£1469	£972			
Decision	BNP	Echo[a]			

Echo, echocardiography; ICER, incremental cost-effectiveness ratio; WTP, willingness to pay.
a Echocardiography all dominant over BNP first strategy.

Chapter 11
Discussion

Symptoms and signs of heart failure

The systematic review identified a number of symptoms and signs that were potentially helpful in the diagnosis of heart failure. Only one of these (dyspnoea) had a sensitivity over 80%. A number were reasonably specific, including history of myocardial infarction (89%), orthopnoea (89%), cardiomegaly (85%), added heart sounds (99%), lung crepitations (81%) and hepatomegaly (97%). In primary care the most potentially useful symptoms/signs in this context would be those with high sensitivity, as this might enable the clinician to rule out heart failure, if the symptom/sign was absent, without the need to refer for further investigation. Dyspnoea is the only clinical feature that comes close to this category with a sensitivity of 87%. As observed in the IPD analysis, in practice this symptom is present in the majority of patients in whom heart failure is suspected, with a frequency as high as 95% in one of the data sets.[88] Nevertheless, a sensitivity of 87% is not high enough to rule out heart failure if dyspnoea is absent.

Symptoms and signs with high specificity are useful for making a positive diagnosis, but their absence does not mean that the diagnosis can be excluded. Therefore, in the primary care context, clinical features of high specificity are of less value. A second factor is that the highly specific signs – added heart sounds and hepatomegaly – are not picked up reliably, even by specialists. For example, in a study of three clinicians examining 80 patients after myocardial infarction,[115] the agreement as measured by the kappa co-efficient was low, ranging from 0–0.16 for hepatomegaly to 0.14–0.37 for a gallop rhythm.

In practice, clinicians do not interpret symptoms and signs in isolation, but rather in the context of the overall clinical picture. The IPD analysis validated a model for diagnosing heart failure based on clinical features that had been derived from the UK BNP study.[88] A clinical model based upon the combination of gender, age, past history of myocardial infarction, presence of ankle oedema and presence of basal crepitations was found to have reasonable predictive validity, with the AUC ranging from 0.66 to 0.79 in the five data sets in which it could be validated. Although breathlessness had been identified from the systematic review as the symptom with the highest sensitivity, it was not included in the clinical model. This was because its prevalence was very high (95%) in the derivation data set, reflecting how often breathlessness is the presenting symptom of heart failure. Nevertheless, the model worked equally well in populations with a lower prevalence of breathlessness. The Cost[97] and Wright *et al*.[87] data sets had the lowest proportions of people with breathlessness (24% and 46% respectively; see *Table 5*) and had AUCs of 0.73 and 0.79, which are similar to the AUC of 0.76 achieved in the Zaphiriou *et al*.[88] derivation data set (*Table 7*). We explored whether adding breathlessness back into the full model (i.e. including BNP or NT-proBNP) would improve its overall accuracy, but we found that this was not the case, with the odds ratio for heart failure in the presence of breathlessness not being significantly greater than 1 once adjusted for the other clinical features and BNP score in the three data sets for which we could provide robust estimates (see *Table 11*). This may reflect the close correlation between factors already in the model, such as basal crepitations, and this symptom, so that, although in univariate analysis (as demonstrated in the systematic review) it was an important predictive symptom, it was less so when its diagnostic value was adjusted for these other factors.

Investigations for heart failure

The systematic review confirmed that ECG and BNP (or NT-proBNP) have high sensitivity for heart failure, and that CXR abnormalities are reasonably specific for heart failure. A problem with ECG reading in primary care is that the high sensitivity obtained when an ECG is read by a cardiologist or by automated reading may be lost if it is read by a GP.[95] However, it is clear that many GPs can detect relevant abnormalities accurately[96] and so the key issue may be one of quality assurance of the ECG reading.[74]

There are a number of different BNP assays available but we found no evidence of superiority of any one assay (BNP or NT-proBNP) over another.

The IPD analysis explored the value of ECG and BNP in addition to clinical features in the diagnosis of heart failure. We found that the best results were obtained when BNP testing was combined with clinical features. BNP plus clinical features performed better than ECG plus clinical features. Therefore, if BNP is available then ECG is not necessary as a screening investigation for heart failure.

Strengths and weaknesses of the systematic review

The report has synthesised all available published data on the diagnosis and investigation of heart failure, including data on symptoms, signs, ECG, CXR and the natriuretic peptides. The main focus of the report has been on the diagnostic accuracy of these tests for the diagnosis of heart failure, using clinical criteria such as the ESC criteria, rather than for the diagnosis of LVSD. The results of studies that investigated the diagnostic accuracy of these tests for the diagnosis of LVSD are shown in Appendix 4. This approach was taken as many patients who present with heart failure requiring further investigation and management in the primary care setting will have preserved systolic function. However, the lack of an objective and universally agreed definition for the reference standard and variability in the way that the reference standard is applied introduce uncertainty into the estimate of the diagnostic accuracy of the tests and increase the heterogeneity of the results.

As the main purpose of the report was to provide assistance for the diagnosis of heart failure in the primary care setting, we have included a prespecified subgroup analysis of those studies that examined the diagnostic accuracy of ECG, CXR and natriuretic peptides for the diagnosis of heart failure in general practice, those referred from general practice, and in accident and emergency and hospital and outpatient settings. There were no differences in the diagnostic accuracy of each of the investigations observed between the clinical settings.

There was considerable heterogeneity in the estimates of sensitivity and specificity for many of the individual clinical features. This is likely to reflect the poor reliability of some of the signs and the varying definitions of the symptoms/signs used in the studies. For example, with the symptom of breathlessness, the more restrictive definitions led to higher specificity and lower sensitivity. Statistical tests of heterogeneity were not used as they may be misleading in the context of systematic reviews of the accuracy of diagnostic tests and they are not supported by the Cochrane diagnostic test accuracy working group.

Development of a simple clinical tool

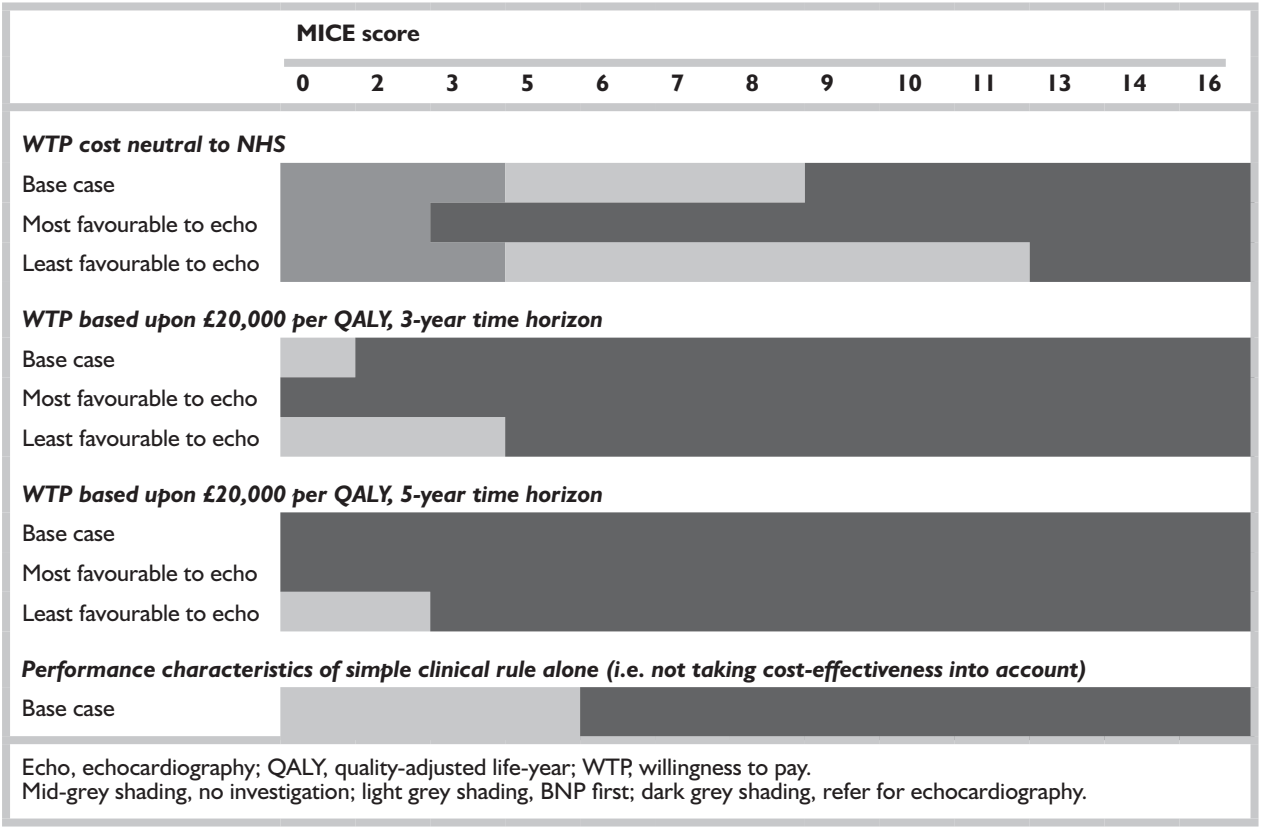
For a tool to be useful in clinical practice it needs to be straightforward to apply. A potential use of the clinical tool would be to discriminate between patients who had a sufficiently high probability of heart failure that they should be referred for echocardiography and those who should have further investigation before proceeding (or not) to echocardiography. A simplification of the model developed by the IPD analysis led to a simple rule:

- in a patient presenting with symptoms in whom heart failure is suspected, refer straight for echocardiography if the patient has any one of:
  - history of myocardial infarction
  - basal crepitations
  - ankle oedema in a male patient
- otherwise carry out a BNP test and refer to echocardiography depending on the results of the test.

Cost-effectiveness of this clinical rule

We tested the cost-effectiveness of this clinical rule by determining the optimum decision points at which to perform a BNP test and/or refer for echocardiography by using a decision analysis based upon willingness to pay (WTP). We used two approaches to WTP. One was highly conservative and assumed that the diagnostic strategy should be cost neutral, with costs of diagnosis offset by savings in terms of admissions avoided as a result of diagnosis. The second approach also took into account the impact that earlier diagnosis would have on survival, using an assumed WTP of £20,000 per QALY gained. This is the threshold that is likely to be considered cost-effective within the NHS, as this is the threshold adopted by NICE. A summary of the results is shown in *Table 25*. For comparison, the simple clinical tool that was developed purely on the basis of its performance characteristics (i.e. not taking cost-effectiveness into account) is shown at the foot of the table.

TABLE 25 *Summary of the results of modelling of the cost-effectiveness of different strategies for the diagnosis of heart failure*



Echo, echocardiography; QALY, quality-adjusted life-year; WTP, willingness to pay.
Mid-grey shading, no investigation; light grey shading, BNP first; dark grey shading, refer for echocardiography.

Key points to make are:

1. The conclusions of the modelling are sensitive to the assumptions made. If the aim was a cost-neutral strategy for the NHS there were some scenarios in which it was appropriate at low MICE scores (i.e. scores of 3 or less, which correspond to a pretest probability of up to 20%) not to investigate further.
2. However, for a cost-effectiveness analysis it is important to take into account the likely impact of early diagnosis on survival. If this is taken into account then the analysis suggests that virtually all patients with suspected heart failure should be referred straight for echocardiography.
3. When BNP (or NT-proBNP) testing is used it is important to take into account the clinical features (i.e. the MICE score) in interpreting the result, as the appropriate cut-off points vary by MICE score.

The simple decision rule that was derived in Chapter 8 sits fairly centrally within the bounds of the modelling in that it falls between the highly conservative analysis based upon a WTP that is cost neutral to the NHS and a WTP that is based upon £20,000 per QALY.

Strengths and weaknesses of the individual patient data analysis

The quality of an IPD analysis is determined both by the willingness of authors to make data sets available and by the definitions of key fields used in the analysis. Our group had authorship of a number of the original data sets and the majority of our colleagues made their data available. We have attempted to eliminate any bias in characterisation of fields by applying, when data were available, a common definition of heart failure, ensuring that peptides were converted to standard units (pg/ml) when necessary and using a consistent classification of an abnormal ECG across data sets when possible.

The clinical rule was developed on a breathless population and therefore designed for use on patients presenting with shortness of breath, which is the most common presentation of

heart failure. However the external validation provides evidence of its discriminatory ability across populations of varying prevalence of breathlessness and therefore it could be used in patients presenting with any symptom of heart failure. Included clinical variables, although elicited by cardiologists in the original studies, are either 'yes/no' clinical history items (gender and previous medical history of myocardial infarction) or straightforwardly ascertained examination points (oedema and crepitations) and so should be transferable to a primary care setting. Nomograms, although novel for BNP interpretation, are commonly used in primary care, for example in the cardiovascular risk charts printed in the back of the BNF. The nomogram could be used by the clinician to estimate the post-test probability of heart failure for a given BNP result. Alternatively, simply the 'cut-off' values for BNP for referral for echocardiography as derived from the decision analysis could be used (for instance by incorporation into standard laboratory results), without need of the nomogram.

There is no 'gold standard' test for all cases of heart failure, particularly in cases of heart failure with preserved ejection fraction. We used the ESC criteria for heart failure, namely appropriate symptoms plus objective evidence of cardiac dysfunction. It is reassuring that the validation and calibration results for the clinical rule across different data sets was reasonably good, despite the subjective nature of the ESC criteria. We could have restricted ourselves to cases with a low ejection fraction, for which echocardiography is an agreed reference standard. However, from the perspective of diagnosis in primary care this would have limited the utility of the approach, as the general practitioner needs to ensure that a diagnosis is made in all patients with suspected heart failure and thus needs to know who should be referred for further investigation (regardless of whether the underlying diagnosis is low ejection fraction heart failure).

The calibration plots indicate that, with the exception of the Cost[97] data, the clinical rule gives reasonably accurate estimates of the probability of heart failure at the lower end of the probability scale. It is in this area of the scale, where primary care patients typically present, that GPs would benefit the most with help in determining whether a patient might have heart failure and should undergo further tests. The variability across the BNP calibration plots could be due to differences between the tests, in particular laboratory versus near patient tests and differing coefficients of variation. The use of the lower prevalence studies to validate the clinical rule also increases the face validity of the results as studies relying on GP referral to secondary care are inevitably adding a 'filter' as opposed to the undifferentiated person with breathlessness who might be considered the typical diagnostic issue for heart failure in primary care.

We were unable to pool individual-level data sets because of evidence of heterogeneity between them. The characteristics that were found to alter the performance of the measurement of plasma concentration of natriuretic peptides were from studies of non-incident participants and may therefore reflect the case selection. The few significant effect modifiers that we identified are likely to reflect spurious effects given the multiple statistical tests that we performed. Indeed, interactions were no longer significant when the Bonferroni adjustment was applied to the probabilities. Therefore, we found no evidence that the test performance of BNP or NT-proBNP is significantly influenced by factors such as age, gender or co-existent disease.

There is a lack of methodology published in the area of IPD meta-analysis in diagnostic testing and further research is therefore warranted in this area.

Strengths and weaknesses of the decision analysis

Not surprisingly there have been no clinical trials to determine the clinical impact of early diagnosis of heart failure and so our estimate of the likely benefit of diagnosis has to be to some extent speculative. In particular, it is difficult to estimate for how long the diagnosis of heart failure will be delayed if it is not made at presentation. In the decision analysis we assumed that if a patient was not referred for echocardiography then the diagnosis would be made after an average delay of 6 months if the patient did not die or was not admitted to hospital before that time interval. There are no data on which to base such an assumption. If the time delay is shorter, the WTP to diagnose a case of heart failure would be reduced. However, in our cost-effectiveness analysis we adopted a conservative time horizon of 3 years. In other words, we did not take into account survival benefits that would be anticipated more than 3 years after diagnosis, although we estimated (see *Figure 40*) that there would be some residual benefit beyond this time. Therefore, despite the inherent limitations of the modelling, it is unlikely that the

general conclusion that echocardiography would be the preferred option for investigation would be overturned. The likelihood is that benefits from early diagnosis are greater than we assumed.

We did not take into account waiting lists for echocardiography, and the model assumed that there was sufficient capacity. In reality in the NHS this is not the case. Recent data from the Healthcare Commission[128] show that 72% of patients referred for echocardiography receive the investigation within 13 weeks. If we built in a 13-week delay to echocardiography this would nullify much of the benefit of early diagnosis.

Costs of BNP tests vary by manufacturer. Nevertheless, we found that the conclusions of our decision analysis were robust to significant changes in the costs of BNP tests and echocardiography. Even in the circumstance most adverse to echocardiography, the cost-effectiveness analyses incorporating quality of life showed that the threshold for referral straight to echocardiography only increased to a clinical score of 5, but the BNP cut-point for referral in these circumstances was low, with a cut-point varying from 17 to 58 pg/ml.

The decision analysis was based upon the assumption that all patients with a diagnosis of heart failure should proceed to echocardiography to inform the diagnosis and provide information on the underlying cause of the heart failure. It is recognised that alternative 'reference standard' investigations might become available/be used, but at the current time our use of echocardiography reflects standard practice, as reflected in the NICE guideline.[50] Furthermore, it is recognised that BNP analysis is increasingly being used as a test with diagnostic value in its own right, independent of the results of echocardiography. For example, heart failure with preserved ejection fraction may have normal echocardiography findings but abnormal BNP. However, this does not remove the need for echocardiography in a patient with abnormal BNP and so does not affect the overall conclusions of this review.

Other recent systematic reviews

Our systematic review findings are broadly consistent with those of other systematic reviews in this area that have been recently published. Khunti and colleagues[71] reviewed four studies that had evaluated the diagnostic accuracy of ECG in the specific context of referral from primary care to echocardiography. They found that sensitivity in these studies varied from 73% to 91% and concluded therefore that the ECG was an inadequate screening tool. Davenport and colleagues[131] reviewed the diagnostic accuracy of natriuretic peptides and ECG in the diagnosis of LVSD and found similar diagnostic accuracy between ECG, BNP and NT-proBNP and no value from combining BNP with ECG. Although we found no value from combining BNP with ECG, we did find evidence that BNP was superior to ECG in both the systematic review and the IPD analysis. Davenport identified two studies [132,133] that provided data evaluating the combination of BNP and ECG. One of these[132] was excluded from our review because the index test was deemed inappropriate (the ECG abnormality was simply prolonged QRS duration) and the other[133] because the reference standard was assessment of LVSD and not heart failure. We found four studies that had data on both ECG and BNP, but only one of these had published the data.[90] The remaining three[82,84,88] provided us with the relevant data so that we could perform the calculations. It is likely that BNP is a more accurate test for heart failure than it is for LVSD. Indeed, a recent systematic review[134] of BNP studies concluded that, although BNP is useful for excluding heart failure, it is more limited for ruling out systolic dysfunction, with an AUC of 0.93 for heart failure but only 0.75 for systolic dysfunction. Clerico and colleagues,[135] like our review, found no evidence of any significant differences in test performance between BNP and NT-proBNP. Other recent reviews of BNP have confirmed its value as a 'rule out' test for heart failure.[136–138]

Interpretation of the research findings in the context of the NHS

The current NICE guideline for heart failure recommends that, in patients with suspected heart failure, a 12-lead ECG and/or a BNP or NT-proBNP test should be performed to exclude heart failure, and only those patients with a positive ECG or BNP should proceed to echocardiography. The systematic review and the IPD analysis have demonstrated that, when taken in combination with clinical features, BNP (or NT-proBNP) is superior to ECG, and performing ECG adds nothing if a BNP test has been performed. The IPD analysis has further demonstrated that a simple clinical score (the MICE score – male 2 points, infarction 6 points, crepitations 5 points, oedema 3 points) can usefully predict the presence of heart failure. On the basis of the test

performance of BNP it was possible to provide a rational strategy by which patients should proceed straight to echocardiography, namely if their MICE score was 5 or more, they should be referred straight for echocardiography, otherwise they should have a BNP test first with referral for echocardiography dependent upon the results of the BNP test. Thus, the analysis we have performed points to the need for important changes to the NICE recommendations. First, BNP (or NT-proBNP) should be recommended over ECG and, second, some patients should be referred straight for echocardiography without undergoing any preliminary investigation. Therefore, BNP (or NT-proBNP) testing should be available in primary care.

The third part of our research, the decision analysis, sought to refine these conclusions by considering cost-effectiveness. Our base-case analysis took into account the cost to the NHS. We estimated that missing a case of heart failure would on average cost the NHS £270 in terms of avoidable hospital admissions, and therefore assumed that the NHS would be willing to pay at least this amount of money to diagnose a new case of heart failure. We then estimated how much the NHS would be willing to pay if we also took into account the impact of improved survival from earlier diagnosis, valuing an additional QALY at £20,000. From these analyses the simple decision rule that we developed is likely to be considered cost-effective as it sits fairly centrally within the bounds of these two analyses. However, the analysis also suggested that the preferred option may be to refer virtually all patients with suspected heart failure straight for echocardiography without undergoing preliminary BNP testing, given that this strategy falls within a WTP threshold that takes into account likely improved survival resulting from earlier diagnosis.

The reality of availability of echocardiography services in the NHS means that referral of all patients straight to echocardiography may not be an immediately viable option. Furthermore, it is not likely to be an option in the near future because of the implications for both training and service provision. In this context the strategy of using the MICE score to determine who should be referred straight to echocardiography and who should be referred after a BNP test has been performed is an attractive option in that it is more cost-effective than current recommended practice and will make less demand on already overstretched echocardiography services than referring all patients straight for echocardiography. If this strategy is adopted, then the question remains of what should be the appropriate cut-points for BNP (or NT-proBNP). It is clear from our analysis that the cut-points should take into account the underlying risk of heart failure (i.e. the MICE score). Given that the rationale for using the MICE score in this instance would be to make optimal use of a scarce resource, it follows that a rational cut-point could be determined by the proportion of patients referred for echocardiography who turn out to have heart failure (i.e. the post-BNP probability). *Table 26* shows what these cut-points would be for different post-test probabilities for BNP and NT-proBNP using the methodology described in Chapter 9 (see Methods for heart failure modelling) and adjusting the WTP to obtain the desired post-test probability. Thus, applying the clinical decision rule, for a MICE score of 0, the appropriate cut-point for BNP might lie between 210 pg/ml (in which case one in five people referred to echocardiography would have heart failure) and 360 pg/ml (in which case three in ten people referred would have heart failure).

TABLE 26 *Cut-points for BNP and NT-proBNP for different post-test probabilities*

		MICE score		
Post-test probability	**Test[a]**	**0**	**2**	**3**
30%	BNP	360	220	180
	NT-proBNP	1060	660	520
25%	BNP	280	170	140
	NT-proBNP	820	510	410
20%	BNP	210	130	100
	NT-proBNP	620	390	190

a Units for BNP and NT-proBNP are pg/ml.

Chapter 12
Conclusions

- A number of symptoms and signs are of some diagnostic value in the clinical assessment of a patient with suspected heart failure. Dyspnoea is the symptom with the highest sensitivity, but it is not sufficiently high that heart failure can be ruled out in its absence.
- ECG, BNP and NT-proBNP all have high sensitivity for heart failure.
- Head-to-head studies identified for the systematic review suggest that BNP is a more accurate investigation than ECG. This was confirmed by the IPD analysis.
- There was no evidence from either the systematic review or the IPD analysis that performing both BNP and ECG led to improved diagnosis of heart failure.
- There was no evidence of any significant differences in accuracy between different BNP assays.
- There was no evidence of any significant differences in accuracy between BNP and NT-proBNP assays from the systematic review.
- There was no evidence from the IPD analysis of any effect modification of patient characteristics on the performance of BNP or NT-proBNP testing.
- A simple clinical score based upon gender, history of myocardial infarction, presence of oedema and presence of basal lung crepitations can usefully discriminate between people with suspected heart failure who should be referred straight for echocardiography and people for whom referral should depend upon the result of a BNP test.
- This score can be simplified to a simple decision rule proposed by the authors (*Box 2*).
- On the basis of the analysis carried out, such a decision rule is likely to be considered cost-effective to the NHS
- The cost-effectiveness analysis further suggested that, if patient benefit in terms of improved life expectancy was taken into account, the optimum strategy would be to refer all patients with symptoms suggestive of heart failure for echocardiography.

Implications for health care

- The analysis that we have performed points to the need for important changes to the NICE recommendations. First, BNP (or NT-proBNP) should be recommended over ECG and, second, some patients should be referred straight for echocardiography without undergoing any preliminary investigation.
- Therefore, natriuretic peptide testing should be available in primary care.
- If there is sufficient local capacity, the evidence synthesised here suggests that many

BOX 2 *Simple clinical rule*

In a patient presenting with symptoms in whom heart failure is suspected, refer straight to echocardiography if the patient has any one of:

- history of myocardial infarction
- basal crepitations
- male patient with ankle oedema

Otherwise, carry out a BNP test and refer for echocardiography depending on the result of the test:

- female patient without ankle oedema – refer for echocardiography if BNP > 210–360 pg/ml depending on local availability of echocardiography (or NT-proBNP > 620–1060 pg/ml)
- male patient without ankle oedema – refer for echocardiography if BNP > 130–220 pg/ml (or NT-proBNP > 390–660 pg/ml)
- female patient with ankle oedema – refer for echocardiography if BNP > 100–180 pg/ml (or NT-proBNP > 190–520 pg/ml)

patients with symptoms indicating possible heart failure should be referred straight for echocardiography.
- In the presence of a limited supply of echocardiography, the authors suggest the following:
  - patients with symptoms suggestive of heart failure such as breathlessness should be referred straight for echocardiography only if they have a history of myocardial infarction or if they have basal crepitations on examination or if they are male with ankle oedema
  - otherwise, they should have a BNP test performed and the decision to refer for echocardiography should depend upon the BNP result interpreted in the light of their gender and the presence/absence of ankle oedema.
- There is no need to perform an ECG as part of the assessment of whether or not heart failure is present (although it is recognised that there may be other indications for performing an ECG).

Recommendations for research

- Evaluation of the diagnostic value of repeated BNP measurements for the diagnosis of heart failure.
- Evaluation of the diagnostic accuracy of automated ECG readings in the diagnosis of heart failure.
- Evaluation of the usability of the clinical rule described above in clinical practice.
- Development of methods to conduct IPD meta-analysis for diagnostic tests.

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Contribution of authors

Jonathan Mant (Professor of Primary Care Stroke Research) was the lead investigator for the study, supported the conduct of the IPD analysis and the economic analysis, and was responsible for editing the final draft. Jenny Doust (Associate Professor of General Practice) led the systematic review. Andrea Roalfe (Senior Lecturer in Statistics) conducted the IPD analysis. Pelham Barton (Senior Lecturer in Mathematical Modelling) conducted the economic modelling. Martin Cowie (Professor of Cardiology) provided expert cardiological input to the systematic review, the IPD analysis and the economic analysis. Paul Glasziou (Professor of General Practice) supported the conduct of the systematic review and provided expert methodological and primary care input to the IPD analysis. David Mant (Professor of General Practice) provided expert primary care cardiological input to the systematic review and the IPD analysis. Richard McManus (Clinical Senior Lecturer in General Practice) provided expert primary care input to the systematic review, the IPD analysis and the economic analysis. Roger Holder (Head of Statistics) provided statistical expertise for the IPD analysis. Jon Deeks (Professor of Statistics) provided statistical expertise for the IPD analysis. Kate Fletcher (Programme Manager) project managed the research and prepared the final document for publication. Michelle Qume (Data Manager) cleaned the data for the IPD analysis and carried out the validation checks. Sundip Sohanpal (Research Associate) carried out the update of the NICE systematic reviews to inform the economic model. Sharon Sanders (Research Associate) carried out the data extraction for the systematic review. Richard Hobbs (Professor of General Practice) provided expert primary care cardiological input to the systematic review and the IPD analysis.

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Appendix 1

Search strategy

The searches for this review were based on search terms for:

1. heart failure AND
2. symptoms and signs of heart failure
3. electrocardiogram
4. chest X-ray OR
5. B-type natriuretic peptides.

The search terms used in MEDLINE to identify studies of heart failure were:

1. exp Heart Failure, Congestive/
2. exp Ventricular Function/
3. heart failure.ab,ti.
4. cardiac failure.ab,ti.
5. ventricular dysfunction.ab,ti.
6. ventricular dysfunction.ab,ti.
7. ventricular systolic dysfunction.ab,ti.
8. cardiac dysfunction.ab,ti.
9. cardiac overload.ab,ti.
10. systolic dysfunction.ab,ti.
11. myocard$dysfunction.ab,ti.
12. cardiac insufficiency.ab,ti.
13. heart insufficiency.ab,ti.
14. CHF.ab,ti.
15. CCF.ab,ti.
16. HF.ab,ti.
17. LVSD.ab,ti.
18. diastolic dysfunction.ab,ti.
19. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18

We then combined this search (using AND) with four separate searches using terms for symptoms and signs of heart failure, electrocardiogram, chest X-ray and B-type natriuretic peptides respectively.

Search terms for symptoms and signs of heart failure were:

1. jugular venous pressure.ab,ti.
2. jugular venous pulse.ab,ti.
3. jugular pressure$.ab,ti.
4. jugular pulse.ab,ti.
5. jugular vein pressure.ab,ti.
6. JVP.ab,ti.
7. venous distention.ab,ti.
8. vein distention.ab,ti.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp Heart Sounds/
11. heart sound$.ab,ti.
12. gallop.ab,ti.
13. oscillation$.ab,ti.
14. S3.ab,ti.
15. S4.ab,ti.
16. crepitation$.ab,ti.
17. crackle$.ab,ti.
18. rale$.ab,ti.
19. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. exp Cardiomegaly/
21. cardiomegal$.ab,ti.
22. displaced apex.ab,ti.
23. apical impulse.ab,ti.
24. 20 or 21 or 22 or 23
25. exp Hepatomegaly/
26. hepatomegal$.ab,ti.
27. enlarged liver.ab,ti.
28. 25 or 26 or 27
29. exp Edema/
30. edema$.ab,ti.
31. oedema$.ab,ti.
32. venous insufficiency.ab,ti.
33. (swelling adj3 limb$).ab,ti.
34. (swelling adj3 leg$).ab,ti.
35. (swelling adj3 extremit$).ab,ti.
36. 29 or 30 or 31 or 32 or 33 or 34 or 35
37. Physical Examination/
38. physical examination.ab,ti.
39. clinical examination.ab,ti.
40. sign$.ab,ti.
41. (sign$adj5 symptom$).ab,ti.
42. 37 or 38 or 39 or40 or41
43. exp Fatigue/
44. fatigue.ti,ab.
45. asthenia.ti,ab.
46. malaise.ti,ab.
47. tired$.ti,ab.
48. 43 or 44 or 45 or 46 or 47
49. exp Dyspnea/
50. dyspnea.ti,ab.
51. SOB.ti,ab.
52. breath$.ti,ab.
53. dyspnoea.ti,ab.
54. 49 or 50 or 51 or 52 or 53
55. orthopnoea.ti,ab.
56. orthopnea.ti,ab.

57. 55 or 56
58. 9 or 19 or 24 or 28 or 36 or 42 or 48 or 54 or 57

Search terms for electrocardiogram were:

1. exp Electrocardiography/
2. electrocardiogra$.ab,ti.
3. cardiogra$.ab,ti.
4. ECG.ab,ti.
5. EKG.ab,ti.
6. 1 or 2 or 3 or 4 or 5

Search terms for chest X-ray were:

1. exp Radiography/
2. thoracic radiogra$.ab,ti.
3. chest x-ray$.ab,ti.
4. thoracic x-ray$.ab,ti.
5. CXR.ab,ti.
6. 1 or 2 or 3 or 4 or 5

Search terms for B-type natriuretic peptides were:

1. Natriuretic Peptide, Brain/
2. BNP.ab,ti.
3. natriuretic peptide$.ab,ti.
4. natruretic peptide$.ab,ti.
5. natiuretic peptide$.ab,ti.
6. pro?BNP.ab,ti.
7. 1 or 2 or 3 or 4 or 5 or 6

Appendix 2

Description of studies included in the systematic review

TABLE 27 *Studies of symptoms and signs versus a clinical diagnosis of heart failure*

Reference	*n*	Location	Setting	Mean age, years (±SD)	Patients	Index test	Reference test
General practice setting							
Alehagen *et al.*, 2003[80]	415	Kinda, Sweden	General practice (primary health-care centre)	72±6	Patients presenting with symptoms and signs of heart failure with no previous diagnosis	Dyspnoea, peripheral oedema, elevated JVP, lung crepitations	LVEF < 40% or atrial fibrillation and symptoms of heart failure
Fonseca *et al.*, 2004[79]	1058	Portugal	General practice (500 practices)	68±15	Randomly selected patients (stratified by age)	Dyspnoea, orthopnoea, PND, oedema (as a symptom), oedema (as a sign), weight gain, hypertension (SBP > 149 mmHg), tachycardia (HR > 90), elevated JVP, added heart sounds (S3/gallop), lung crepitations, hepatomegaly, abdominojugular reflex	ESC criteria (one clinician)
Galasko *et al.*, 2005[81]	376	Middlesex and London, UK	General practice (seven practices)	67±11	Patients with symptoms of heart failure or on loop diuretics	History of MI	EF < 40% or atrial fibrillation or valve disease and symptoms of heart failure
Hobbs *et al.*, 2002[82]	273	England	General practice (four practices)	66±11	Randomly selected patients (stratified by age): patients presenting with symptoms and signs of heart failure	History of MI, dyspnoea, oedema, crepitations	ESC criteria (panel of three clinicians in equivocal cases)
Rutten *et al.*, 2005[83]	405	Netherlands	General practice (51 practices)	73±5	COPD patients with no previous diagnosis of heart failure	History of MI, orthopnoea, oedema (as a sign), tachycardia, elevated JVP, displaced apex beat, crepitations	Clinical consensus (two cardiologists, one GP and one pulmonologist)
GP patients referred to open access HF or echocardiography clinics							
Cowie *et al.*, 1997[84]	122	London, UK	General practice (31 practices)	67±12	Patients referred to a rapid access heart failure clinic	History of MI, dyspnoea, oedema	ESC criteria (three cardiologists)
Fox *et al.*, 2000[85]	383	London, UK	Rapid access heart failure clinic	74±10	Patients referred to an open access heart failure clinic	History of MI, peripheral oedema, hypertension, crepitations	ESC criteria (one cardiologist)
Lim *et al.*, 2006[86]	137	UK	Specialist echocardiography unit	71±13	Patients referred to a specialist unit for echocardiography	Oedema	EF < 40% or atrial fibrillation or valve disease and symptoms of heart failure

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Reference	*n*	Location	Setting	Mean age, years (±SD)	Patients	Index test	Reference test
Wright *et al.*, 2003[87]	305	Auckland and Christchurch, New Zealand	General practice (92 GPs)	72±12	Patients with dyspnoea and/or oedema referred for assessment in study	Crepitations	Clinical consensus (three cardiologists and one GP)
Zaphiriou *et al.*, 2005[88]	302	Aberdeen, Glasgow and London, UK	Rapid access heart failure clinics in five hospitals	72±11	Patients referred to rapid access heart failure clinic	History of MI, oedema (as a sign), crepitations	ESC criteria (one cardiologist)
Emergency department setting							
Jose *et al.*, 2003[89]	119	Vellore, India	Emergency department	54±12	Patients with acute or chronic dyspnoea (excluded patients with ACS, includes patients in outpatient settings)	Orthopnoea, oedema (as a sign), tachycardia at rest, elevated JVP, added heart sounds, crepitations	Framingham criteria including echocardiogram results
Knudsen *et al.*, 2004[90]	880	USA and Europe (Breathing Not Properly Study)	Emergency department	64±16	Patients with dyspnoea as predominant symptom	History of MI, orthopnoea, oedema (as a sign), hypertension, elevated JVP (> 6 cm), added heart sounds, crepitations	Clinical consensus (two cardiologists)
Logeart *et al.*, 2002[91]	163	Paris, France	Emergency department	65±15	Patients with acute severe dyspnoea	History of MI, orthopnoea, pedal oedema, elevated JVP, added heart sounds, crepitations	Clinical consensus (two cardiologists and one pneumotologist)
Morrison *et al.*, 2002[92]	276	San Diego, USA	Emergency department	NR	Patients with dyspnoea	Dyspnoea, orthopnoea, PND, oedema (as a symptom), elevated JVP, added heart sounds, crepitations	Clinical consensus (two cardiologists using Framingham criteria)
Mueller *et al.*, 2005[93]	452	Linz, Austria,	Emergency department	71±15	Patients with dyspnoea	PND, oedema (as a sign), elevated JVP, added heart sounds, crepitations	Framingham criteria and echocardiographic criteria or systolic or diastolic dysfunction (one cardiologist)

ACS, acute coronary syndrome; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; ESC, European Society of Cardiology; HF, heart failure; HR, heart rate; JVP, jugular venous pressure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PND, paroxysmal nocturnal dyspnoea; SBP, systolic blood pressure.

TABLE 28: *Studies of electrocardiography versus a clinical diagnosis of heart failure*

Reference	*n*	Location	Setting	Mean age, years (±SD)	Patients	Index test	Reference test
General practice setting							
Alehagen *et al.*, 2003[80]	415	Kinda, Sweden	General practice (primary health-care centre)	72±6	Patients presenting with symptoms and signs of heart failure with no previous diagnosis	ECG not in sinus rhythm or atrial fibrillation or sign of past ischaemic myocardial damage	LVEF < 40% or atrial fibrillation and symptoms of heart failure
Fonseca *et al.*, 2004[79]	1058	Portugal	General practice (500 practices)	68±15	Randomly selected patients (stratified by age)	Abnormal rhythm, atrial abnormalities, conduction disturbances, presence of abnormal Q waves, poor R-wave progression in precordial leads, LVH, abnormal ST-segment T-wave changes (read by cardiologist)	ESC criteria (one clinician)
Galasko *et al.*, 2005[81]	376	Middlesex and London, UK	General practice (seven practices)	67±11	Patients with symptoms of heart failure or on loop diuretics	Abnormal ECG	EF < 40% or atrial fibrillation or valve disease and symptoms of heart failure
Hobbs *et al.*, 2002[82]	273	England	General practice (four practices)	66±11	Randomly selected patients (stratified by age) Subgroups: patients presenting with symptoms and signs of heart failure; patients at risk of heart failure; patients > 45 years; patients taking diuretics; patients with a previous diagnosis of heart failure	Any abnormality (read by cardiologist)	ESC criteria (panel of three clinicians in equivocal cases)
Rutten *et al.*, 2005[83]	405	Netherlands	General practice (51 practices)	73±5	COPD patients with no previous diagnosis of heart failure	Evidence of previous MI, complete or incomplete left BBB, LVH, atrial fibrillation, ST and/or T-wave abnormalities and sinus tachycardia (read by cardiologist)	Clinical consensus (two cardiologists, one GP and one pulmonologist)

Reference	*n*	Location	Setting	Mean age, years (±SD)	Patients	Index test	Reference test
GP patients referred to open access HF or echocardiography clinics							
Cowie *et al.*, 1997[84]	122	London, UK	General practice (31 practices)	67±12	Patients referred to a rapid access heart failure clinic	Any abnormality	ESC criteria (three cardiologists)
Fox *et al.*, 2000[85]	383	London, UK	Rapid access heart failure clinic	74±10	Patients referred to an open access heart failure clinic	Any abnormality	ESC criteria (one cardiologist)
Lim *et al.*, 2006[86]	137	UK	Specialist echocardiography unit	71±13	Patients referred to a specialist unit for echocardiography	Any abnormality	EF < 40% or atrial fibrillation or valve disease and symptoms of heart failure
Wright *et al.*, 2003[87]	305	Auckland and Christchurch, New Zealand	General practice (92 GPs)	72±12	Patients with dyspnoea and/or oedema referred for assessment in study	Not in sinus rhythm, presence of Q waves, ST abnormalities, T-wave abnormalities, LVH, BBB, QRS duration > 120 ms	Clinical consensus (three cardiologists and one GP)
Zaphiriou *et al.*, 2005[88]	302	Aberdeen, Glasgow and London, UK	Rapid access heart failure clinics in five hospitals	72±11	Patients referred to rapid access heart failure clinic	Any abnormality	ESC criteria (one cardiologist)
Emergency department setting							
Knudsen *et al.*, 2004[90]	880	USA and Europe (Breathing Not Properly Study)	Emergency department [California, Michigan, Ohio, Pennsylvania and Connecticut and two European (France, Norway)]	64±16	Patients with dyspnoea as predominant symptom	Evidence of previous MI, atrial fibrillation, atrial flutter, right or left BBB, ST-segment deviation (read by attending physician)	Clinical consensus (two cardiologists)

BBB, bundle branch block; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; ESC, European Society of Cardiology; HF, heart failure; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MI, myocardial infarction.

Table 29 *Studies of chest X-ray versus a clinical diagnosis of heart failure*

Reference	*n*	Location	Setting	Mean age, years (SD)	Patients	Index test	Reference test
General practice setting							
Alehagen *et al.*, 2003[80]	415	Kinda, Sweden	General practice (primary health-care centre)	72±6	Patients presenting with symptoms and signs of heart failure with no previous diagnosis	Pulmonary congestion or cardiomegaly	LVEF < 40% or atrial fibrillation and symptoms of heart failure
Fonseca *et al.*, 2004[79]	1058	Portugal	General practice (500 practices)	68±15	Randomly selected patients (stratified by age)	Any abnormality, increased CTR	ESC criteria (one clinician)
GP patients referred to open access HF or echocardiography clinics							
Cowie *et al.*, 1997[84]	122	London, UK	General practice (31 practices)	67±12	Patients referred to a rapid access heart failure clinic	Any abnormality	ESC criteria (three cardiologists)
Fox *et al.*, 2000[85]	383	London, UK	Rapid access heart failure clinic	74±10	Patients referred to an open access heart failure clinic	Any abnormality	ESC criteria (one cardiologist)
Wright *et al.*, 2003[87]	305	Auckland and Christchurch, New Zealand	General practice (92 GPs)	72±12	Patients with dyspnoea and/or oedema referred for assessment in study	Increased CTR or pulmonary oedema or pulmonary venous hypertension or interstitial pulmonary oedema	Clinical consensus (three cardiologists and one GP)
Emergency department setting							
Jose *et al.*, 2003[89]	119	Vellore, India	Emergency department	54±12	Patients with acute or chronic dyspnoea (excluded patients with ACS, includes patients in outpatient settings)	Increased CTR	Framingham criteria including echocardiogram results
Knudsen *et al.*, 2004[90]	880	USA and Europe (Breathing Not Properly Study)	Emergency department	64±16	Patients with dyspnoea as predominant symptom	Increased CTR	Clinical consensus (two cardiologists)
Logeart *et al.*, 2002[91]	163	Paris, France	Emergency department	65±15	Patients with acute severe dyspnoea	Increased CTR	Clinical consensus (two cardiologists and one pneumotologist)
Morrison *et al.*, 2002[92]	276	San Diego, USA	Emergency department	NR	Patients with dyspnoea	Increased CTR	Clinical consensus (two cardiologists using Framingham criteria)

CTR, cardiothoracic ratio; ESC, European Society of Cardiology; HF, heart failure; LVEF, left ventricular ejection fraction; NR, not reported.

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TABLE 30 *Studies of BNP versus a clinical diagnosis of heart failure*

Reference	*n*	Location	Setting	Mean age, years (±SD)	Patients	Index test	Reference test
General practice setting							
Hobbs *et al.*, 2002[82]	273	England	General practice (four practices)	66±11	Randomly selected patients (stratified by age) Subgroups: patients presenting with symptoms and signs of heart failure; patients at risk of heart failure; patients > 45 years; patients taking diuretics; patients with a previous diagnosis of heart failure	Shionogi	ESC criteria (panel of three clinicians in equivocal cases)
Cost, 2000[97]	405	Netherlands	General practice (51 practices)	73±5	COPD patients with no previous diagnosis of heart failure		Clinical consensus (two cardiologists, one GP and one pulmonologist)
GP patients referred to open access HF or echocardiography clinics							
Cowie *et al.*, 1997[84]	122	London, UK	General practice (31 practices)	67±12	Patients referred to a rapid access heart failure clinic	Peninsula	ESC criteria (three cardiologists)
Misuraca *et al.*, 2002[98]	83	Italy	Hospital outpatient clinic	73±10	Patients referred with diagnosis of heart failure	Shionogi	Clinical symptoms and signs and echocardiographic criteria of systolic and diastolic dysfunction
Zaphiriou *et al.*, 2005[88]	302	Aberdeen, Glasgow and London, UK	Rapid access heart failure clinics in five hospitals	72±11	Patients referred to rapid access heart failure clinic	Triage	ESC criteria (one cardiologist)

continued

TABLE 30 *Studies of BNP versus a clinical diagnosis of heart failure (continued)*

Reference	*n*	Location	Setting	Mean age, years (±SD)	Patients	Index test	Reference test
Emergency department setting							
Ababsa *et al.*, 2005[99]	192	Paris, France	Emergency department	83±6	Patients > 75 years with dyspnoea and suspected heart failure	Triage	Clinical consensus (two cardiologists)
Alibay *et al.*, 2005[100]	160	Paris, France	Emergency department	80±14	Patients with dyspnoea	Triage	Clinical consensus (two cardiologists)
Barcarse *et al.*, 2004[101]	98	San Diego, USA	Emergency department	64±0.2	Patients with acute dyspnoea	Triage	Clinical diagnosis (one cardiologist)
El Mahmoud *et al.*, 2006[102]	103	Paris, France	Emergency department	89±6	Patients > 75 years with dyspnoea	Triage	Clinical diagnosis (two independent cardiologists)
Jourdain *et al.*, 2002[106]	125	Paris, France	Emergency department	72±NR	Patients with dyspnoea	Triage	Clinical diagnosis
Lainchbury *et al.*, 2003[103]	205	Christchurch, New Zealand	Emergency department	70±14	Patients with acute dyspnoea	Triage	ESC criteria (two independent cardiologists)
Logeart *et al.*, 2002[91]	163	Paris, France	Emergency department	65±15	Patients with severe dyspnoea	Triage	Clinical consensus (two cardiologists and one pneumotologist)
Maisel *et al.*, 2002[104]	1586	USA and Europe (Breathing Not Properly Study)	Emergency department	64±17	Patients with dyspnoea	Triage	Clinical consensus (two cardiologists)
Morrison *et al.*, 2002[92]	321	San Diego, USA	Emergency department	NR	Patients with dyspnoea	Triage	Clinical consensus (two cardiologists using Framingham criteria)

Reference	*n*	Location	Setting	Mean age, years (±SD)	Patients	Index test	Reference test
Mueller *et al.*, 2005[93]	251	Basel, Switzerland	Emergency department	71±15	Patients with acute dyspnoea as the primary complaint.	Abbott	Framingham criteria and echocardiographic criteria or systolic or diastolic dysfunction (one cardiologist)
Ray *et al.*, 2004[107]	313	Paris, France	Emergency department	80±8	Patients > 65 years with acute dyspnoea	Triage	Clinical consensus (two independent physicians)
Villacorta *et al.*, 2002[105]	70	Rio de Janeiro, Brazil	Emergency department	72±15	Patients with acute dyspnoea	Triage	Clinical diagnosis (one cardiologist)
Inpatient setting							
Davis *et al.*, 1994[108]	52	Christchurch, New Zealand	Inpatients	Mean (range) 74 (49–89)	Patients admitted for acute dyspnoea	NR	Clinical consensus (panel of physicians and radiologist)
Dokainish *et al.*, 2004[109]	122	Houston, USA	Inpatients	56±13	Patients referred to consultancy service for suspected heart failure	Triage	Framingham criteria (clinical examination by one cardiologist)
McLean *et al.*, 2003[110]	84	Sydney, Australia	ICU	60.9 (17–86)	Patients admitted to ICU	Triage	Clinical diagnosis by senior intensivists

COPD, chronic obstructive pulmonary disease; ESC, European Society of Cardiology; HF, heart failure; ICU, intensive care unit; NR, not reported.

TABLE 31 *Studies of NT-proBNP versus a clinical diagnosis of heart failure*

Reference	*n*	Location	Setting	Mean age, years (±SD)	Patients	Index test	Reference test
General practice setting							
Alehagen *et al.*, 2003[80]	415	Kinda, Sweden	General practice (primary health-care centre)	72±6	Patients presenting with symptoms and signs of heart failure with no previous diagnosis	In-house assay	LVEF < 40% or atrial fibrillation and symptoms of heart failure
Galasko *et al.*, 2005[81]	376	Middlesex and London, UK	General practice (seven practices)	67±11	Patients with symptoms of heart failure or on loop diuretics	Roche	EF < 40% or atrial fibrillation or valve disease and symptoms of heart failure
Hobbs *et al.*, 2002[82]	273	England	General practice (four practices)	66±11	Randomly selected patients (stratified by age) Subgroups: patients presenting with symptoms and signs of heart failure; patients at risk of heart failure; patients > 45 years; patients taking diuretics; patients with a previous diagnosis of heart failure	Roche	ESC criteria (panel of three clinicians in equivocal cases)
Rutten *et al.*, 2005[83]	405	Netherlands	General practice (51 practices)	73±5	COPD patients with no previous diagnosis of heart failure	Roche	Clinical consensus (two cardiologists, one GP and one pulmonologist)
GP patients referred to open access HF or echocardiography clinics							
Lim *et al.*, 2006[86]	137	UK	Specialist echocardiography unit	71±13	Patients referred to a specialist unit for echocardiography	Roche	EF < 40% or atrial fibrillation or valve disease and symptoms of heart failure
Nielsen *et al.*, 2004[111]	287	Haderslev, Denmark	Heart failure clinic	Mean (range) 65 (18–89)	Patients referred with dyspnoea < 2 weeks duration	Roche	ESC criteria (one cardiologist)
Wright *et al.*, 2003[87]	305	Auckland and Christchurch, New Zealand	General practice (92 GPs)	72±12	Patients with dyspnoea and/or oedema referred for assessment in study	In-house	Clinical consensus (three cardiologists and one GP)
Zaphiriou *et al.*, 2005[88]	302	Aberdeen, Glasgow and London, UK	Rapid access heart failure clinics in five hospitals	72 11	Patients referred to rapid access heart failure clinic	Roche	ESC criteria (one cardiologist)

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Reference	*n*	Location	Setting	Mean age, years (±SD)	Patients	Index test	Reference test
Emergency department setting							
Alibay *et al.*, 2005[100]	160	Paris, France	Emergency department	80±14	Patients with dyspnoea	Roche	Clinical consensus (two cardiologists)
Bayes-Genis *et al.*, 2004[112]	89	Barcelona, Spain	Emergency department	Range: 40–88	Patients with dyspnoea	Roche	Clinical consensus (two cardiologists)
El Mahmoud *et al.*, 2006[102]	103	Paris, France	Emergency department	89±6	Patients > 75 years with dyspnoea	Roche	Clinical diagnosis (two independent cardiologists)
Januzzi *et al.*, 2005[113]	599	Boston, USA	Emergency department	57±16	Patients > 21 years with dyspnoea	Roche	Clinical consensus (emergency department physician and three cardiologists)
Lainchbury *et al.*, 2003[103]	205	Christchurch, New Zealand	Emergency department	70±14	Patients with acute dyspnoea	Roche	ESC criteria (two independent cardiologists)
Mueller *et al.*, 2005[93]	251	Basel, Switzerland	Emergency department	71±15	Patients with acute dyspnoea as the primary complaint	Abbott	Framingham criteria and echocardiographic criteria or systolic or diastolic dysfunction (one cardiologist)
Outpatient setting							
Jose *et al.*, 2003[89]	119	Vellore, India	Emergency department	54±12	Patients with acute or chronic dyspnoea (excluded patients with ACS, includes patients in outpatient settings)	Biomedica	Framingham criteria including echocardiogram results
Inpatient setting							
Berdague *et al.*, 2006[114]	254	Béziers, France	Hospital	81±7	Patients > 70 years admitted from emergency department with dyspnoea	Roche	Clinical consensus (two cardiologists)

ACS, acute coronary syndrome; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; ESC, European Society of Cardiology; HF, heart failure; LVEF, left ventricular ejection fraction.

TABLE 32 *Studies of symptoms and signs versus left ventricular systolic dysfunction*

Reference	*n*	Location	Setting	Mean age, years (±SD)	Patients	Index test	Reference test
General practice setting							
Hobbs *et al.*, 2002[82]	273	England	General practice (four practices)	66±11	Randomly selected patients (stratified by age): patients presenting with symptoms and signs of heart failure	Dyspnoea, oedema, crepitations	ESC criteria (panel of three clinicians in equivocal cases)
McDonagh *et al.*, 1997[10]	1252	Glasgow, UK	General practice (30 practices)	50±14	Random selection of patients 25–74 years, participants in Glasgow MONICA study	Hypertension	LVEF < 30%
Morgan *et al.*, 1999[11]	817	Dorset, UK	General practice (four practices)	76±4	Random sample of patients in primary health-care centre	Dyspnoea on walking, elevated JVP, lung crepitations, sign of oedema	LVSD
Nielsen *et al.*, 2000[139]	126	Copenhagen, Denmark	General practice (three practices)	Median: 71	Patients with symptoms or signs of heart disease from medical record	Heart rate > diastolic blood pressure	LVEF < 45%
Sparrow *et al.*, 2003[140]	621	Nottingham UK	General practice (seven practices)	75± NR	Patients prescribed loop diuretics	Dyspnoea on exertion, orthopnoea, PND, elevated JVP, displaced apex beat, added heart sounds, lung crepitations, sign of oedema	LVEF < 40%
GP patients referred to open access HF or echocardiography clinics							
Davie *et al.*, 1997[141]	259	Glasgow, UK	Open access echocardiography clinic	NR	Patients referred with suspected heart failure	Orthopnoea, PND, oedema as a symptom, tachycardia (HR > 100), elevated JVP, displaced apex beat, added heart sounds, lung crepitations, oedema as a sign	FS < 25%
Fuat *et al.*, 2006[142]	297	Darlington/ Dales, UK	One-stop diagnostic clinic	74±NR	Patients referred to heart failure clinic	Hypertension	LVSD
Gustafsson *et al.*, 2005[143]	367	Copenhagen Denmark	Echocardiography clinic	Median (range) 69 (39–84)	Patients referred by GP for echocardiographic evaluation for suspected heart failure	Hypertension	LVEF < 30%, 40%

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Reference	*n*	Location	Setting	Mean age, years (±SD)	Patients	Index test	Reference test
Outpatient setting							
Mattleman *et al.*, 1983[144]	99	Philadelphia, USA	Ventriculography clinic	Mean (range) 57 (32–82)	Patients referred for ventriculography	Dyspnoea on exertion, displaced apex beat, added heart sounds, lung crepitations	LVEF < 50%
Rihal *et al.*, 1995[145]	14,507	Seattle, USA	Patients in Coronary Artery Surgery Study Registry	53±9	Patients with chest pain referred for angiography and who had had estimation of EF	Added heart sounds, lung crepitations	LVEF < 50%
Wattanabe *et al.*, 2005[146]	141	Tokyo, Japan	Outpatient clinic	64±9	Patients with a history of MI but no symptoms of HF	Hypertension	LVEF < 55%
Inpatient setting							
Gadsboll *et al.*, 1989[115]	98	Copenhagen, Denmark	Coronary care unit	61, range 38–81	Patients post MI	Dyspnoea, elevated JVP, displaced apex beat, added heart sounds, lung crepitations, hepatomegaly, sign of oedema	LVEF < 40%
Jain *et al.*, 1993[147]	43	Rural India	Patients admitted with MI	Range 48–80	Patients post MI	Hypertension, elevated JVP, added heart sounds, lung crepitations	LVEF < 40%
Mueller *et al.*, 2004[67]	180	Linz, Austria	Cardiology ward	51, range 40–63	Patients admitted for cardiac evaluation plus 27 patients with stable heart failure	Hypertension	LVEF < 35%, < 60%
Narain *et al.*, 2005[148]	110	Lucknow, India	Patients admitted with ACS	NR	Patients with ACS	Added heart sounds	LVEF < 45%
Talreja *et al.*, 2000[149]	300	Virginia, USA	Inpatients referred to echocardiographic laboratory	64±16	Inpatients referred for echocardiography	Hypertension, dyspnoea, elevated JVP, added heart sounds, lung crepitations, sign of oedema	LVEF < 45%
Zema *et al.*, 1984[150]	37	New York, USA	General hospital	61±8	Inpatients with symptoms and signs of COPD	Dyspnoea, orthopnoea, PND, oedema as a sign, elevated JVP, lung crepitations	LVEF < 50%

ACS, acute coronary syndrome; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; ESC, European Society of Cardiology; FS, fractional shortening; HF, heart failure; HR, heart rate; JVP, jugular venous pressure; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; MI, myocardial infarction; NR, not reported; PND, paroxysmal nocturnal dyspnoea.

TABLE 33 *Studies of electrocardiography versus left ventricular systolic dysfunction*

Reference	*n*	Location	Setting	Mean age, years (SD)	Patients	Index test	Reference test
General practice setting							
Alehagen *et al.*, 2003[80]	415	Kinda, Sweden	General practice (primary health-care centre)	72±6	Patients presenting with symptoms and signs of heart failure with no previous diagnosis	ECG not in sinus rhythm or atrial fibrillation or sign of past ischaemic myocardial damage	LVEF < 40%
Galasko *et al.*, 2005[81]	761	London, UK	General practice (seven practices)	Population: 60±10; high risk: 66±11	Patients with symptoms of heart failure or on diuretics	Abnormal ECG	LVEF < 40%, < 50%
Hobbs *et al.*, 2002[82]	273	England	General practice (four practices)	66±11	Randomly selected patients (stratified by age) Subgroups: patients presenting with symptoms and signs of heart failure	Any abnormality (read by cardiologist)	ESC criteria (panel of 3 clinicians in equivocal cases)
McDonagh *et al.*, 1997[10]	1394	Glasgow, UK	General practice (30 practices)	50±14	Random selection of patients 25–74 years, participants in Glasgow MONICA study	Presence of Q wave, left BBB, ST/T segment abnormality, voltage criteria for LVH, atrial fibrillation or flutter (read by two coders)	LVEF < 30%
Ng *et al.*, 2003[151]	1331	Leicester, UK	General practice (21 practices)	63, range 45–80	Randomly selected patients without heart failure	Presence of Q wave, left and right BBB, LVH, atrial fibrillation or flutter, LAD, R-wave progression, atrial hypertrophy, ST-segment change, sinus bradycardia or tachycardia assessed	LVEF < 45%, 35%
Nielsen *et al.*, 2000[139]	126	Copenhagen, Denmark	General practice	Median: 71	Patients with any past or present symptoms or signs of heart disease	QRS or ST/T changes, or both	LVEF < 45%
Sparrow *et al.*, 2003[140]	621	Nottingham UK	General practice (seven practices)	75±NR	Patients prescribed loop diuretics	QRS or ST/T wave changes	LVEF < 40%

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Reference	*n*	Location	Setting	Mean age, years (SD)	Patients	Index test	Reference test
GP patients referred to open access HF or echocardiography clinics							
Davie *et al.*, 1997[141]	259	Glasgow, UK	Open access echocardiography clinic	NR	Patients with suspected heart failure	Evidence of atrial fibrillation, previous MI, LVH, BBB, LAD	FS < 25%
Fuat *et al.*, 2006[142]	297	Darlington/ Dales, UK	One-stop diagnostic clinic	74±NR	Patients referred to heart failure clinic	Any abnormality	LVSD
Landray *et al.*, 2000[152]	126	UK	Open access heart failure clinic	75±9	Patients with suspected heart failure	Presence of Q waves, BBB, T-wave inversion, LVH	Qualitative assessment of LVSD
Lim *et al.*, 2006[86]	137	London, UK	Community echocardiography service	71±13	Patients with suspected heart failure	Evidence of atrial fibrillation or flutter, ventricular arrhythmia, intraventricular conduction, ST/T wave, Q wave, LVH	LVSD
Lindsay *et al.*, 2000[153]	416	Glasgow, UK	Open access echocardiography clinic	NR	Patients with suspected heart failure	Evidence of Q waves, previous MI, ST/T changes, LAD, left atrial enlargement, BBB, atrial fibrillation, heart block and R-wave progression assessed	Qualitative assessment of LVSD
Sandler *et al.*, 2000[154]	240	Chesterfield, UK	Open access echocardiography clinic	68, range 13–94	Patients referred for echocardiography	Any abnormality	LVSD
Population cohort or screening studies							
Hedberg *et al.*, 2004[155]	407	Vasteras, Sweden	Population	75	Random sample of 75-year-olds in general population	Major or minor changes: AV block, LAD, incomplete BBB, borderline Q-wave or high R-wave amplitude	LVSD
Mosterd *et al.*, 1997[156]	865	Rotterdam, Netherlands	Population	66±8	Invitation to inhabitants of Rotterdam aged ≥ 55 years	Evidence of MI, atrial fibrillation, LVH. Analysed using the MEANS software program	FS < 25%

continued

TABLE 33 *Studies of electrocardiography versus left ventricular systolic dysfunction (continued)*

Reference	*n*	Location	Setting	Mean age, years (SD)	Patients	Index test	Reference test
Outpatient setting							
Baker *et al.*, 2003[157]	481	Ohio, USA	General medicine and geriatric clinics	69±NR	Patients with risk factors and no documented heart failure	Conduction and axis abnormalities, LVH, previous MI	LVEF < 45%
Christian *et al.*, 1997[158]	2267	Rochester, USA	Nuclear medicine clinic	NR	Patients referred for nuclear imaging perfusion studies	Any abnormality	LVEF < 50%
Houghton *et al.*, 1997[159]	200	Nottingham, UK	Heart failure clinic	63± NR	Patients who had undergone echocardiography and ECG	Any abnormality	LVEF < 40%
Hutcheon *et al.*, 2002[133]	304	Dundee, UK	Day hospital	Median (range) 79 (61–98)	Patients who were referred to the day hospital	Evidence of Q waves, BBB, conduction defect, ST/T segment abnormalities, LVH, atrial fibrillation/flutter	Qualitative assessment of LVSD
Rihal *et al.*, 1995[145]	14,507	Seattle, USA	Patients in Coronary Artery Surgery Study Registry	53±9	Patients with chest pain referred for angiography and who had had estimation of EF	Any abnormality	LVEF < 50%
Talwar *et al.*, 1999[160]	222	Leicester, UK	Echocardiography clinic	Median (range) 73 (20–94)	Patients referred for echocardiography and at risk of heart failure	Sinus bradycardia, tachycardia, prolonged PR interval, IV conduction defects, RA deviation, broadening of the QRS complex, non-specific ST/T wave changes	LWMI > 1.2
Inpatient setting							
Gillespie *et al.*, 1997[161]	71	Dundee, UK	General medical unit	73 (33–95)	Patients with acute dyspnoea or dyspnoea as a major component of their overall symptoms	Any abnormality	LVSD
Talreja *et al.*, 2000[149]	330	Virginia, USA	Inpatients	64±16	Patients referred for echocardiography	Evidence of Q waves, R-wave progression, LVH, ST/T wave changes, left BBB, arrhythmia	LVEF < 45%

BBB, bundle branch block; ESC, European Society of Cardiology; FS, fractional shortening; HF, heart failure; IV, intraventricular; LAD, left axis deviation; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; LVH, left ventricular hypertrophy; LWMI, left ventricaular wall motion index; MI, myocardial infarction; NR, not reported; RA, right axis.

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TABLE 34 *Studies of chest X-ray versus left ventricular systolic dysfunction*

Reference	*n*	Location	Setting	Mean age, years (SD)	Patients	Index test	Reference test
GP patients referred to open access HF or echocardiography clinics							
Landray *et al.*, 2000[152]	126	UK	Open access heart failure clinic	74±9	Patients with suspected heart failure	Pulmonary oedema or increased CTR	Qualitative assessment of LVSD
Mattleman *et al.*, 1983[144]	99	Philadelphia, USA	Ventriculography clinic	Mean (range) 57 (32–82)	Patients referred for ventriculography	Increased CTR or pulmonary congestion	LVEF < 50%
Sandler *et al.*, 2000[154]	240	Chesterfield, UK	Open access echocardiography clinic	68, range 13–94	Patients referred for echocardiography	Any abnormality	LVSD
Hendry *et al.*, 1999[162]	61	Glasgow, UK	Hospital wards	82, range 71–96	Patients admitted with heart failure	Pulmonary congestion	LVSD
Jain *et al.*, 1993[147]	43	Rural India	Hospital wards	NR, range 48–80	Patients post MI	Increased CTR or pulmonary congestion	LVEF < 40%
Outpatient setting							
Madsen *et al.*, 1984[163]	229	San Diego, USA and British Columbia, Canada	Cardiology clinic	Mean (range) 63 (30–95)	Patients discharged post MI	Increased CTR or pulmonary congestion	LVEF < 50%
Rihal *et al.*, 1995[145]	14,507	Seattle, USA	Patients in Coronary Artery Surgery Study Registry	53±9	Patients with chest pain referred for angiography and who had had estimation of EF	Increased CTR	LVEF < 50%
Zema *et al.*, 1983[150]	37	New York, USA	Hospital wards	61 8	Inpatients with symptoms and signs of COPD	Increased CTR or pulmonary congestion	LVEF < 50%
Inpatient setting							
Gadsboll *et al.*, 1989[164]	98	Copenhagen, Denmark	Coronary care unit	61, range 38–81	Patients with MI admitted less than 24 hours after onset of symptoms	Pulmonary congestion	LVEF < 50%
Gillespie *et al.*, 1997[161]	71	Dundee, UK	General medical unit	73, range 33–95	Patients with acute dyspnoea or had dyspnoea as a major component of their overall symptoms	Increased CTR or pulmonary congestion	LVSD
Talreja *et al.*, 2000[149]	300	Virginia, USA	Hospital wards	64±16	Inpatients referred for echocardiography	Increased CTR or pulmonary congestion	LVEF < 45%

CTR, cardiothoracic ratio; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; HF, heart failure; LVSD, left ventricular systolic dysfunction; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

TABLE 35 *Studies of BNP versus left ventricular systolic dysfunction*

Reference	*n*	Location	Setting	Mean age (± SD)	Patients	Index test	Reference test
General practice setting							
Hobbs *et al.*, 2002[82]	273	England	General practice (four practices)	66±11	Randomly selected patients (stratified by age): subgroup of patients presenting with symptoms and signs of heart failure	Shionogi	ESC criteria (panel of three clinicians in equivocal cases)
McDonagh *et al.*, 1998[165]	1252	Glasgow, UK	General practice (patients recruited for MONICA study)	51±14	Randomly selected patients 25–74 years	Peninsula	LVEF < 30%
McGeoch *et al.*, 2002[166]	100	Christchurch, New Zealand	General practice (two practices)	76 (54–90)	Patients being treated for heart failure	In-house RIA	LVEF < 45%
Ng *et al.*, 2003[151]	1331	Leicester, UK	General practice (21 practices)	Mean (range) 63 (45–80)	Randomly selected patients without heart failure	Peninsula	LVEF < 35%, < 45%
Nielsen *et al.*, 2003[139]	1252	Glasgow, UK	General practice (patients in MONICA study)	51 (14.0)	Randomly selected patients aged 25–74 years	Peninsula	LVEF < 32%, < 40%
Smith *et al.*, 2000[167]	155	Dorset, UK	General practice (four practices)	76±4	Randomly selected patients aged 70–80 years	Peninsula	Qualitative assessment of LVSD
Sparrow *et al.*, 2003[140]	621	Nottingham UK	General practice (seven practices)	75±NR	Patients taking loop diuretics	Peninsula	LVEF < 40%
GP patients referred to open access HF or echocardiography clinics							
Fuat *et al.*, 2006[142]	263	Auckland and South Durham, New Zealand	One-stop diagnostic clinics	74±NR	Patients referred from general practice	Triage	LVSD
Landray *et al.*, 2000[152]	126	Banbury, UK	Heart failure clinics (one clinic)	74±9	Patients referred from general practice with suspected heart failure	Shionogi	Qualitative assessment of LVSD
Sim *et al.*, 2003[168]	83	Gwent, UK	Open access echoradiography	Median (range) 72 (37–87)	Patients with dyspnoea	Bachem RIA	LVEF < 35%

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Reference	*n*	Location	Setting	Mean age (± SD)	Patients	Index test	Reference test
Population cohort or screening studies							
Costello-Boerrigter *et al.*, 2006[169]	1869	Olmsted County, USA	Population	62±10	Random sample of population > 45 years	Triage	LVEF < 40%, < 50%
Hedberg *et al.*, 2004[155]	407	Vasteras, Sweden	Population	75	Random sample of population > 75 years	Shionogi	LVSD
Luchner *et al.*, 2000[170]	479	Augsburg, Germany	Population	Range 50–67	Participants in Augsburg, MONICA study	Shionogi	FS < 28%
Lukowic *et al.*, 2005[171]	1678	Augsburg, Germany	Population	49±14	Participants in Augsburg, MONICA study	Shionogi	LVEF < 40%
Vasan *et al.*, 2002[172]	3177	Framingham, USA	Population	58±10	Participants in the Framingham Offspring Study	Shionogi	LVEF < 40% and/or FS < 22%
Outpatient setting							
Atisha *et al.*, 2004[173]	202	San Diego, USA	Echocardiography clinic	65±14	Patients referred for echocardiography with no previous history of heart failure but with fatigue, dyspnoea or oedema	Triage	LVEF < 50% or any wall motion abnormality
Bibbins-Domingo *et al.*, 2004[174]	298	San Francisco and Palo Alto, USA	Cardiology clinic	67±11	Patients with coronary disease	Triage	LVEF < 45%, 55%
Falkensammer *et al.*, 2005[175]	51	Innsbruck, Austria	Nuclear medicine clinic	Median (range) 68 (24–91)	Patients referred for radionuclide ventriculography	Shionogi	LVEF < 50%
Hutcheon *et al.*, 2002[133]	299	Dundee, UK	Day hospital	Median (range) 79 (61–98)	Patients attending day hospital	Peninsula	Qualitative assessment of LVSD
Krishaswamy *et al.*, 2001[176]	400	San Diego, USA	Echocardiography clinic	60±12	Patients referred for echocardiography	Triage	LVEF < 50%
Kruger *et al.*, 2004[132]	124	Aachen, Germany	Cardiology clinic	61±11	Patients with suspected cardiac disease or known heart failure	Triage	LVEF < 50%
Mallamaci *et al.*, 2001[177]	246	Calabria, Italy	Patients with end-stage renal disease on regular dialysis for at least 6 months	60±15	Patients on renal dialysis with no overt sign of heart failure	Peninsula	LVEF < 45%

continued

TABLE 35 *Studies of BNP versus left ventricular systolic dysfunction (continued)*

Reference	*n*	Location	Setting	Mean age (± SD)	Patients	Index test	Reference test
Richards *et al.*, 2006[178]	1049	Sydney, Australia; Christchurch and Auckland, New Zealand	Patients discharged from cardiology units	63±10	Patients with stable heart failure or IHD in trial	NR	LVEF < 30%, < 40%, < 50%
Valli *et al.*, 2001[179]	153	Pessac, France	Nuclear medicine clinic	55 (21–83)	Patients referred for radionuclide ventriculography	CIS Bio	LVEF < 40%
Vanderheyden *et al.*, 2006[180]	72	Belgium	Cardiac catheterisation clinic	65 (28–90)	Patients referred for elective catheterisation	Triage	LVEF < 45%
Wattanabe *et al.*, 2005[146]	141	Tokyo, Japan	Outpatient clinic	65±9	Patients post MI but with no symptoms of heart failure	Tosoh II	LVEF < 55%
Yamamoto *et al.*, 1996[181]	94	Rochester MN, USA	Cardiac catheterisation clinic	62±12	Patients referred for elective catheterisation	Shionogi	LVEF < 45%
Yamamoto *et al.*, 2000[182]	466	Rochester MN, USA	Echocardiography clinic	65±NR	Patients with symptoms of heart failure or at high risk of LVSD	Shionogi	LVEF < 45%
Inpatient setting							
Bal *et al.*, 2006[183]	41	Evry, France	ICU	53±20	Patients admitted to ICU for acute respiratory distress and/or shock	Triage	LVEF < 50%
Bettencourt *et al.*, 2000[184]	101	Porto, Portugal	Heart failure clinic	60	Consecutive patients referred by internists or cardiologists	Shionogi	LVEF < 40%
Byrne *et al.*, 1996[185]	94	Glasgow, UK	Coronary care unit	NR	Patients post MI	NR	LVEF < 30%
Choy *et al.*, 1994[186]	57	Dundee, UK	Coronary care unit	Mean (range) 64 (46–88)	Patients post MI	Peninsula	LVEF < 35%, < 40%, < 45%
Mueller *et al.*, 2004[67]	180	Linz, Austria	Internal medicine ward	Mean (range) 51 (40–63)	Patients admitted for cardiac evaluation	Bayer	LVEF < 35%, < 60%
Osca *et al.*, 2002[187]	101	Valencia, Spain	Hospital wards	66±NR	Patients with symptomatic heart failure	Shionogi	LVEF < 45%
Pfister *et al.*, 2002[188]	150	Koln, Germany	Hospitalised cardiac patients	64±NR	Inpatients referred for cardiac catheterisation	Shionogi	LVEF < 40%, < 60%
Richards *et al.*, 1998[189]	297	Christchurch, New Zealand	Coronary care unit	64±10	Patients post MI	NR	LVEF < 40%

ESC, European Society of Cardiology; FS, fractional shortening; ICU, intensive care unit; IHD, ischaemic heart disease; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; MI, myocardial infarction; NR, not reported; RIA, radioimmunoassay.

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TABLE 36 *Studies of NT-proBNP versus left ventricular systolic dysfunction*

Reference	*n*	Location	Setting	Mean age (± SD)	Patients	Index test	Reference test
General practice setting							
Galasko *et al.*, 2005[81]	761	London, UK	General practice (seven practices)	Population: 60±10; high risk: 66±11	Patients with symptoms of heart failure or on diuretics	Roche	LVEF < 40%, < 50%
Groenning *et al.*, 2004[190]	672	Copenhagen, Denmark	General practice (four practices)	Median (range) 68.1 (51–91)	Patients 50–90 years	In-house	LVEF < 40%, < 45%, < 50%
Hobbs *et al.*, 2002[82]	273	West Midlands, UK	General practice (16 practices)	66±11	Patients ≥ 45 years	Roche	LVEF < 40%
Ng *et al.*, 2003[151]	1331	Leicester, UK	General practice (21 practices)	63 (45–80)	Randomly selected patients without heart failure	In-house	LVEF 35%, < 45%
GP patients referred to open access HF or echocardiography clinics							
Fuat *et al.*, 2006[142]	263	Auckland and South Durham, New Zealand	One-stop diagnostic clinics	74±NR	Patients referred from general practice	Roche	LVSD
Gustafsson *et al.*, 2005[143]	367	Copenhagen, Denmark	Echocardiography clinic	Median (range) 68 (39–84)	Patients with suspected heart failure	Roche	LVEF < 30%, < 40%
Lim *et al.*, 2006[86]	116	Middlesex, UK	Echocardiography clinic	69±14	Patients referred from general practice	Roche	LVEF < 50%
Sivakumar *et al.*, 2006[191]	100	Stevenage, UK	Echocardiography clinic	82, range 72–94	Patients > 75 years referred for echocardiography	Roche	LVEF < 50%
Population cohort or screening studies							
Costello-Boerrigter *et al.*, 2006[169]	1869	Olmsted County, USA	Population (selected from medical records)	62±10	Random sample of population > 45 years	Roche	LVEF < 40%, < 50%

continued

TABLE 36 *Studies of NT-proBNP versus left ventricular systolic dysfunction*

Reference	*n*	Location	Setting	Mean age (± SD)	Patients	Index test	Reference test
Outpatient setting							
Falkensammer *et al.*, 2005[175]	51	Innsbruck, Austria	Nuclear medicine clinic	Median (range) 68 (24–91)	Patients referred for radionuclide ventriculography	Roche	LVEF < 50%
Richards *et al.*, 2006[178]	1049	Australia, New Zealand	Patients discharged from cardiology units	63 ± 10	Patients with stable heart failure or IHD in trial	In house	LVEF < 30%, < 40%, < 50%
Thackray *et al.*, 2006[192]	261	East Yorkshire, UK	Pacemaker clinics (four clinics)	72 ± 12	Patients attending clinic	Biomedica	LVEF < 40%
Vanderheyden *et al.*, 2006[180]	72	Belgium	Cardiac catheterisation clinic	65 (28–90)	Patients referred for elective catheterisation	Roche	LVEF < 45%
Inpatient setting							
Bal *et al.*, 2006[183]	41	Evry, France	ICU	53 ± 20	Patients admitted to ICU for acute respiratory distress and/or shock	Roche	LVEF < 50%
Bay *et al.*, 2003[193]	2193	Copenhagen, Denmark	General hospital	Median (range) 73 (40–104)	All admitted patients > 40 years	In-house ELISA	LVEF < 40%
Mueller *et al.*, 2004[194]	180	Linz, Austria	Internal medicine ward	Mean (range) 51 (40–63)	Patients admitted for cardiac evaluation	Roche	LVEF < 35%, < 60%
Pfister *et al.*, 2002[188]	150	Koln, Germany	Hospitalised cardiac patients	64 ± NR	Inpatients referred for cardiac catheterisation	Roche	LVEF < 40%, < 60%
Richards *et al.*, 1998[178]	297	Christchurch, New Zealand	Coronary care unit	64 ± 10	Patients post MI	NR	LVEF < 40%

ELISA, enzyme-linked immunosorbent assay; HF, heart failure; ICU, intensive care unit; IHD, ischaemic heart disease; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; MI, myocardial infarction; NR, not reported.

Appendix 3

Quality assessment of studies included in the review

TABLE 37 *Quality of studies assessing the diagnostic accuracy of symptoms and signs versus a clinical diagnosis of heart failure*

Reference	Consecutive series or random sample of consecutive series of patients	Selection criteria clearly described	Reference standard likely to correctly classify the target condition	Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	Whole or random selection of sample received verification using the reference standard of diagnosis
GP setting					
Alehagen *et al*., 2003[80]					
Fonseca *et al*., 2004[79]			U		
Galasko *et al*., 2005[81]					
Hobbs *et al*., 2002[82]					
Rutten *et al*., 2005[83]					
GP patients referred to open access heart failure or echocardiography clinics					
Cowie *et al*., 1997[84]					
Fox *et al*., 2000[85]					
Lim *et al*., 2006[86]					
Wright *et al*., 2003[87]					
Zaphiriou *et al*., 2005[88]					
Emergency department settings					
Jose *et al*., 2003[89]					
Knudsen *et al*., 2004[90]					
Logeart *et al*., 2002[91]					
Morrison *et al*., 2002[92]					
Mueller *et al*., 2005[93]					

Dark grey shading, yes; light grey shading, unclear; unshaded, no; U, unpublished.

TABLE 38 *Quality of studies assessing the diagnostic accuracy of electrocardiography versus a clinical diagnosis of heart failure*

Reference	Consecutive series or random sample of consecutive series of patients	Selection criteria clearly described	Reference standard likely to correctly classify the target condition	Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	Whole or random selection of sample received verification using the reference standard of diagnosis
GP setting					
Alehagen *et al*., 2003[80]					
Fonseca *et al*., 2004[79]					
Galasko *et al*., 2005[81]					
Hobbs *et al*., 2002[82]					
Rutten *et al*., 2005[83]					
GP patients referred to open access heart failure or echocardiography clinics					
Cowie *et al*., 1997[84]					
Fox *et al*., 2000[85]					
Lim *et al*., 2006[86]					
Wright *et al*., 2003[87]					
Zaphiriou *et al*., 2005[88]					
Emergency department settings					
Knudsen *et al*., 2004[90]					

Dark grey shading, yes; light grey shading, unclear; unshaded, no; U, unpublished.

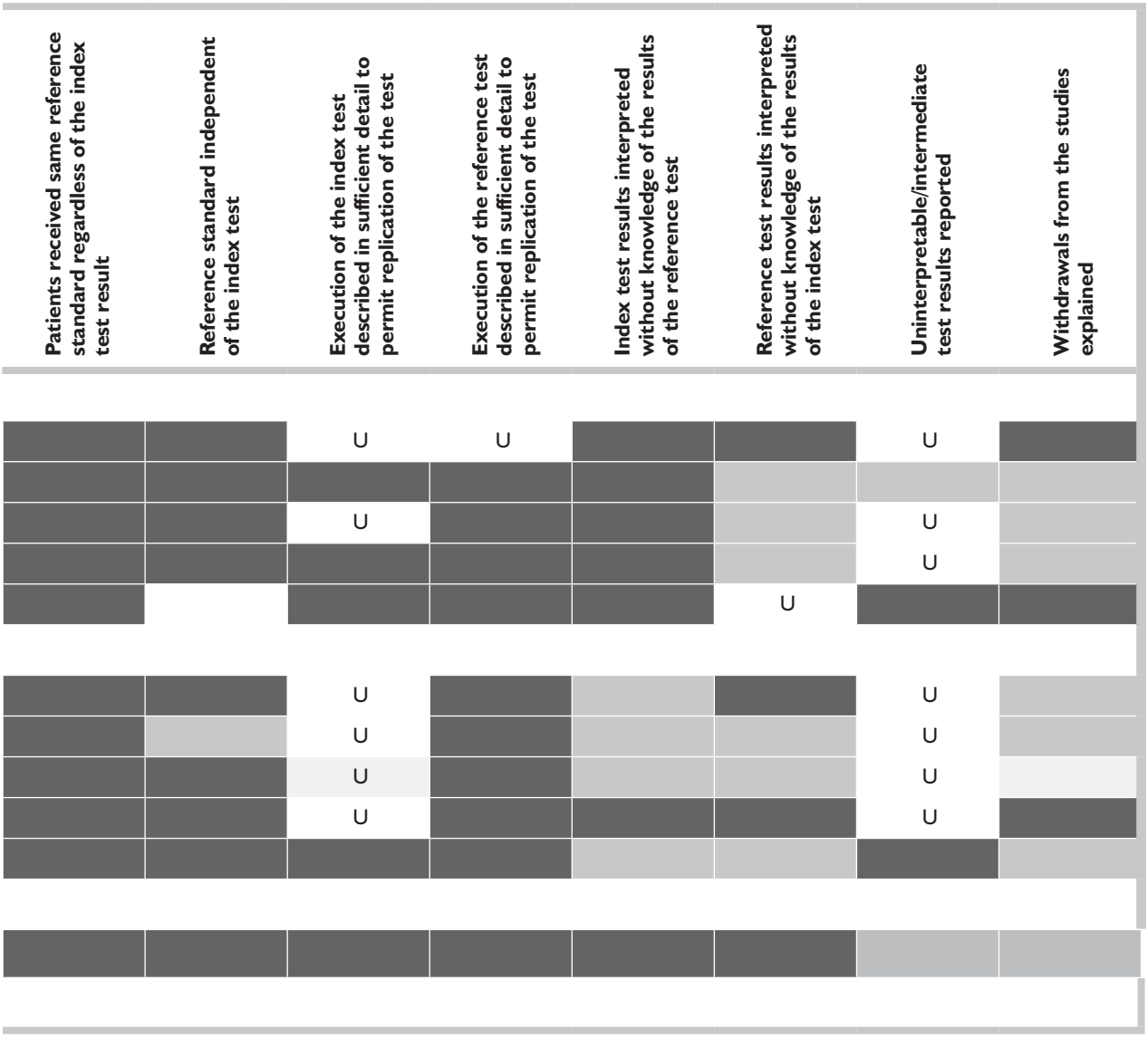


TABLE 39 *Quality of studies assessing the diagnostic accuracy of chest X-ray versus a clinical diagnosis of heart failure*

Reference	Consecutive series or random sample of consecutive series of patients	Selection criteria clearly described	Reference standard likely to correctly classify the target condition	Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	Whole or random selection of sample received verification using the reference standard of diagnosis
GP setting					
Alehagen *et al*., 2003[80]					
Fonseca *et al*., 2004[79]					
GP patients referred to open access heart failure or echocardiography clinics					
Cowie *et al*., 1997[84]					
Fox *et al*., 2000[85]					
Wright *et al*., 2003[87]					
Emergency department settings					
Jose *et al*., 2003[89]					
Knudsen *et al*., 2004[90]					
Logeart *et al*., 2002[91]					
Morrison *et al*., 2002[92]					

Dark grey shading, yes; light grey shading, unclear; unshaded, no; U, unpublished.

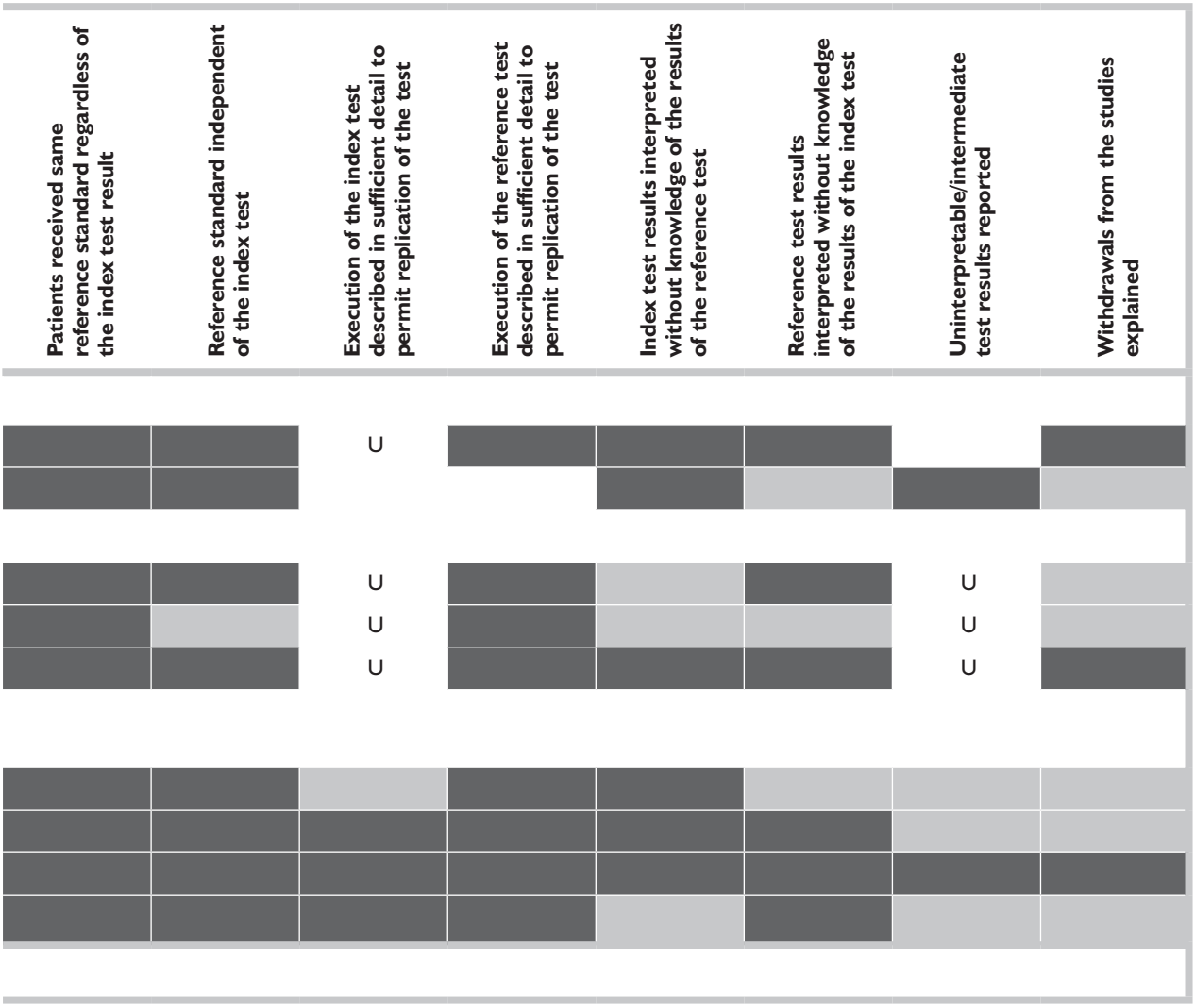


TABLE 40 *Quality of studies assessing the diagnostic accuracy of BNP versus a clinical diagnosis of heart failure*

Reference	Consecutive series or random sample of consecutive series of patients	Selection criteria clearly described	Reference standard likely to correctly classify the target condition	Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	Whole or random selection of sample received verification using the reference standard of diagnosis
GP setting					
Hobbs *et al*., 2002[82]					
Cost 2000[97]					
GP patients referred to open access heart failure or echocardiography clinics					
Cowie *et al*., 1997[84]					
Misuraca *et al*., 2002[98]					
Zaphiriou *et al*., 2005[88]					
Emergency department setting					
Ababsa *et al*., 2005[99]					
Alibay *et al*., 2005[100]					
Barcarse *et al*., 2004[101]					
El Mahmoud *et al*., 2006[102]					
Jourdain *et al*., 2002[106]					
Lainchbury *et al*., 2003[103]					
Logeart *et al*., 2002[91]					
Maisel *et al*., 2002[104]					
Morrison *et al*., 2002[92]					
Mueller *et al*., 2005[93]					
Ray *et al*., 2004[107]					
Villacorta *et al*., 2002[105]					
Inpatient setting					
Davis *et al*., 1994[108]					
Dokainish *et al*., 2004[109]					
McLean *et al*., 2003[110]					

Dark grey shading, yes; light grey shading, unclear; unshaded, no; U, unpublished.

TABLE 41 *Quality of studies assessing the diagnostic accuracy of NT-proBNP versus a clinical diagnosis of heart failure*

Reference	Consecutive series or random sample of consecutive series of patients	Selection criteria clearly described	Reference standard likely to correctly classify the target condition	Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	Whole or random selection of sample received verification using the reference standard of diagnosis
GP setting					
Alehagen *et al*., 2003[80]	■	■	■		▒
Galasko *et al*., 2005[81]	■	■	■	▒	■
Hobbs *et al*., 2002[82]	■	■	■	▒	■
Rutten *et al*., 2005[83]		■	■	■	■
GP patients referred to open access heart failure or echocardiography clinics					
Lim *et al*., 2006[86]	▒		▒	▒	■
Nielsen *et al*., 2004[111]	■	■	▒	■	■
Wright *et al*., 2003[87]		■	■	■	■
Zaphiriou *et al*., 2005[88]	■	■	▒	■	■
Emergency department setting					
Alibay *et al*., 2005[100]	■		■	■	■
Bayes-Genis *et al*., 2004[112]	■	■	■	■	■
El Mahmoud *et al*., 2006[102]			■		
Januzzi *et al*., 2005[113]	■	■	■	■	■
Lainchbury *et al*., 2003[103]	▒	■	■	■	■
Mueller *et al*., 2005[93]	■	■	▒	■	■
Outpatient setting					
Jose *et al*., 2003[89]	▒	■	▒	▒	■
Inpatient setting					
Berdague *et al*., 2006[114]	■	■	■	■	■

Dark grey shading, yes; light grey shading, unclear; unshaded, no; U, unpublished.

TABLE 42 *Quality of studies assessing the diagnostic accuracy of symptoms and signs versus left ventricular systolic dysfunction*

Reference	Consecutive series or random sample of consecutive series of patients	Selection criteria clearly described	Reference standard likely to correctly classify the target condition	Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	Whole or random selection of sample received verification using the reference standard of diagnosis	Patients received same reference standard regardless of the index test result
GP setting						
Hobbs *et al.*, 2002[82]						
McDonagh *et al.*, 1997[10]						
Morgan *et al.*, 1999[11]						
Nielsen *et al.*, 2000[139]						
Sparrow *et al.*, 2003[140]						
GP patients referred to open access heart failure or echocardiography clinics						
Davie *et al.*, 1997[141]						
Fuat *et al.*, 2006[142]						
Gustafsson *et al.*, 2005[143]						
Outpatient setting						
Mattleman *et al.*, 1983[144]						
Rihal *et al.*, 1995[145]						
Wattanabe *et al.*, 2005[146]						
Inpatient setting						
Gadsboll *et al.*, 1989[167]						
Jain *et al.*, 1993[147]						
Mueller *et al.*, 2004[194]						
Narain *et al.*, 2005[148]						
Talreja *et al.*, 2000[149]						
Zema *et al.*, 1984[150]						

Dark grey shading, yes; light grey shading, unclear; unshaded, no; U, unpublished.

TABLE 43 *Quality of studies assessing the diagnostic accuracy of electrocardiography versus left ventricular systolic dysfunction*

Reference	Consecutive series or random sample of consecutive series of patients	Selection criteria clearly described	Reference standard likely to correctly classify the target condition	Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	Whole or random selection of sample received verification using the reference standard of diagnosis
GP setting					
Alehagen *et al.*, 2003[80]					
Galasko *et al.*, 2005[81]					
Hobbs *et al.*, 2002[82]					
McDonagh *et al.*, 1997[10]					
Ng *et al.*, 2003[151]					
Nielsen *et al.*, 2000[139]					
Sparrow *et al.*, 2003[140]					
GP patients referred to open access heart failure or echocardiography clinics					
Davie *et al.*, 1997[141]					
Fuat *et al.*, 2006[142]					
Landray *et al.*, 2000[152]					
Lim *et al.*, 2006[86]					
Lindsay *et al.*, 2000[153]					
Sandler *et al.*, 2000[154]					
Population cohort or screening studies					
Hedberg *et al.*, 2004[155]					
Mosterd *et al.*, 1997[156]					
Outpatient setting					
Baker *et al.*, 2003[157]					
Christian *et al.*, 1997[158]					
Houghton *et al.*, 1997[159]					
Hutcheon *et al.*, 2002[133]					
Rihal *et al.*, 1995[145]					
Talwar *et al.*, 1999[160]					
Inpatient setting					
Gillespie *et al.*, 1997[161]					
Talreja *et al.*, 2000[149]					

Dark grey shading, yes; light grey shading, unclear; unshaded, no; U, unpublished.

TABLE 44 *Quality of studies assessing the diagnostic accuracy of chest X-ray versus left ventricular systolic dysfunction*

Reference	Consecutive series or random sample of consecutive series of patients	Selection criteria clearly described	Reference standard likely to correctly classify the target condition	Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	Whole or random selection of sample received verification using the reference standard of diagnosis	Patients received same reference standard regardless of the index test result
GP patients referred to open access heart failure or echocardiography clinics						
Landray *et al.*, 2000[152]						
Mattleman *et al.*, 1983[144]						
Rihal *et al.*, 1995[145]						
Sandler *et al.*, 2000[154]						
Outpatient settings						
Madsen *et al.*, 1984[163]						
Talreja *et al.*, 2000[149]						
Zema *et al.*, 1983[150]						
Inpatient settings						
Gadsboll *et al.*, 1989[164]						
Gillespie *et al.*, 1997[161]						
Hendry *et al.*, 1999[162]						
Jain *et al.*, 1993[147]						

Dark grey shading, yes; light grey shading, unclear; unshaded, no.

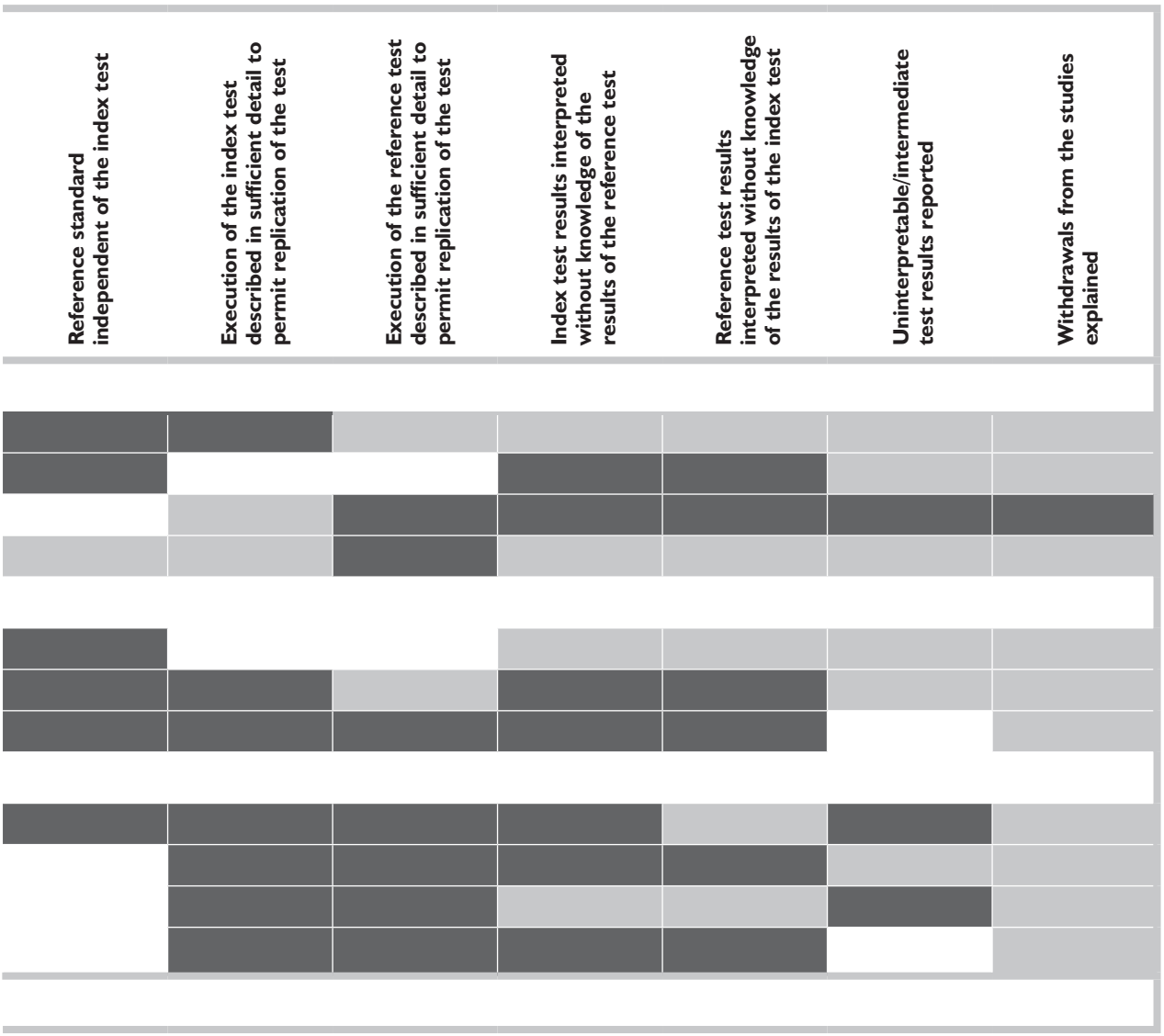


TABLE 45 *Quality of studies assessing the diagnostic accuracy of BNP versus left ventricular systolic dysfunction*

Reference	Consecutive series or random sample of consecutive series of patients	Selection criteria clearly described	Reference standard likely to correctly classify the target condition	Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	Whole or random selection of sample received verification using the reference standard of diagnosis
GP setting					
Hobbs *et al.*, 2004[82]					
McDonagh *et al.*, 1998[165]					
McGeoch *et al.*, 2002[166]					
Ng *et al.*, 2003[151]					
Nielsen *et al.*, 2003[139]					
Smith *et al.*, 2000[167]					
Sparrow *et al.*, 2003[140]					
GP patients referred to open access heart failure or echocardiography clinics					
Fuat *et al.*, 2006[142]					
Landray *et al.*, 2000[152]					
Sim *et al.*, 2003[168]					
Population cohort or screening studies					
Costello-Boerrigter *et al.*, 2006[169]					
Hedberg *et al.*, 2004[155]					
Luchner *et al.*, 2000[170]					
Lukowic *et al.*, 2005[171]					
Vasan *et al.*, 2002[172]					
Outpatient setting					
Atisha *et al.*, 2004[173]					
Bibbins-Domingo *et al.*, 2004[174]					
Falkensammer *et al.*, 2005[175]					
Krishnaswamy *et al.*, 2001[176]					
Kruger *et al.*, 2004[132]					
Mallamaci *et al.*, 2001[177]					
Richards *et al.*, 2006[178]					
Valli *et al.*, 2001[179]					

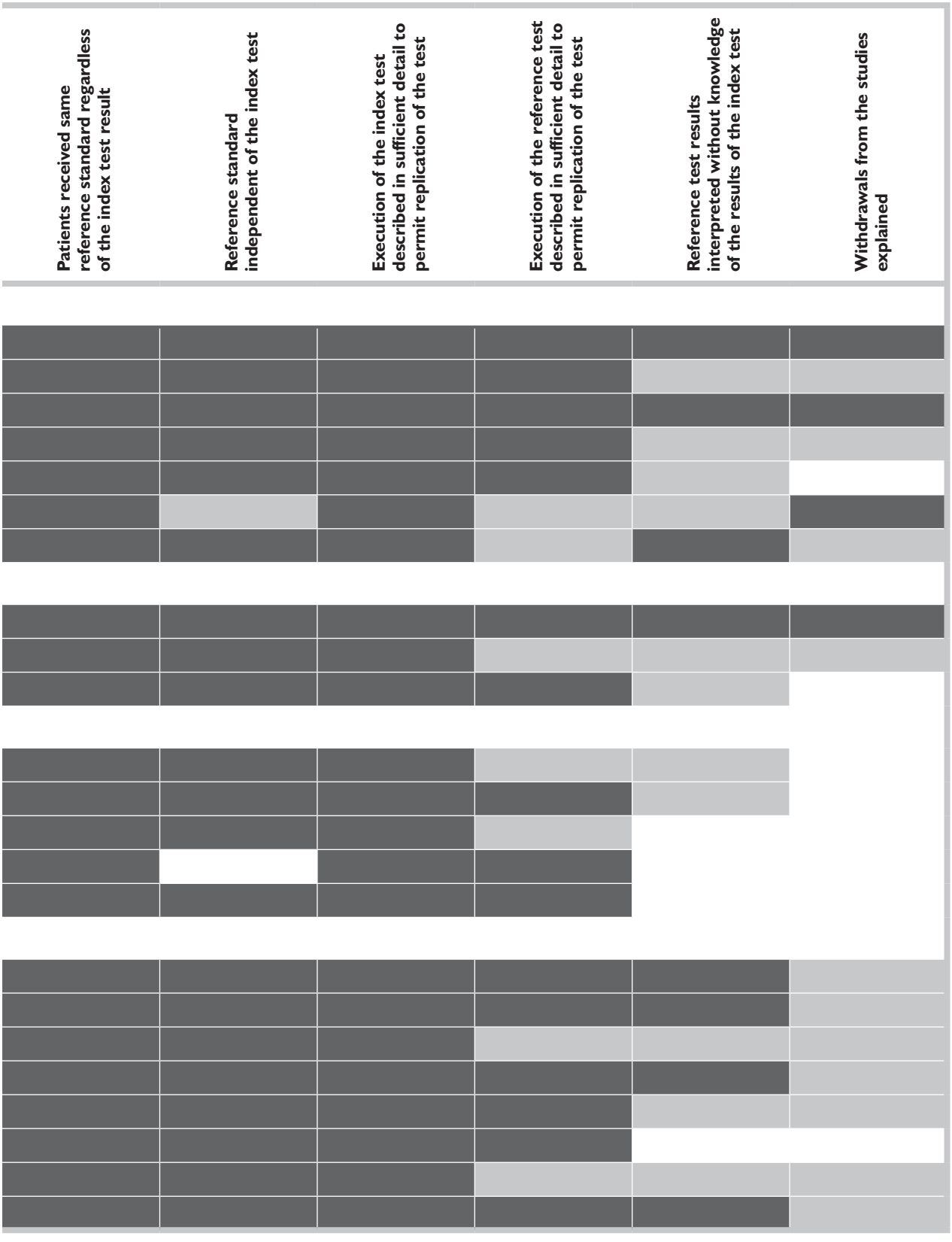


TABLE 45 *Quality of studies assessing the diagnostic accuracy of BNP versus left ventricular systolic dysfunction (continued)*

Reference	Consecutive series or random sample of consecutive series of patients	Selection criteria clearly described	Reference standard likely to correctly classify the target condition	Time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests	Whole or random selection of sample received verification using the reference standard of diagnosis
Vanderheyden *et al.*, 2006[180]	■	■	□	■	■
Wattanabe *et al.*, 2005[146]	□	□	■	■	■
Yamamoto *et al.*, 2000[182]	■	■	■	■	■
Yamamoto *et al.*, 1996[181]	■		■	■	■
Inpatient setting					
Bal *et al.*, 2006[183]	■		■	■	■
Bettencourt *et al.*, 2000[184]	■	■	■	■	■
Byrne *et al.*, 1996[185]	□	□	■	□	□
Choy *et al.*, 1994[186]	■	■	■	■	■
Mueller *et al.*, 2004[194]	■	■	■	■	■
Osca *et al.*, 2002[187]	■	■	■	□	
Pfister *et al.*, 2002[188]	■	■	■	□	■
Richards *et al.*, 1998[189]	■		■	■	■

Dark grey shading, yes; light grey shading, unclear; unshaded, no.

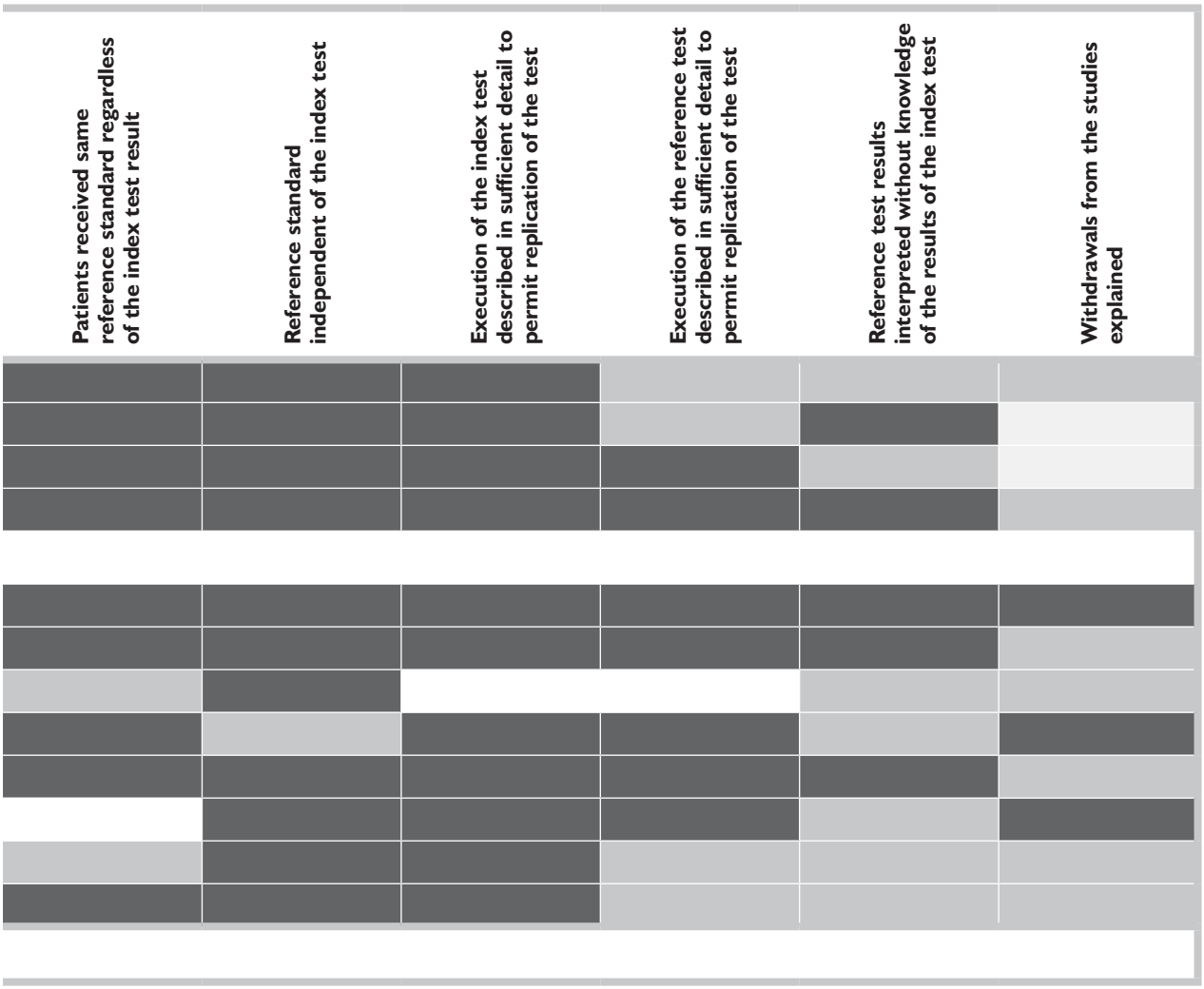
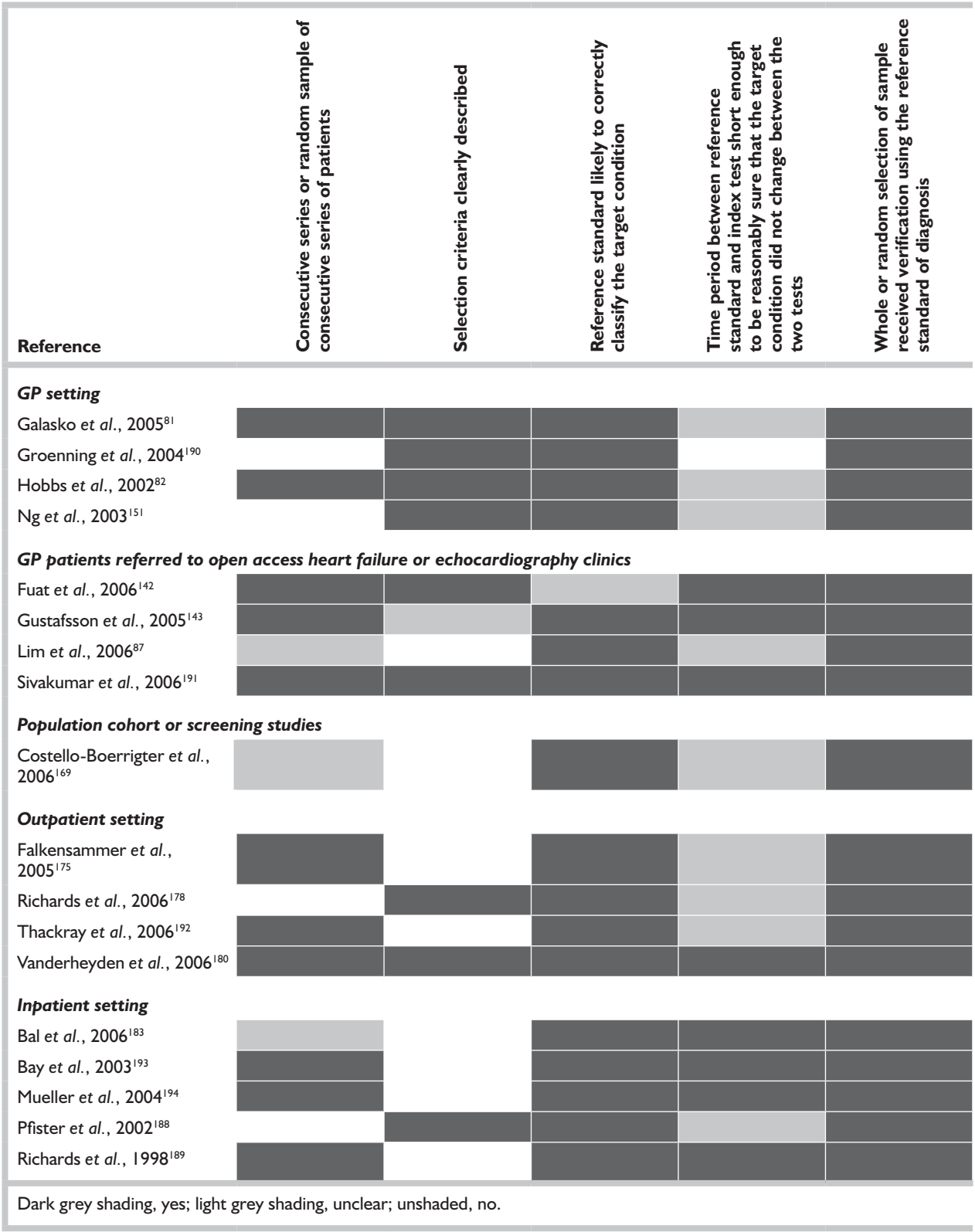
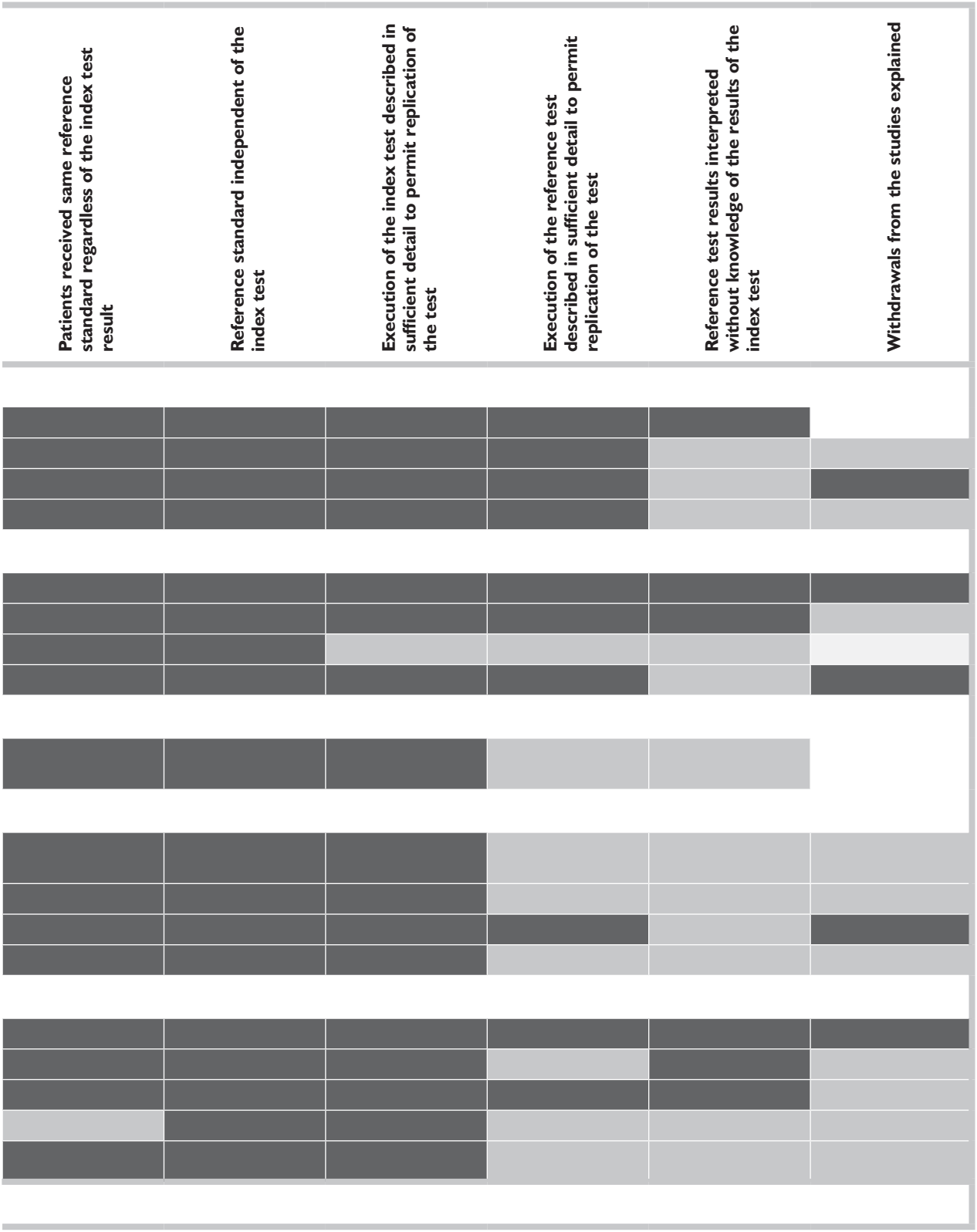


TABLE 46 *Quality of studies assessing the diagnostic accuracy of NT-proBNP versus left ventricular systolic dysfunction*



Dark grey shading, yes; light grey shading, unclear; unshaded, no.



The quality of the included studies was assessed using items from QUADAS, a validated tool for assessing the quality of diagnostic studies.[76] QUADAS contains 14 items relating to patient spectrum, reference standard, disease progression bias, verification bias, review bias, incorporation bias, test execution, study withdrawals and intermediate results.

The items that were included in the assessment of quality and how they were assessed are as follows:

1. We included an item on the method of recruitment (random or consecutive sample of patients). This was included to demonstrate the representativeness of the patient sample to those of interest to this review, that is, patients presenting in whom the diagnosis of heart failure is suspected. The usual first question from the QUADAS list on the representativeness of the patient spectrum was dropped, and studies were grouped by the clinical setting, including subgroup analyses of studies conducted in primary care settings.
2. Was a clear description given of selection criteria?
3. Is the reference standard likely to classify the target condition? This was assessed as satisfactory in studies using a diagnosis of heart failure if the study used a recognised clinical definition of heart failure (such as ESC criteria) and more than one clinician was involved in the assessment of the diagnosis. In studies that used a reference standard of LVSD, this was considered satisfactory if the method for establishing the left ventricular ejection fraction was described and was satisfactory.
4. Time between the index and reference tests.
5. Was partial verification prevented?
6. Was differential verification prevented?
7. The independence of the index test and the reference test.
8. Was the execution of the index test reported in sufficient detail to allow replication?
9. Was the execution of the reference test reported in sufficient detail to allow replication?
10. Was the index test interpreted blind to the reference test? This item was omitted for the BNP and NT-proBNP studies as the results are objective and do not require interpretation.
11. Was the reference test interpreted blind to the index test?
12. Was the same information provided to the researchers as would be available in clinical practice? This question was omitted as it was unclear from study reports what clinical information was provided within the research studies and if this was similar to the information that would be available in clinical practice.
13. Were uninterpretable or intermediate results reported? This item was omitted from the quality assessment of diagnostic accuracy studies involving BNP and NT-proBNP as the tests are automated and uninterpretable or intermediate results are unlikely to occur.
14. Were withdrawals from the studies explained?

Appendix 4

Summary of results from included studies

TABLE 47 *Accuracy of symptoms and signs versus a clinical diagnosis of heart failure*

Reference	*n*	Patients	Index test	Reference test	TP	FP	TN	FN	LR+	LR–
History of MI										
General practice setting										
Galasko *et al.*, 2005[81]	376	Patients with symptoms of heart failure or on loop diuretics	History of MI	ESC criteria	30	51	260	35	2.81	0.64
Hobbs *et al.*, 2002[82]	273	Randomly selected patients (stratified by age): subgroup of patients presenting with symptoms and signs of heart failure	History of MI	ESC criteria	6	36	220	11	2.51	0.75
Cost 2000[97]	149	Patients with symptoms of heart failure referred for assessment	History of MI	Clinical consensus	8	9	96	36	2.12	0.89
GP patients referred to open access heart failure or echocardiography clinics										
Cowie *et al.*, 1997[84]	122	Patients referred to a rapid access heart failure clinic	History of MI	ESC criteria	5	3	84	30	4.14	0.89
Fox *et al.*, 2000[85]	383	Patients referred to an open access heart failure clinic	History of MI	ESC criteria	13	30	249	88	1.20	0.98
Wright *et al.*, 2003[87]	305	Patients with dyspnoea and/or oedema referred for assessment in study	History of MI	Clinical consensus	26	18	210	51	4.28	0.72
Zaphiriou *et al.*, 2005[88]	302	Patients referred to rapid access heart failure clinic	History of MI	ESC criteria	28	14	188	76	3.88	0.79
Emergency department setting										
Jose *et al.*, 2003[89]	119	Patients with acute or chronic dyspnoea (excluded patients with ACS, includes patients in outpatient settings)	History of MI	Framingham criteria including echocardiography results	28	6	40	45	2.94	0.71
Knudsen *et al.*, 2004[90]	880	Patients with dyspnoea as predominant symptom	History of MI	Clinical consensus	248	328	265	39	1.56	0.30
Logeart *et al.*, 2002[91]	163	Patients with acute severe dyspnoea	History of MI	Clinical consensus	49	4	44	66	5.11	0.63
Dyspnoea										
General practice setting										
Alehagen *et al.*, 2003[80]	415	Patients presenting with symptoms and signs of heart failure with no previous diagnosis	Dyspnoea	LVEF < 40% or atrial fibrillation and symptoms of heart failure	44	142	249	23	1.81	0.54

Reference	n	Patients	Index test	Reference test	TP	FP	TN	FN	LR+	LR–
Fonseca *et al.*, 2004[79]	1058	Randomly selected patients (stratified by age)	Dyspnoea	ESC criteria	501	46	461	50	10.03	0.10
Hobbs *et al.*, 2002[82]	273	Randomly selected patients (stratified by age): subgroup of patients presenting with symptoms and signs of heart failure	Dyspnoea	ESC criteria	17	141	115	0	1.82	0.00
GP patients referred to open access heart failure or echocardiography clinics										
Cowie *et al.*, 1997[84]	122	Patients referred to a rapid access heart failure clinic	Dyspnoea	ESC criteria	30	61	26	5	1.22	0.48
Emergency department setting										
Morrison *et al.*, 2002[92]	276	Patients with dyspnoea	Dyspnoea	Clinical consensus	70	86	101	64	1.14	0.88
Fonseca *et al.*, 2004[79]	1058	Randomly selected patients (stratified by age)	Dyspnoea at rest	ESC criteria	61	5	502	490	11.00	0.90
Fonseca *et al.*, 2004[79]	1058	Randomly selected patients (stratified by age)	Dyspnoea on exertion	ESC criteria	435	81	426	116	4.94	0.25
Morrison *et al.*, 2002[92]	276	Patients with dyspnoea	Dyspnoea on exertion	Clinical consensus	114	127	60	20	1.25	0.47
Fonseca *et al.*, 2004[79]	1058	Randomly selected patients (stratified by age)	Dyspnoea when walking on the flat	ESC criteria	198	5	502	353	36.00	0.65
Fonseca *et al.*, 2004[79]	1058	Randomly selected patients (stratified by age)	Dyspnoea when walking fast or slightly uphill	ESC criteria	424	91	416	127	4.28	0.28
Fonseca *et al.*, 2004[79]	1058	Randomly selected patients (stratified by age)	Dyspnoea when walking uphill	ESC criteria	485	117	390	66	3.83	0.16
Orthopnoea										
General practice setting										
Fonseca *et al.*, 2004[79]	1058	Randomly selected patients (stratified by age)	Orthopnoea	ESC criteria	138	31	504	413	4.31	0.80
Rutten *et al.*, 2005[83]	405	COPD patients with no previous diagnosis of heart failure	Orthopnoea	Clinical consensus	25	83	239	58	1.17	0.94
Emergency department setting										
Jose *et al.*, 2003[89]	119	Patients with acute or chronic dyspnoea (excluded patients with ACS, includes patients in outpatient settings)	Orthopnoea	Framingham criteria	42	3	43	31	8.82	0.45

continued

TABLE 47 *Accuracy of symptoms and signs versus a clinical diagnosis of heart failure (continued)*

Reference	*n*	Patients	Index test	Reference test	TP	FP	TN	FN	LR+	LR–
Knudsen *et al.*, 2004[90]	880	Patients with dyspnoea as predominant symptom	Orthopnoea	Clinical consensus	295	186	247	152	1.53	0.60
Logeart *et al.*, 2002[91]	163	Patients with acute severe dyspnoea	Orthopnoea	Clinical consensus	49	7	41	66	2.92	0.67
Morrison *et al.*, 2002[92]	276	Patients with dyspnoea	Orthopnoea	Clinical consensus	62	32	155	72	2.70	0.65
PND										
General practice setting										
Fonseca *et al.*, 2004[79]	1058	Randomly selected patients (stratified by age)	PND	ESC criteria	160	98	497	391	1.76	0.85
Morrison *et al.*, 2002[92]	276	Patients with dyspnoea	PND	Clinical consensus	46	26	161	88	2.47	0.76
Mueller *et al.*, 2005[93]	452	Patients with dyspnoea	PND	Framingham criteria	102	64	171	115	1.73	0.73
Oedema										
General practice setting										
Fonseca *et al.*, 2004[79]	1058	Randomly selected patients (stratified by age)	Oedema	ESC criteria	309	56	451	242	5.07	0.49
Hobbs *et al.*, 2002[82]	273	Randomly selected patients (stratified by age): subgroup of patients presenting with symptoms and signs of heart failure	Oedema	ESC criteria	9	118	138	8	1.15	0.87
Rutten *et al.*, 2005[83]	405	COPD patients with no previous diagnosis of heart failure	Oedema	Clinical consensus	22	54	268	61	1.58	0.88
GP patients referred to open access heart failure or echocardiography clinics										
Cowie *et al.*, 1997[84]	122	Patients referred to a rapid access heart failure clinic	Oedema	ESC criteria	20	42	45	15	1.18	0.83
Fox *et al.*, 2000[85]	383	Patients referred to an open access heart failure clinic	Oedema	ESC criteria	53	100	178	48	1.46	0.74
Lim *et al.*, 2006[86]	137	Patients referred to a specialist unit for echocardiography	Oedema	LVEF < 40% or atrial fibrillation or valve disease and symptoms of heart failure	14	39	67	17	1.23	0.87

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Reference	*n*	Patients	Index test	Reference test	TP	FP	TN	FN	LR+	LR–
Zaphiriou *et al.*, 2005[88]	302	Patients referred to rapid access heart failure clinic	Oedema	ESC criteria	79	118	84	25	1.30	0.58
Emergency department setting										
Jose *et al.*, 2003[89]	119	Patients with acute or chronic dyspnoea (excluded patients with ACS, includes patients in outpatient settings)	Oedema	Framingham criteria	52	5	41	21	6.55	0.32
Knudsen *et al.*, 2004[90]	880	Patients with dyspnoea as predominant symptom	Oedema	Clinical consensus	286	113	320	161	2.46	0.49
Logeart *et al.*, 2002[91]	163	Patients with acute severe dyspnoea	Oedema	Clinical consensus	37	7	41	98	1.88	0.85
Morrison *et al.*, 2002[92]	276	Patients with dyspnoea	Oedema	Clinical consensus	101	55	180	116	1.99	0.70
Elevated JVP										
General practice setting										
Fonseca *et al.*, 2004[79]	1058	Randomly selected patients (stratified by age)	Elevated JVP	ESC criteria	182	15	492	369	11.00	0.69
Rutten *et al.*, 2005[83]	405	COPD patients with no previous diagnosis of heart failure	Elevated JVP	Clinical consensus	26	75	247	57	1.34	0.90
Emergency department setting										
Knudsen *et al.*, 2004[90]	880	Patients with dyspnoea as predominant symptom	Elevated JVP	Clinical consensus	170	43	390	277	3.80	0.69
Jose *et al.*, 2003[89]	119	Patients with acute or chronic dyspnoea (excluded patients with ACS, includes patients in outpatient settings)	Elevated JVP	Framingham criteria	50	11	35	23	2.86	0.41
Logeart *et al.*, 2002[91]	163	Patients with acute severe dyspnoea	Elevated JVP	Clinical consensus	68	10	38	47	2.84	0.52
Morrison *et al.*, 2002[92]	276	Patients with dyspnoea	Elevated JVP	Clinical consensus	50	13	174	84	5.37	0.67
Mueller *et al.*, 2005[93]	452	Patients with dyspnoea	Elevated JVP	Framingham criteria	49	15	220	168	3.54	0.83

continued

TABLE 47 *Accuracy of symptoms and signs versus a clinical diagnosis of heart failure (continued)*

Reference	*n*	Patients	Index test	Reference test	TP	FP	TN	FN	LR+	LR–
Cardiomegaly										
General practice setting										
Rutten *et al.*, 2005[83]	405	COPD patients with no previous diagnosis of heart failure	Cardiomegaly	Clinical consensus	22	48	274	61	1.78	0.86
Added heart sounds										
General practice setting										
Fonseca *et al.*, 2004[79]	1058	Randomly selected patients (stratified by age)	Added heart sounds	ESC criteria	18	1	506	533	30.00	0.97
Emergency department setting										
Knudsen *et al.*, 2004[90]	880	Patients with dyspnoea as predominant symptom	Added heart sounds	Clinical consensus	58	9	424	389	6.50	0.89
Morrison *et al.*, 2002[92]	276	Patients with dyspnoea	Added heart sounds	Clinical consensus	17	2	185	117	11.86	0.88
Jose *et al.*, 2003[89]	119	Patients with acute or chronic dyspnoea (excluded patients with ACS, includes patients in outpatient settings)	Added heart sounds	Framingham criteria	36	2	44	37	11.34	0.53
Logeart *et al.*, 2002[91]	163	Patients with acute severe dyspnoea	Added heart sounds	Clinical consensus	19	3	45	96	2.64	0.89
Mueller *et al.*, 2005[93]	452	Patients with dyspnoea	Added heart sounds	Framingham criteria	6	0	211	235	Cannot calculate	0.98
Lung crepitations										
General practice setting										
Fonseca *et al.*, 2004[79]	1058	Randomly selected patients (stratified by age)	Lung crepitations	ESC criteria	204	152	355	347	11.86	0.65
Hobbs *et al.*, 2002[82]	273	Randomly selected patients (stratified by age): subgroup of patients presenting with symptoms and signs of heart failure	Lung crepitations	ESC criteria	4	17	239	13	3.54	0.82
Rutten *et al.*, 2005[83]	405	COPD patients with no previous diagnosis of heart failure	Lung crepitations	Clinical consensus	31	97	225	52	1.24	0.90

Reference	n	Patients	Index test	Reference test	TP	FP	TN	FN	LR+	LR–
GP patients referred to open access heart failure or echocardiography clinics										
Fox *et al.*, 2000[85]	383	Patients referred to an open access heart failure clinic	Lung crepitations	ESC criteria	54	76	206	47	1.98	0.64
Wright *et al.*, 2003[87]	305	Patients with dyspnoea and/or oedema referred for assessment in study	Lung crepitations	Clinical consensus	37	32	195	40	3.41	0.60
Zaphiriou *et al.*, 2005[88]	302	Patients referred to rapid access heart failure clinic	Lung crepitations	ESC criteria	50	38	164	54	2.56	0.64
Emergency department setting										
Knudsen *et al.*, 2004[90]	880	Patients with dyspnoea as predominant symptom	Lung crepitations	Clinical consensus	264	100	333	183	2.57	0.53
Logeart *et al.*, 2002[91]	163	Patients with acute severe dyspnoea	Lung crepitations	Clinical consensus	87	18	30	28	2.02	0.39
Morrison *et al.*, 2002[92]	276	Patients with dyspnoea	Lung crepitations	Clinical consensus	66	36	151	68	2.56	0.63
Mueller *et al.*, 2005[93]	452	Patients with dyspnoea	Lung crepitations	Framingham criteria	130	77	158	87	1.83	0.60
Hepatomegaly										
General practice setting										
Fonseca *et al.*, 2004[79]	1058	Randomly selected patients (stratified by age)	Hepatomegaly	ESC criteria	94	141	366	457	5.67	0.86

ACS, acute coronary syndrome; COPD, chronic obstructive pulmonary disease; ESC, European Society of Cardiology; FN, false negative; FP, false positive; HF, heart failure; JVP, jugular venous pressure; LR+, likelihood ratio of a positive test; LR–, likelihood ratio of a negative test; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PND, paroxysmal nocturnal dyspnoea; TN, true negative; TP, true positive.

TABLE 48 *Accuracy of electrocardiography versus a clinical diagnosis of heart failure*

Reference	*n*	Patients	Index test	Reference test	TP	FP	TN	FN	LR+	LR–
General practice setting										
Alehagen *et al.*, 2003[80]	415	Patients presenting with symptoms and signs of heart failure with no previous diagnosis	ECG not in sinus rhythm or atrial fibrillation or sign of past ischaemic myocardial damage	LVEF < 40% or atrial fibrillation and symptoms of heart failure	44	59	332	23	4.35	0.40
Fonseca *et al.*, 2004[79]	1058	Randomly selected patients (stratified by age)	Abnormal rhythm, atrial abnormalities, conduction disturbances, presence of abnormal Q waves, poor R-wave progression in precordial leads, LVH, abnormal ST-segment T-wave changes (read by cardiologist)	ESC criteria (one clinician)	446	248	259	105	1.65	0.37
Galasko *et al.*, 2005[81]	376	Patients with symptoms of heart failure or on loop diuretics	Any abnormality	EF <40% or atrial fibrillation or valve disease and symptoms of heart failure	59	124	187	6	2.28	0.15
Hobbs *et al.*, 2002[82]	273	Randomly selected patients (stratified by age): subgroup of patients presenting with symptoms and signs of heart failure	Any abnormality	ESC criteria (panel of three clinicians in equivocal cases)	16	136	120	1	1.77	0.13
Rutten *et al.*, 2005[83]	405	COPD patients with no previous diagnosis of heart failure	Evidence of previous MI, complete or incomplete left BBB, LVH, atrial fibrillation, ST and/or T-wave abnormalities and sinus tachycardia (read by cardiologist)	Clinical consensus (two cardiologists, one GP and one pulmonologist)	52	231	91	31	0.87	1.32

Reference	*n*	Patients	Index test	Reference test	TP	FP	TN	FN	LR+	LR–
GP patients referred to open access heart failure or echocardiography clinics										
Cowie *et al.*, 1997[84]	122	Patients referred to a rapid access heart failure clinic	Any abnormality	ESC criteria (three cardiologists)	35	36	51	0	2.42	0.00
Fox *et al.*, 2000[85]	383	Patients referred to an open access heart failure clinic	Any abnormality (read by specialist registrar in cardiology)	ESC criteria (one cardiologist)	101	162	120	0	1.74	0.00
Lim *et al.*, 2006[86]	137	Patients referred to a specialist unit for echocardiography	Any abnormality	EF < 40% or atrial fibrillation or valve disease and symptoms of heart failure	29	52	54	2	1.91	0.13
Wright *et al.*, 2003[87]	305	Patients with dyspnoea and/or oedema referred for assessment in study	Not in sinus rhythm, presence of Q waves, ST abnormalities, T-wave abnormalities, LVH, BBB, QRS duration > 120 ms	Clinical consensus (three cardiologists and one GP)	71	125	103	6	1.68	0.17
Zaphiriou *et al.*, 2005[88]	302	Patients referred to rapid access heart failure clinic	Any abnormality	ESC criteria (one cardiologist)	84	81	121	20	2.01	0.32
Emergency department setting										
Knudsen *et al.*, 2004[90]	880	Patients with dyspnoea as predominant symptom	Evidence of previous MI, atrial fibrillation, atrial flutter, right or left BBB, ST-segment deviation (read by attending physician)	Clinical consensus (two cardiologists)	334	67	237	242	2.63	0.54

BBB, bundle branch block; EF, ejection fraction; ESC, European Society of Cardiology; FN, false negative; FP, false positive; HF, heart failure; LR+, likelihood ratio of a positive test; LR–, likelihood ratio of a negative test; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MI. myocardial infarction; TN, true negative; TP, true positive.

TABLE 49 *Accuracy of chest X-ray versus a clinical diagnosis of heart failure*

Reference	*n*	Patients	Index test	Reference test	TP	FP	TN	FN	LR+	LR–
General practice setting										
Alehagen *et al.*, 2003[80]	415	Patients presenting with symptoms and signs of heart failure with no previous diagnosis	Increased CTR or pulmonary congestion	LVEF < 40% or atrial fibrillation and symptoms of heart failure	49	148	243	18	1.93	0.43
Fonseca *et al.*, 2004[79]	1058	Randomly selected patients (stratified by age)	Increased CTR or pulmonary congestion	ESC criteria (one clinician)	314	112	395	237	2.59	0.55
GP patients referred to open access heart failure or echocardiography clinics										
Cowie *et al.*, 1997[84]	122	Patients referred to a rapid access heart failure clinic	Increased CTR or pulmonary congestion	ESC criteria (three cardiologists)	35	30	57	0	2.90	0.00
Fox *et al.*, 2000[85]	383	Patients referred to an open access heart failure clinic	Increased CTR or pulmonary congestion	ESC criteria (one cardiologist)	40	11	268	61	10.05	0.63
Wright *et al.*, 2003[87]	305	Patients with dyspnoea and/or oedema referred for assessment in study	Increased CTR or pulmonary congestion	Clinical consensus (three cardiologists and one GP)	36	16	210	40	6.69	0.57
Emergency department setting										
Jose *et al.*, 2003[89]	119	Patients with acute or chronic dyspnoea (excluded patients with ACS, includes patients in outpatient settings)	Increased CTR	Framingham criteria including echocardiogram results	44	9	37	29	3.08	0.49
Knudsen *et al.*, 2004[90]	880	Patients with dyspnoea as predominant symptom	Increased CTR	Clinical consensus (two cardiologists)	353	87	346	94	3.95	0.26
Logeart *et al.*, 2002[91]	163	Patients with acute severe dyspnoea	Increased CTR	Clinical consensus (two cardiologists and one pneumotologist)	81	16	32	34	8.80	0.32
Morrison *et al.*, 2002[92]	276	Patients with dyspnoea	Increased CTR	Clinical consensus (two cardiologists using Framingham criteria)	71	19	168	63	5.21	0.52

ACS, acute coronary syndrome; CTR, cardiothoracic ratio; ESC, European Society of Cardiology; FN, false negative; FP, false positive; HF, heart failure; LR+, likelihood of a positive result; LR–, likelihood of a negative result; LVEF, left ventricular ejection fraction; TN, true negative; TP, true positive.

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TABLE 50 *Accuracy of BNP versus a clinical diagnosis of heart failure*

Reference	*n*	Patients	Index test; cut-off closest to 70 pg/ml	Reference test	TP	FP	TN	FN	LR+	LR–
General practice setting										
Hobbs *et al.*, 2002[82]	273	Randomly selected patients (stratified by age): subgroup of patients presenting with symptoms and signs of heart failure	Shionogi; 83	ESC criteria (panel of three clinicians in equivocal cases)	15	84	172	2	2.69	0.18
Rutten *et al.*, 2005[83]	405	COPD patients with no previous diagnosis of heart failure	Roche; 56	Clinical consensus (two cardiologists, one GP and one pulmonologist)	52	231	91	31	0.87	1.32
GP patients referred to open access heart failure or echocardiography clinics										
Cowie *et al.*, 1997[84]	122	Patients referred to a rapid access heart failure clinic	Peninsula; 79	ESC criteria (three cardiologists)	28	12	65	1	6.20	0.04
Misuraca *et al.*, 2002[98]	83	Patients referred with diagnosis of heart failure	Shionogi; 20	Clinical symptoms and signs and echocardiographic criteria of systolic and diastolic dysfunction	42	25	13	3	1.41	0.21
Zaphiriou *et al.*, 2005[88]	302	Patients referred to rapid access heart failure clinic	Triage; 100	ESC criteria (one cardiologist)	82	55	142	22	2.82	0.29
Emergency department setting										
Ababsa *et al.*, 2004[99]	192	Patients > 75 years with dyspnoea and suspected heart failure	Triage; 50	Clinical consensus (two cardiologists)	176	4	8	4	2.93	0.03
Alibay *et al.*, 2005[100]	160	Patients with dyspnoea	Triage; 150	Clinical consensus (two cardiologists)	56	39	61	4	2.39	0.11
Barcarse *et al.*, 2004[101]	98	Patients with acute dyspnoea	Triage; 110	Clinical diagnosis (one cardiologist)	55	4	37	2	9.89	0.04
El Mahmoud *et al.*, 2006[102]	103	Patients > 75 years with dyspnoea	Triage; 100	Clinical diagnosis (two independent cardiologists)	44	36	18	5	1.35	0.31
Jourdain *et al.*, 2002[106]	125	Patients with dyspnoea	Triage; 300	Clinical diagnosis	85	5	30	5	6.71	0.07
Lainchbury *et al.*, 2003[103]	205	Patients with acute dyspnoea	Triage; 208	ESC criteria (two independent cardiologists)	66	41	95	4	3.13	0.08

continued

TABLE 50 *Accuracy of BNP versus a clinical diagnosis of heart failure (continued)*

Reference	*n*	Patients	Index test; cut-off closest to 70 pg/ml	Reference test	TP	FP	TN	FN	LR+	LR–
Logeart *et al.*, 2002[91]	163	Patients with severe dyspnoea	Triage; 80	Clinical consensus (two cardiologists and one pneumotologist)	112	35	13	3	1.34	0.10
Maisel *et al.*, 2002[104]	1586	Patients with dyspnoea	Triage; 50	Clinical consensus (two cardiologists)	722	320	522	22	2.55	0.05
Morrison *et al.*, 2002[92]	321	Patients with dyspnoea	Triage; 94	Clinical consensus (two cardiologists using Framingham criteria)	113	4	182	19	39.81	0.15
Mueller *et al.*, 2005[93]	251	Patients with acute dyspnoea as the primary complaint.	Abbott; 118	Framingham criteria and echocardiographic criteria or systolic or diastolic dysfunction (one cardiologist)	130	41	73	7	2.64	0.08
Ray *et al.*, 2004[107]	313	Patients > 65 years with acute dyspnoea	Triage; 250	Clinical consensus (two independent physicians)	128	68	98	14	2.20	0.17
Villacorta *et al.*, 2002[105]	70	Patients with acute dyspnoea	Triage; 200	Clinical diagnosis (one cardiologist)	36	1	33	0	34.00	0.00
Inpatient setting										
Davis *et al.*, 1994[108]	52	Patients admitted for acute dyspnoea	NR; 76	Clinical consensus (panel of physicians and radiologist)	30	2	18	2	9.38	0.07
Dokainish *et al.*, 2004[109]	122	Patients referred to consultancy service for suspected heart failure	Boisite; 250	Framingham criteria (clinical examination by one cardiologist)	60	12	40	10	3.71	0.19
McLean *et al.*, 2003[110]	84	Patients admitted to ICU	Triage; 144	Clinical diagnosis by senior intensivists	24	8	50	2	6.69	0.09

COPD, chronic obstructive pulmonary disease; ESC, European Society of Cardiology; FN, false negative; FP, false positive; HF, heart failure; ICU, intensive care unit; LR+, likelihood of a positive result; LR–, likelihood of a negative result; TN, true negative; TP, true positive.

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TABLE 51 *Accuracy of NT-proBNP versus a clinical diagnosis of heart failure*

Reference	*n*	Patients	Index test; cut-off closest to 300 pg/ml	Reference test	TP	FP	TN	FN	LR+	LR–
General practice setting										
Alehagen *et al.*, 2003[80]	458	Patients presenting with symptoms and signs of heart failure with no previous diagnosis	In-house; 664	LVEF < 40% or atrial fibrillation and symptoms of heart failure	52	119	272	15	2.55	0.32
Galasko *et al.*, 2005[81]	566	Patients with symptoms of heart failure or on loop diuretics	Roche; 176	EF < 40% or atrial fibrillation or valve disease and symptoms of heart failure	59	153	149	5	1.82	0.16
Hobbs *et al.*, 2002[82]	273	Randomly selected patients (stratified by age): subgroup of patients presenting with symptoms and signs of heart failure	Roche; 304	ESC criteria (panel of three clinicians in equivocal cases)	16	122	133	1	1.97	0.11
Rutten *et al.*, 2005[83]	405	COPD patients with no previous diagnosis of heart failure	Roche; 125	Clinical consensus (two cardiologists, one GP and one pulmonologist)	65	140	182	18	1.80	0.38
GP patients referred to open access heart failure or echocardiography clinics										
Lim *et al.*, 2006[86]	137	Patients referred to a specialist unit for echocardiography	Roche; 846	EF < 40% or atrial fibrillation or valve disease and symptoms of heart failure	27	27	79	4	3.42	0.17
Nielsen *et al.*, 2004[111]	287	Patients referred with dyspnoea of < 2 weeks duration	Roche; 93	ESC criteria (one cardiologist)	46	40	60	0	2.50	0.00
Wright *et al.*, 2003[87]	305	Patients with dyspnoea and/or oedema referred for assessment in study	In-house; 846	Clinical consensus (three cardiologists and one GP)	57	40	188	20	4.22	0.32
Zaphiriou *et al.*, 2005[88]	302	Patients referred to rapid access heart failure clinic	Roche; 125	ESC criteria (one cardiologist)	102	129	69	2	1.51	0.06
Emergency department setting										
Alibay *et al.*, 2005[100]	160	Patients with dyspnoea	Roche; 1000	Clinical consensus (two cardiologists)	58	37	63	2	2.61	0.05
Bayes-Genis *et al.*, 2004[112]	89	Patients with dyspnoea	Roche; 253	Clinical consensus (two cardiologists)	73	8	7	1	1.85	0.03

continued

TABLE 51 *Accuracy of NT-proBNP versus a clinical diagnosis of heart failure (continued)*

Reference	*n*	Patients	Index test; cut-off closest to 300 pg/ml	Reference test	TP	FP	TN	FN	LR+	LR–
El Mahmoud *et al.*, 2006[102]	103	Patients > 75 years with dyspnoea	Roche; 500	Clinical diagnosis (two independent cardiologists)	45	33	21	4	1.50	0.21
Januzzi *et al.*, 2005[113]	599	Patients > 21 years with dyspnoea	Roche; 900	Clinical consensus (emergency department physician and three cardiologists)	188	58	332	21	6.05	0.12
Jose *et al.*, 2003[89]	119	Patients with acute or chronic dyspnoea (excluded patients with ACS, includes patients in outpatient settings)	Biomedica; 1691	Framingham criteria including echocardiogram results	71	5	46	2	9.92	0.03
Lainchbury *et al.*, 2003[103]	205	Patients with acute dyspnoea	Roche; 2875	ESC criteria (two independent cardiologists)	56	18	117	14	6.00	0.23
Mueller *et al.*, 2005[93]	251	Patients with acute dyspnoea as the primary complaint	Abbott; 476	Framingham criteria and echocardiographic criteria or systolic or diastolic dysfunction (one cardiologist)	123	40	74	14	2.56	0.16
Inpatient setting										
Berdague *et al.*, 2006[114]	254	Patients > 70 years admitted from emergency department with dyspnoea	Roche; 1691	Clinical consensus (two cardiologists)	138	57	108	4	2.81	0.04

ACS, acute coronary syndrome; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; ESC, European Society of Cardiology; FN, false negative; FP, false positive; HF, heart failure; ICU, intensive care unit; LR+, likelihood ratio of a positive test; LR–, likelihood ratio of a negative test; LVEF, left ventricular ejection fraction; TN, true negative; TP, true positive.

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TABLE 52 *Accuracy of symptoms and signs for the diagnosis of left ventricular systolic dysfunction*

Study	*n*	Setting	Index test	Reference test	TP	FP	TN	FN	LR+	LR–
Dyspnoea										
General practice setting										
Hobbs *et al.*, 2004[82]	273	Randomly selected patients (stratified by age): subgroup of patients presenting with symptoms and signs of heart failure	Dyspnoea	LVEF < 40%	8	150	113	2	1.40	0.47
Inpatient setting										
Talreja *et al.*, 2000[149]	300	Inpatients referred for echocardiography	Dyspnoea	LVEF < 45%	86	93	83	38	1.31	0.65
Gadsboll *et al.*, 1989[164]	98	Patients post MI	Dyspnoea	LVEF < 40%	18	7	49	24	3.43	0.65
General practice setting										
Morgan *et al.*, 1999[11]	817	Random sample of patients aged 70–81 years	Dyspnoea on walking	LVSD	9	23	733	52	4.85	0.88
Sparrow *et al.*, 2003[140]	621	Patients prescribed loop diuretics	Dyspnoea on exertion	LVEF < 40%	228	191	116	86	1.17	0.72
GP patients referred to open access heart failure or echocardiography clinics										
Davie *et al.*, 1997[141]	259	Patients referred for echocardiography	Dyspnoea on exertion	FS < 25%	41	181	37	0	1.20	0.00
Outpatient setting										
Mattleman *et al.*, 1983[144]	99	Patients referred for ventriculography	Dyspnoea on exertion	LVEF < 50%	15	5	39	40	2.40	0.82
Inpatient setting										
Zema *et al.*, 1983[150]	37	Inpatients with symptoms and signs of COPD	Dyspnoea on exertion	LVEF < 50%	17	16	4	0	1.25	0.00
Orthopnoea										
General practice setting										
Sparrow *et al.*, 2003[140]	621	Patients prescribed loop diuretics	Orthopnoea	LVEF < 40%	116	87	220	198	1.30	0.88

continued

TABLE 52 *Accuracy of symptoms and signs for the diagnosis of left ventricular systolic dysfunction (continued)*

Study	*n*	Setting	Index test	Reference test	TP	FP	TN	FN	LR+	LR–
GP patients referred to open access heart failure or echocardiography clinics										
Davie *et al.*, 1997[141]	259	Patients referred for echocardiography	Orthopnoea	FS < 25%	9	57	161	32	0.84	1.06
Inpatient setting										
Zema *et al.*, 1983[150]	37	Inpatients with symptoms and signs of COPD	Orthopnoea	LVEF < 50%	12	7	13	5	2.02	0.45
PND										
General practice setting										
Sparrow *et al.*, 2003[140]	621	Patients prescribed loop diuretics	PND	LVEF < 40%	32	28	279	282	1.12	0.99
GP patients referred to open access heart failure or echocardiography clinics										
Davie *et al.*, 1997[141]	259	Patients referred for echocardiography	PND	FS < 25%	16	44	174	25	1.93	0.76
Inpatient setting										
Zema *et al.*, 1983[150]	37	Inpatients with symptoms and signs of COPD	PND	LVEF < 50%	8	5	15	9	1.88	0.71
Oedema										
General practice setting										
Hobbs *et al.*, 2004[82]	273	Randomly selected patients (stratified by age): subgroup of patients presenting with symptoms and signs of heart failure	Swelling of ankles	LVEF < 40%	5	122	141	5	1.08	0.93
Morgan *et al.*, 1999[11]	817	General practice patients	Bilateral peripheral oedema	LVSD	11	68	688	50	2.00	0.90
GP patients referred to open access heart failure or echocardiography clinics										
Davie *et al.*, 1997[141]	259	Patients referred for echocardiography	Oedema as a symptom	FS < 25%	20	161	102	21	0.80	1.32
Inpatient setting										
Gadsboll *et al.*, 1989[164]	98	Patients post MI	Dependent oedema	LVEF < 40%	5	0	56	37	Cannot calculate	0.88
Talreja *et al.*, 2000[149]	300	Inpatients referred for echocardiography	Pretibial oedema	LVEF < 45%	43	60	116	81	1.02	0.99
Zema *et al.*, 1983[150]	37	Inpatients with symptoms and signs of COPD	Oedema	LVEF < 50%	7	5	15	10	1.65	0.78

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Study	*n*	Setting	Index test	Reference test	TP	FP	TN	FN	LR+	LR–
Heart rate										
General practice setting										
Nielsen *et al.*, 2000[139]	126	Patients in general practice with symptoms or signs of heart disease	Resting supine heart rate (bpm) > diastolic blood pressure (mmHg)	LVEF < 45%	8	15	95	7	3.91	0.54
GP patients referred to open access heart failure or echocardiography clinics										
Davie *et al.*, 1997[141]	259	Patients referred for echocardiography	Heart rate > 100 bpm	FS < 25%	9	17	201	32	2.81	0.85
Inpatient setting										
Jain *et al.*, 1993[147]	43	Patients post MI	Heart rate > 100 bpm	LVEF < 40%	14	6	13	10	1.85	0.61
McNamara *et al.*, 1988[195]	812	Patients post MI	Heart rate > 100 bpm	LVEF < 40%	116	229	292	175	0.91	1.07
Hypertension										
General practice setting										
Wattanabe *et al.*, 2005[146]	141	Patients with a history of MI but no symptoms of heart failure	Hypertension	LVEF < 55%	27	35	36	43	0.78	1.21
GP patients referred to open access heart failure or echocardiography clinics										
Fuat *et al.*, 2006[142]	297	Patients referred to a direct access heart failure clinic	Hypertension	LVSD	31	71	112	83	0.70	1.19
Gustafsson *et al.*, 2005[143]	367	Echocardiography clinic	Hypertension	LVEF < 40%	4	64	270	29	0.63	1.09
McDonagh *et al.*, 1997[10]	1394	Patients recruited from MONICA Glasgow study	Systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg	LVEF < 35%	41	1378	46	2	0.99	1.44
Inpatient setting										
Jain *et al.*, 1993[147]	43	Patients post MI	Systolic blood pressure > 150 mmHg or diastolic blood pressure > 90 mmHg	LVEF < 40%	6	7	12	18	0.68	1.19

continued

TABLE 52 *Accuracy of symptoms and signs for the diagnosis of left ventricular systolic dysfunction (continued)*

Study	*n*	Setting	Index test	Reference test	TP	FP	TN	FN	LR+	LR–
Mueller *et al.*, 2004[194]	180	Patients admitted for cardiac evaluation plus 27 patients with stable heart failure	Hypertension	LVEF < 35%	21	87	61	20	0.87	1.18
Jugular venous pressure										
General practice setting										
Morgan *et al.*, 1999[11]	817	Random sample of patients aged 70–81 years in a four-centre general practice	JVP > 5 cm	LVSD	7	23	733	54	3.77	0.91
Sparrow *et al.*, 2003[140]	621	Patients prescribed loop diuretics	Elevated JVP	LVEF < 40%	49	18	289	265	2.66	0.90
GP patients referred to open access heart failure or echocardiography clinics										
Davie *et al.*, 1997[141]	259	Patients referred for echocardiography	Elevated JVP	FS < 25%	7	4	214	34	9.30	0.84
Inpatient setting										
Gadsboll *et al.*, 1989[164]	98	Patients post MI	Elevated JVP	LVEF < 40%	4	0	56	38	Cannot calculate	0.90
Jain *et al.*, 1993[147]	43	Patients post MI	Elevated JVP	LVEF < 40%	3	1	18	21	2.38	0.92
Talreja *et al.*, 2000[149]	300	Inpatients referred for echocardiography	Elevated JVP	LVEF < 45%	42	18	158	8	8.21	0.18
Apex beat										
General practice setting										
Sparrow *et al.*, 2003[140]	621	Patients prescribed loop diuretics	Apex beat displaced	LVEF < 40%	51	80	227	263	0.62	1.13
GP patients referred to open access heart failure or echocardiography clinics										
Davie *et al.*, 1997[141]	259	Patients referred for echocardiography	Apex beat displaced	FS < 25%	27	9	209	14	15.95	0.36
Outpatient setting										
Mattleman *et al.*, 1983[144]	99	Patients referred for ventriculography	Displaced apical impulse	LVEF < 50%	17	1	43	38	13.60	0.71
Inpatient setting										
Gadsboll *et al.*, 1989[164]	98	Patients post MI	Apex beat on or outside midclavicular line	LVEF < 40%	15	3	53	27	6.67	0.68

Study	*n*	Setting	Index test	Reference test	TP	FP	TN	FN	LR+	LR–
Heart sounds										
General practice setting										
Sparrow *et al.*, 2003[140]	621	Patients prescribed loop diuretics	Added heart sound	LVEF < 40%	43	27	280	271	1.56	0.95
GP patients referred to open access heart failure or echocardiography clinics										
Davie *et al.*, 1997[141]	259	Patients referred for echocardiography	Gallop	FS < 25%	10	2	216	31	26.59	0.76
Outpatient setting										
Mattleman *et al.*, 1983[144]	99	Patients referred for ventriculography	S3	LVEF < 50%	24	5	39	31	3.84	0.64
Rihal *et al.*, 1995[145]	14,507	Patients with chest pain	S3	LVEF < 50%	299	255	10,883	3070	3.88	0.93
Inpatient setting										
Gadsboll *et al.*, 1989[164]	98	Patients post MI	S3	LVEF < 40%	19	21	61	9	2.65	0.43
Jain *et al.*, 1993[147]	43	Patients post MI	S3	LVEF < 40%	6	1	55	36	8.00	0.87
Narain *et al.*, 2005[148]	110	Patients admitted with acute coronary syndrome	S3	LVEF < 45%	23	4	15	1	4.55	0.05
Talreja *et al.*, 2000[149]	300	Inpatients referred for echocardiography	S3	LVEF < 45%	26	11	165	98	3.35	0.84
Crepitations										
General practice setting										
Hobbs *et al.*, 2004[82]	273	Randomly selected patients (stratified by age): subgroup of patients presenting with symptoms and signs of heart failure	Crepitations	LVEF < 40%	2	19	244	8	2.77	0.86
Morgan *et al.*, 1999[11]	817	General practice patients	Crepitations	LVSD	27	136	620	34	2.46	0.68
Sparrow *et al.*, 2003[140]	621	Patients prescribed loop diuretics	Crepitations	LVEF < 40%	70	55	252	244	1.24	0.95
GP patients referred to open access heart failure or echocardiography clinics										
Davie *et al.*, 1997[141]	259	Patients referred for echocardiography	Crepitations	FS < 25%	12	50	168	29	1.28	0.92

continued

TABLE 52 *Accuracy of symptoms and signs for the diagnosis of left ventricular systolic dysfunction (continued)*

Study	*n*	Setting	Index test	Reference test	TP	FP	TN	FN	LR+	LR–
Outpatient setting										
Mattleman *et al.*, 1983[144]	99	Patients referred for ventriculography	Crepitations	LVEF < 50%	13	1	43	42	10.40	0.78
Rihal *et al.*, 1995[145]	14,507	Patients enrolled in chest pain registry who had echocardiography	Crepitations	LVEF < 50%	157	184	11,049	3117	2.93	0.97
Inpatient setting										
Gadsboll *et al.*, 1989[164]	98	Patients post MI	Crepitations 5 cm above lung bases	LVEF < 40%	6	4	52	36	2.00	0.92
Jain *et al.*, 1993[147]	43	Patients post MI	Crepitations	LVEF < 40%	21	5	14	3	3.33	0.17
Talreja *et al.*, 2000[149]	300	Inpatients referred for echocardiography	Crepitations	LVEF < 45%	83	100	76	41	1.18	0.77
Liver span										
Inpatient setting										
Gadsboll *et al.*, 1989[164]	98	Patients post-MI	Liver span > 9 cm	LVEF < 40%	1	2	54	41	0.67	1.01

COPD, chronic obstructive pulmonary disease; FN, false negative; FP, false positive; FS, fractional shortening; HF, heart failure; JVP, jugular venous pressure; LR+, likelihood ratio of a positive test; LR–, likelihood ratio of a negative test; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; MI, myocardial infarction; PND, paroxysmal nocturnal dyspnoea; TN, true negative; TP, true positive.

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TABLE 53 *Accuracy of electrocardiography for the diagnosis of left ventricular systolic dysfunction*

Study	*n*	Setting	Index test	Reference test	TP	FP	TN	FN	LR+	LR–
General practice setting										
Alehagen *et al.*, 2003[80]	458	Patients presenting with symptoms and signs of heart failure with no previous diagnosis	ECG not in sinus rhythm or atrial fibrillation or sign of past ischaemic myocardial damage	LVEF < 40%	27	76	327	28	2.60	0.63
Galasko *et al.*, 2005[81]	376	Patients with symptoms of heart failure or on diuretics	Any abnormality	LVSD	59	124	187	6	2.28	0.15
Hobbs *et al.*, 2004[82]	273	Randomly selected patients (stratified by age): subgroup of patients presenting with symptoms and signs of heart failure	Any abnormality	LVEF < 40%	10	142	121	0	1.85	0.00
McDonagh *et al.*, 1997[10]	1394	Patients recruited from MONICA Glasgow study	Q waves, left BBB, ST-segment depression, T-wave abnormalities, LVH, atrial fibrillation	LVEF < 30%	42	1352	72	1	1.03	0.46
Ng *et al.*, 2003[151]	1331	Patients randomly selected from 21 general practices	Q waves, BBB, LVH, atrial fibrillation, LAD, poor R-wave progression, atrial hypertrophy, ST change, sinus bradycardia or tachycardia	LWMI > 2	15	516	798	2	2.25	0.19
Nielsen *et al.*, 2000[139]	126	General practice patients with symptoms or signs of heart failure	QRS prolongation and/or ST changes	LVEF < 45%	13	49	62	2	1.96	0.24
Sparrow *et al.*, 2003[140]	621	Patients prescribed loop diuretics	Any abnormality	LVEF < 40%	215	162	145	99	1.30	0.67
GP patients referred to open access heart failure or echocardiography clinics										
Davie *et al.*, 1996[141]	534	Patients referred for echocardiography	Atrial fibrillation, previous MI, LVH, BBB, LAD	LVSD	90	169	269	6	2.43	0.10
Fuat *et al.*, 2006[142]	297	Patients referred to a direct access heart failure clinic	Any abnormality	LVSD	93	77	106	21	1.94	0.32
Khandekar *et al.*, 1996[196]	137	Patients referred for echocardiography	Major abnormality: atrial fibrillation, LVH, BBB or Q wave	LVSD or valve lesion	36	50	37	14	1.25	0.66
Khandekar *et al.*, 1996[196]	137	Patients referred for echocardiography	Major or minor abnormality: above + non-specific ST/T wave changes and atrial hypertrophy	LVSD or valve lesion	39	70	17	11	0.97	1.13

continued

TABLE 53 *Accuracy of electrocardiography for the diagnosis of left ventricular systolic dysfunction (continued)*

Study	*n*	Setting	Index test	Reference test	TP	FP	TN	FN	LR+	LR–
Landray *et al.*, 2000[152]	126	Patients referred for echocardiography	Q waves, poor R-wave progression, LVH, left BBB	LVSD	16	11	75	24	3.13	0.69
Lim *et al.*, 2006[86]	137	Patients with suspected heart failure	Atrial fibrillation or flutter, ventricular arrhythmia, intraventricular conduction, ST/T wave, Q wave, LVH (read by GP)		10	44	74	9	1.41	0.76
Lim *et al.*, 2006[86]	137	Patients with suspected heart failure	Atrial fibrillation or flutter, ventricular arrhythmia, intraventricular conduction, ST/T wave, Q wave, LVH (read by hospital physician)		18	63	55	1	1.77	0.11
Lindsay *et al.*, 2000[153]	416	Patients referred for echocardiography	Q waves, ST/T changes, LAD, left atrial enlargement, BBB, atrial fibrillation, heart block or poor R-wave progression	LVSD	86	112	209	9	2.59	0.15
Sandler *et al.*, 2000[154]	240	Patients referred for echocardiography	Any abnormality	LVSD	52	80	89	19	1.55	0.51
Population cohort or screening studies										
Hedberg *et al.*, 2004[155]	407	Random sample of population aged 75 years	Major or minor changes: atrial fibrillation, BBB, Q wave, ST change, T-wave inversion or LVH, atrioventricular block, LAD, incomplete BBB, borderline Q wave or high R-wave amplitude	LVSD	27	117	262	1	3.12	0.05
Mosterd *et al.*, 1997[156]	1980	Prospective cohort (Rotterdam study)	Atrial fibrillation, LVH, BBB	FS < 25%	32	409	1512	27	2.55	0.58
Outpatient setting										
Baker *et al.*, 2003[157]	481	Patients with risk factors and no documented heart failure	Conduction and axis abnormalities, LVH, previous MI	LVEF < 50%	23	237	206	15	1.13	0.85
Christian *et al.*, 1997[158]	2267	Patients referred for ventriculography	ST or T-wave abnormalities, Q waves, BBB, LVH, ventricular rhythm, digitalis effect, any other abnormality	LVEF < 50%	379	1136	722	30	1.52	0.19

Study	*n*	Setting	Index test	Reference test	TP	FP	TN	FN	LR+	LR–
Houghton *et al.*, 1997[159]	200	Retrospective study of patients in heart failure clinic with ECG and echocardiography	Brady- or tachycardia, LAD, atrial fibrillation, abnormal PR interval, abnormal QRS shape or duration, ST changes, abnormal QT interval, abnormal T-wave morphology, abnormal U waves	LVSD	147	19	16	18	1.64	0.24
Hutcheon *et al.*, 2002[133]	304	Patients who were referred to the day hospital	Q waves, BBB, conduction defect, ST/T segment abnormalities, LVH, atrial fibrillation or flutter	LVSD	30	135	133	1	1.92	0.07
Rihal *et al.*, 1995[145]	14,507	Patients enrolled in chest pain registry who had echocardiography	Any abnormality	LVEF < 50%	2957	7307	3702	332	1.35	0.30
Talwar *et al.*, 1999[160]	222	Patients referred for echocardiography	Major or minor changes: atrial fibrillation, previous MI, LVH, LAD, left BBB, bradycardia, tachycardia, poor R-wave progression, RAD, ST/T changes, first-degree heart block, atrial enlargement	LWMI > 1.2	84	102	24	112	0.53	3.00
Inpatient setting										
Gillespie *et al.*, 1997[161]	71	Patients admitted to an acute medical ward	Major abnormalities on ECG	LVSD	44	8	18	1	3.18	0.03
Talreja *et al.*, 2000[149]	300	Inpatients referred for echocardiography	Q waves, poor R-wave progression, LVH, left BBB, ST abnormalities	LVEF < 45%	118	64	116	2	2.77	0.03

BBB, bundle branch block; FN, false negative; FP, false positive; FS, fractional shortening; HF, heart failure; LAD, left axis deviation; LR+, likelihood ratio of a positive test; LR–, likelihood ratio of a negative test; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVSD, left ventricular systolic dysfunction; LWMI, left ventricular wall motion index; MI, myocardial infarction; RAD, right axis deviation; TN, true negative; TP, true positive.

TABLE 54 *Accuracy of chest X-ray for the diagnosis of left ventricular systolic dysfunction*

Study	*n*	Setting	Index test	Reference test	TP	FP	TN	FN	LR+	LR–
GP patients referred to open access heart failure or echocardiography clinics										
Landray *et al.*, 2000[152]	126	Patients referred for echocardiography	Increased CTR and/or pulmonary congestion	LVSD	26	47	39	14	1.19	0.77
Sandler *et al.*, 2000[154]	267	Patients referred for echocardiography	Any abnormality	LVSD	53	90	95	29	1.33	0.69
Outpatient setting										
Mattleman *et al.*, 1983[144]	99	Patients referred for ventriculography	Increased CTR	LVEF < 50%	39	3	41	16	10.40	0.31
Mattleman *et al.*, 1983[144]	99	Patients referred for ventriculography	Pulmonary congestion	LVEF < 50%	21	3	41	34	5.60	0.66
Inpatient setting										
Gadsboll *et al.*, 1989[164]	98	Patients post MI	Increased CTR	LVEF < 40%	38	33	22	4	1.51	0.24
Gillespie *et al.*, 1997[161]	71	Patients admitted to an acute medical ward	Increased CTR and/or pulmonary congestion	LVSD	32	2	24	13	9.24	0.31
Hendry *et al.*, 1999[162]	61	Patients admitted with heart failure	Increased CTR and/or pulmonary congestion	LVSD	32	11	8	10	1.32	0.57
Jain *et al.*, 1993[147]	43	Patients post MI	Increased CTR and/or pulmonary congestion	LVEF < 40%	14	2	17	10	5.54	0.47
Madsen *et al.*, 1984[163]	229	Post MI	Increased CTR and/or pulmonary congestion	LVEF < 50%	68	33	57	61	1.44	0.75
Talreja *et al.*, 2000[149]	300	Inpatients referred for echocardiography	Increased CTR and/or pulmonary congestion	LVEF < 45%	67	49	127	57	1.94	0.64
Zema *et al.*, 1983[150]	37	Inpatients with symptoms and signs of COPD	Increased CTR and/or pulmonary congestion	LVEF < 50%	10	1	17	7	10.59	0.44
Rihal *et al.*, 1995[145]	14,507	Patients enrolled in chest pain registry who had echocardiography	Increased CTR	LVEF < 50%	475	922	7377	1961	1.76	0.91

COPD, chronic obstructive pulmonary disease; CTR, cardiothoracic ratio; FN, false negative; FP, false positive; HF, heart failure; LR+, likelihood ratio of a positive test; LR–, likelihood ratio of a negative test; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; MI, myocardial infarction; TN, true negative; TP, true positive.

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TABLE 55 *Accuracy of BNP for the diagnosis of left ventricular ejection fraction < 40% or left ventricular systolic dysfunction*

Study	*n*	Setting	Index test; cut-off closest to 50 pg/ml	Reference test criteria	TP	FP	TN	FN	LR+	LR–
General practice setting										
Hobbs *et al.*, 2004[82]	273	Randomly selected patients (stratified by age): subgroup of patients presenting with symptoms and signs of heart failure	Shionogi; 114	LVEF < 40%	6	67	196	4	2.36	0.54
Nielsen *et al.*, 2003[139]	1252	Randomly selected patients aged 25–74 years	Peninsula; 8	LVEF < 40%	44	568	641	4	1.95	0.16
Smith *et al.*, 2000[167]	155	General practice patients aged 70–84 years, England	Peninsula; 64	Qualitative assessment of LVSD	11	1	93	50	2.62	0.13
Sparrow *et al.*, 2003[140]	571	Patients prescribed loop diuretics	Peninsula; 53	LVEF < 40%	173	141	173	134	1.26	0.80
GP patients referred to open access heart failure or echocardiography clinics										
Fuat *et al.*, 2006[142]	263	Patients referred from GP	Triage; 40	LVSD	105	113	70	9	1.49	0.21
Landray *et al.*, 2000[152]	126	Patients referred to hospital clinic with suspected heart failure	Shionogi; 18	Qualitative assessment of LVSD	26	14	75	11	5.08	0.40
Population cohort or screening studies										
Costello-Boerrigter *et al.*, 2006[169]	1869	Random sample of population > 45 years	Triage; 66	LVEF < 40%	30	346	1486	7	4.29	0.23
Hedberg *et al.*, 2004[155]	407	Random sample of population > 75 years	Shionogi; 73	LVSD	22	42	337	6	7.09	0.24
Lukowicz *et al.*, 2005[171]	1678	Participants in Augsburg, MONICA study	Shionogi; 27	LVEF < 40%	4	116	1002	1	7.70	0.22
Vasan *et al.*, 2002[172]	1707	Female Framingham study participants	Shionogi; 51	LVEF < 40% and/or FS < 22%	4	6	1612	85	7.99	0.63
Vasan *et al.*, 2002[172]	1470	Male Framingham study participants	Shionogi; 50	LVEF < 40% and/or FS < 22%	20	40	1340	71	6.62	0.70
Outpatient setting										
Hutcheon *et al.*, 2002[133]	299	Patients referred to day hospital with suspected cardiovascular disease	Peninsula; 49	Qualitative assessment of LVSD	29	2	102	166	1.51	0.17

continued

TABLE 55 *Accuracy of BNP for the diagnosis of left ventricular ejection fraction < 40% or left ventricular systolic dysfunction (continued)*

Study	*n*	Setting	Index test; cut-off closest to 50 pg/ml	Reference test criteria	TP	FP	TN	FN	LR+	LR–
Richards *et al.*, 2006[178]	1049	Patients with stable heart failure or IHD in a trial	In-house; 54	LVEF < 40%	257	252	467	73	2.22	0.34
Valli *et al.*, 2001[179]	153	Patients referred for radionuclide ventriculography	CIS Bio; 52	LVEF < 40%	49	9	78	17	4.72	0.19
Inpatient setting										
Bettencourt *et al.*, 2000[184]	101	Patients days 4 and 5 post MI	Shionogi; 142	LVEF < 40%	29	7	46	19	2.76	0.27
Choy *et al.*, 1994[186]	75	Patients day 3+ post MI	Peninsula; 52	LVEF < 40%	34	6	22	13	2.29	0.24
Pfister *et al.*, 2002[188]	150	Patients referred for cardiac catheterisation in hospital	CIS Bio; 27	LVEF < 40%	9	0	63	78	1.81	0.11
Richards *et al.*, 1998[189]	297	Patients post MI	In-house; 111	LVEF < 40%	28	24	64	5	3.11	0.21

FN, false negative; FP, false positive; FS, fractional shortening ; HF, heart failure; IHD, ischaemic heart disease; LR+, likelihood ratio of a positive test; LR–, likelihood ratio of a negative test; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; MI, myocardial infarction; TN, true negative; TP, true positive.

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TABLE 56 *Accuracy of NT-proBNP for the diagnosis of left ventricular ejection fraction < 40% or left ventricular systolic dysfunction*

Study	*n*	Setting	Index test; cut-off closest to 15 pmol/l	Reference test criteria	TP	FP	TN	FN	LR+	LR–
General practice setting										
Galasko *et al.*, 2005[81]	376	Patients with symptoms of heart failure or on diuretics	Roche; 40	LVSD	27	185	152	2	1.70	0.15
Groenning *et al.*, 2004[190]	672	Patients recruited from general practice, Copenhagen	NR; 902	LVEF < 40%	29	9	425	209	2.31	0.35
Hobbs *et al.*, 2004[82]	273	Randomly selected patients (stratified by age): subgroup of patients presenting with symptoms and signs of heart failure	Roche; 338	LVEF < 40%	8	126	136	2	1.66	0.39
GP patients referred to open access heart failure or echocardiography clinics										
Fuat *et al.*, 2006[142]	263	Patients referred from GP	Roche; 150	LVSD	107	110	73	0	1.66	0.00
Outpatient setting										
Gustaffson *et al.*, 2005[143]	367	Patients with suspected heart failure	Roche; 125	LVEF < 40%	32	180	154	1	1.80	0.07
Thackray *et al.*, 2006[192]	261	Patients attending pacemaker clinic	Biomedica; 2258	LVEF < 40%	54	62	127	18	2.29	0.37
Bay *et al.*, 2003[193]	2193	All patients admitted to a general city hospital, Copenhagen	NR; 3019	LVEF < 40%	115	42	1669	367	4.06	0.33
Richards *et al.*, 2006[178]	1049	Patients with stable heart failure or IHD in a trial	In-house; 588	LVEF < 40%	234	244	457	96	2.04	0.45
Inpatient setting										
Richards *et al.*, 1998[189]	297	Patients post MI	In-house; 1226	LVEF < 40%	27	27	61	6	2.67	0.26
Pfister *et al.*, 2002[188]	150	Patients referred for cardiac catheterisation in hospital, Cologne, Germany	Roche; 360	LVEF < 40%	9	0	90	41	3.03	0.08

FN, false negative; FP, false positive; HF, heart failure; IHD, ischaemic heart disease; LR+, likelihood ratio of a positive test; LR–, likelihood ratio of a negative test; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; MI, myocardial infarction; NR, not reported; TN, true negative; TP, true positive.

TABLE 57 *The accuracy of BNP for the diagnosis of LVEF ≤ 45–55%*

Study	*n*	Setting	Index test; cut-off closest to 50 pg/ml	Reference test criteria	TP	FP	TN	FN	LR+	LR–
General practice setting										
McGeoch *et al.*, 2002[166]	91	Patients being treated for heart failure, Christchurch	In-house; 1212	LVEF < 45%	38	17	24	12	2.07	0.46
Ng *et al.*, 2003[151]	1331	Patients without a previous diagnosis of heart failure randomly selected from 21 general practices, Leicestershire	Peninsula; 66	LVEF < 45% or LWMI > 1.6	30	0	386	914	1.42	0.00
Population cohort or screening studies										
Luchner *et al.*, 2000[170]	479	MONICA study participants, Augsburg	Shionogi; 34	FS < 28%	11	28	378	62	2.00	0.84
Outpatient setting										
Falkensammer *et al.*, 2005[175]	51	Patients referred for radionuclide ventriculography	Shionogi; 60	LVEF < 50%	17	12	16	6	1.72	0.46
Krishnaswamy *et al.*, 2001[176]	400	Patients referred for echocardiography, San Diego	Triage; 54	LVEF < 50% or global hypokinesis or wall motion abnormality	204	20	99	77	2.08	0.16
Kruger *et al.*, 2004[132]	128	Patients referred to clinic with suspected cardiac disease or known heart failure, Aachen, Germany	Triage; 80	LVEF < 50%	59	7	34	28	1.98	0.19
Mallamaci *et al.*, 2001[177]	246	Patients on renal dialysis with no overt sign of heart failure	Peninsula; 135	LVEF < 45%	23	52	163	8	3.07	0.34
Vanderheyden *et al.*, 2006[180]	72	Patients referred for elective catheterisation	Triage; 54	LVEF < 45%	31	24	16	1	1.61	0.08
Wattanabe *et al.*, 2005[146]	141	Patients post MI but with no symptoms of heart failure	Tosoh II; 89	LVEF < 55%	64	31	40	6	2.09	0.15
Yamamoto *et al.*, 1996[181]	94	Patients referred for cardiac catheterisation, Mayo Clinic	Shionogi; 51	LVEF < 45%	18	6	58	12	4.38	0.30
Yamamoto *et al.*, 2000[182]	466	Patients referred for echocardiography to assess ventricular function, Mayo Clinic	Shionogi; 37	LVEF < 45%	40	11	266	149	2.18	0.34
Inpatient setting										
Bal *et al.*, 2006[183]	41	Patients admitted to ICU for acute respiratory distress and/or shock	Triage; 221	LVEF < 50%	17	2	14	8	5.44	0.37
Osca *et al.*, 2002[187]	101	Patients admitted for heart failure	Shionogi; 64	LVEF < 55%	43	19	25	14	1.93	0.48

FN, false negative; FP, false positive; FS, fractional shortening; ICU, intensive care unit; IHD, ischaemic heart disease; LR+, likelihood ratio of a positive test; LR–, likelihood ratio of a negative test; LVEF, left ventricular ejection fraction; LWMI, left ventricular wall motion index; MI, myocardial infarction; NR, not reported; TN, true negative; TP, true positive.

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TABLE 58 *The accuracy of NT-proBNP for the diagnosis of left ventricular ejection fraction 45–55%*

Study	*n*	Setting	Index test; cut-off closest to 300 pg/ml	Reference test criteria	TP	FP	TN	FN	LR+	LR–
General practice setting										
Groenning *et al.*, 2004[190]	672	Patients recruited from general practice	NR; 902	LVEF < 40%	54	23	375	220	1.9	0.47
Ng *et al.*, 2003[151]	1331	Patients without a previous diagnosis of heart failure randomly selected from 21 general practices	NR; 48	LVEF < 45% or LWMI > 1.6	30	0	0	1301	1.00	Cannot be calculated
GP patients referred to open access HF or echocardiography clinics										
Lim *et al.*, 2006[86]	116	Patients referred from general practice	Roche; 338	LVEF < 50%	13	41	82	1	2.79	0.11
Population cohort or screening studies										
Costello-Boerrigter *et al.*, 2006[169]	1869	Random sample of population > 45 years	Roche; 228	LVEF < 50%	32	256	1576	5	6.19	0.16
Outpatient setting										
Falkensammer *et al.*, 2005[175]	51	Patients referred for radionuclide ventriculography	Roche; 230	LVEF < 50%	28	5	15	3	3.61	0.13
Richards *et al.*, 2006[178]	1049	Patients with stable heart failure or IHD in a trial	In-house; 562	LVEF < 50%	32	32	8	0	1.25	0.00
Sivakumar *et al.*, 2006[191]	100	Patients referred for echocardiography	Roche; 424	LVEF < 50%	24	41	34	1	1.76	0.09
Vanderheyden *et al.*, 2006[180]	72	Patients referred for elective catheterisation	Roche; 358	LVEF < 45%	40	26	6	0	1.23	0
Inpatient setting										
Bal *et al.*, 2006[183]	41	Patients admitted to ICU for acute respiratory distress and/or shock	Roche; separate cut-offs for men and women	LVEF < 50%	13	41	82	1	2.79	0.11

FN, false negative; FP, false positive; ICU, intensive care unit; IHD, ischaemic heart disease; LR+, likelihood ratio of a positive test; LR–, likelihood ratio of a negative test; LVEF, left ventricular ejection fraction; LWMI, ; NR, not reported; TN, true negative; TP, true positive.

TABLE 59 *The accuracy of BNP for the diagnosis of left ventricular ejection fraction ≤ 30–35%*

Study	*n*	Setting	Index test; cut-off closest to 50 pg/ml	Reference test criteria	TP	FP	TN	FN	LR+	LR–
General practice setting										
McDonagh *et al.*, 1998[165]	1252	MONICA study participants	Peninsula; 18	LVEF < 30%	28	9	1057	158	5.82	0.28
Ng *et al.*, 2003[151]	1331	Patients with no previous diagnosis of heart failure randomly selected from 21 general practices	Peninsula; 66	LVEF < 35% or LWMI > 2	17	0	582	732	1.80	0.06
GP patients referred to open access heart failure or echocardiography clinics										
Sim *et al.*, 2003[168]	83	Patients referred to an open access echocardiography service	Bachem; 19	LVEF < 35%	26	0	28	29	1.96	0.04
Outpatient setting										
Byrne *et al.*, 1996[185]	94	Patients post MI	NR	LVEF < 30%	35	11	36	12	3.18	0.33
Mueller *et al.*, 2004[194]	157	Patients attending a cardiology clinic	Bayer; 137	LVEF < 35%	27	5	139	9	13.9	0.17

FN, false negative; FP, false positive; HF, heart failure; LR+, likelihood ratio of a positive test; LR–, likelihood ratio of a negative test; LVEF, left ventricular ejection fraction; LWMI, left ventricular wall motion index; NR, not reported; TN, true negative; TP, true positive.

TABLE 60 *The accuracy of NT-proBNP for the diagnosis of left ventricular ejection fraction 30–35%*

Study	*n*	Setting	Index test; cut-off closest to 300 pg/ml	Reference test criteria	TP	FN	TN	FP	LR+	LR–
General practice setting										
Ng *et al.*, 2003[151]	1331	Patients with no previous diagnosis of heart failure randomly selected from 21 general practices	NR; 318	LVEF < 35% or LWMI > 2	17	0	611	703	1.87	0.06
GP patients referred to open access HF or echocardiography clinics										
Gustaffson *et al.*, 2005[143]	367	Patients with suspected heart failure	Roche; 125	LVEF < 40%	14	155	198	0	2.28	0.00
Outpatient setting										
Mueller *et al.*, 2004[194]	157	Patients attending a cardiology clinic	Roche; 211	LVEF < 35%	30	2	112	36	3.9	0.08

FN, false negative; FP, false positive; HF, heart failure; LR+, likelihood ratio of a positive test; LR–, likelihood ratio of a negative test; LVEF, left ventricular ejection fraction; LWMI, left ventricular wall motion index; NR, not reported; TN, true negative; TP, true positive.

Appendix 5

Studies excluded from the systematic review

TABLE 61 *Studies excluded from the review of symptoms and signs for heart failure*

Reference	Reason for exclusion
Ahmed *et al*., 2003	All patients had heart failure; study assessed the sensitivity and specificity of symptoms and signs to differentiate between systolic and diastolic heart failure
Ahmed *et al*., 2004	All patients had heart failure; study assessed the sensitivity and specificity of dyspnoea at rest versus the Framingham criteria
Butman *et al*., 1993	All patients had heart failure
Cease *et al*., 1986	Logistic regression of heart rate, blood pressure and chest X-ray measurements
Chakko *et al*., 1991	All patients had heart failure
Clark *et al*., 2000	All patients had heart failure; correlation between cardiothoracic ratio on chest X-ray and LVEF
Collin-Chavagnac *et al*., 2006	Case–control study
Costanzo *et al*., 1988	Inappropriate reference test (pulmonary arteriolar resistance)
Dans *et al*., 1995	Inappropriate reference test (LVEDP)
Ducas *et al*., 1983	Case–control study
Eagle *et al*., 1988	Study assessed the correlation between symptoms, signs, ECG, chest X-ray findings and gated blood pool scan results
Echeverria *et al*., 1983	All patients had heart failure
Eilen *et al*., 1983	Only included patients with a palpable apex beat
Eriksson *et al*., 1987	Study compared the symptoms and signs of heart failure versus a pulmonary and cardiac scoring system
Ewy *et al*., 1988	Inappropriate reference test (PCWP > 18 mmHg)
Harlan *et al*., 1977	Inappropriate reference test (LVEDP)
Heckerling *et al*., 1993	Inappropriate reference test (LVEDV)
Heckerling *et al*., 1991	Inappropriate reference test (enlarged cardiothoracic ratio on chest X-ray)
Knudsen *et al*., 2005	Subset of Maisel *et al*., 2002[104] (patients with atrial fibrillation)
Lien *et al*., 2002	All patients had heart failure
McNamara *et al*., 1988	Used logistic regression, cannot extract data for 2 × 2 table
Marantz *et al*., 1990	Inappropriate reference test (Boston criteria for heart failure)
Marcus *et al*., 2004	Study assessing diagnostic accuracy of S3 against elevated BNP
Marcus *et al*., 2005	Inappropriate index test (computerised S3 and S4)
Mittal *et al*., 1985	Commentary on JVP
O'Neill *et al*., 1989	Assesses the diagnostic accuracy of a displaced apex beat versus cardiomegaly on chest X-ray
Patel *et al*., 1993	Inappropriate reference test (LVEDV)
Remes *et al*., 1991	Inappropriate reference test (Boston criteria)
Rohde *et al*., 2004	All patients had heart failure
Rusconi *et al*., 1991	Commentary on Remes *et al*., 1991

continued

TABLE 61 *Studies excluded from the review of symptoms and signs for heart failure (continued)*

Reference	Reason for exclusion
Shah *et al*., 2004	Provides negative predictive value for ECG and chest X-ray, cannot extract data for a 2×2 table
Singh *et al*., 1973	Study size only $n = 11$
Sjoland *et al*., 1997	Inappropriate reference test (LVEF < 60%)
Spodick *et al*., 1994	Commentary on Heckerling *et al*., 1991
Stapleton *et al*., 1987	Commentary on Ismail *et al*., 1987
Stevenson and Perloff, 1989	All patients had heart failure
Wang *et al*., 2005	Systematic review
Wyer *et al*., 2006	Commentary on Wang *et al*., 2005
Zema *et al*., 1980	Signs were considered positive if at least one physician of three detected the sign
Zhao *et al*., 2006	Case–control study

JVP, jugular venous pressure; LVEDP, left ventricular end-diastolic pressure; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; PCWP, pulmonary capillary wedge pressure.

TABLE 62 *Studies excluded from the review of electrocardiography for heart failure*

Reference	Reason for exclusion
Al-Mesimani *et al*., 2005	Correlation between BNP and echocardiography results in different types of cardiac disease
Atisha *et al*., 2004	Inappropriate reference test (any ventricular dysfunction)
Bettencourt *et al*., 2000	Inappropriate reference test (any ventricular dysfunction)
Bibbins-Domingo *et al*., 2004	Inappropriate reference test (any ventricular dysfunction)
Epshteyn *et al*., 2003	Inappropriate reference test
Felker *et al*., 2006	Review article
Halling *et al*., 2003	Study looking at how heart failure is diagnosed and managed in elderly with non-insulin-dependent diabetes mellitus
Hoilund-Carlsen *et al*., 2005	Inappropriate reference test (ischaemic heart disease)
Hurst *et al*., 2005	Review article
Kelly *et al*., 2000	Review article
Krishnaswamy *et al*., 2001	Inappropriate reference test (any ventricular dysfunction)
Kruger *et al*., 2004	Inappropriate index test (ECG abnormality: prolonged QRS duration)
McClure *et al*., 1998	Cannot extract 2×2 data
Mattleman *et al*., 1983	Inappropriate reference test (ECG abnormality: evidence of MI)
Mikkelsen *et al*., 2005	Inappropriate reference test (any ventricular abnormality)
Murkofsky *et al*., 1998	Inappropriate index test (ECG abnormality: QRS prolongation and Q waves)

continued

TABLE 62 *Studies excluded from the review of electrocardiography for heart failure (continued)*

Reference	Reason for exclusion
Nakae *et al*., 2005	Correlation of levels between echocardiography, SPECT and BNP
Nakamura *et al*., 2005	Inappropriate reference test (any heart disease)
Pfister *et al*., 2002	Inappropriate reference test (right ventricular dysfunction)
Pope *et al*., 2004	Prognosis in ACS
Porter *et al*., 2000	Correlation between ECG and LWMI
Segawa *et al*., 2005	Inappropriate reference test (patients at risk of heart failure)
Shah *et al*., 2004	Cannot extract 2×2 data
Steg *et al*., 2005	Subset of Maisel *et al*., 2002[104] (only those patients who had an echocardiogram)
Wang *et al*., 2005	Systematic review
Wyer *et al*., 2006	Commentary on Wang *et al*., 2005

ACS, acute coronary syndrome; EF, ejection fraction; LWMI, left ventricular wall motion index; MI, myocardial infarction; SPECT, single photon emission computerised tomography.

TABLE 63 *Studies excluded from the review of chest X-ray for heart failure*

Reference	Reason for exclusion
Badgett, *et al*., 1997	Systematic review
Butman *et al*., 1993	Inappropriate reference test (PCWP)
Chakko *et al*., 1991	All patients had heart failure
Collins *et al*., 2006	Inappropriate reference test (discharge on diagnosis)
Dao *et al*., 2001	Subset of Morrison *et al*., 2002[92]
Harlan *et al*., 1977	Inappropriate reference test (LVEDP)
Hendry *et al*., 1999	Inappropriate population (patients admitted with heart failure)
Henriksson *et al*., 2004	Commentary on Knudsen *et al*., 2004[90]
Kragelund *et al*., 2006	Inappropriate reference test (coronary atherosclerosis)
Kundel *et al*., 1982	All patients had heart failure
Quinones *et al*., 2005	Review article
Render *et al*., 1995	Comparison of chest X-ray patients with systolic vs diastolic function
Shah *et al*., 2004	Cannot extract 2×2 data
Wang *et al*., 2005	Systematic review
Wyer *et al*., 2006	Commentary on Wang *et al*., 2005

LVEDP, left ventricular end-diastolic pressure; PCWP, pulmonary capillary wedge pressure.

TABLE 64 *Studies excluded from the review of BNP and NT-proBNP for heart failure*

Reference	Reason for exclusion
Al-Meslmani *et al*., 2005	Correlation study (BNP and echocardiography results in different types of cardiac disease)
Apple *et al*., 2003	Inappropriate reference test (hospital discharge diagnosis including BNP)
Arad *et al*., 1996	Case–control study
Arques *et al*., 2005	Case–control study
Barclay *et al*., 2006	Correlation study (BNP and left ventricular filling pressure)
Bassan *et al*., 2005	Inappropriate reference test (acute myocardial infarction)
Belovicova *et al*., 2005	Correlation study (BNP and NYHA)
Bettencourt *et al*., 1999	Case–control study
Bettencourt *et al*., 2000	Provides ROC curves but not 2×2 data
Bhalla *et al*., 2005	Retrospective study of only patients with both BNP and echocardiography results
Cabanes *et al*., 2001	Case–control study
Campbell *et al*., 2000	Case–control study
Campbell *et al*., 2001	Inappropriate reference test (chest X-ray findings)
Castro *et al*., 2001	Inappropriate reference test (diastolic heart failure)
Chen *et al*., 2006	Substudy of PRIDE (comparison of BNP and echocardiography for prognosis)
Chung *et al*., 2006	Review article (references checked)
Clerico *et al*., 1998	Case–control study
Collin-Chavagnac *et al*., 2006	Case–control study
Collins *et al*., 2006	Inappropriate index test (electronically detected S3 or S3 + BNP)
Conen *et al*., 2006	Inappropriate reference test (LVH)
Daggubati *et al*., 1997	Case–control study
Davidson *et al*., 1996	Comparison of BNP and NT-proBNP for LVSD using AUC
De Boer *et al*., 2001	Case–control study
Del Ry *et al*., 2000	Case–control study
Dokanish *et al*., 2006	Comparison of BNP and echocardiogram for predicting outcome
Falcao *et al*., 2004	Case–control study
Fleischer *et al*., 1997	Inappropriate reference test (emergency room diagnosis)
Folk *et al*., 2005	Retrospective study of 17 obstetric patients and only two had cardiac dysfunction
Fonseca *et al*., 200480	Case–control study
Francis *et al*., 1998	Commentary on McDonagh *et al*., 1998
Friedl *et al*., 1996	Case–control study
Fruhwald *et al*., 1999	Correlation study (BNP and echocardiogram)
Furumoto *et al*., 2006	Correlation study (BNP and hypertension + diastolic dysfunction)
Galasko *et al*., 2006	Cost-effectiveness study using data from Galasko *et al*., 2005[81]
Gegenhuber *et al*., 2006	Comparison of BNP and NT-proBNP in the same cohort as in Mueller *et al*., 2005[93]
Groenning *et al*., 2001	Case–control study
Groenning *et al*., 2002	Case–control study
Hall *et al*., 2003	Case–control study
Hammerer-Lercher *et al*., 2001	All patients had heart failure

TABLE 64 *Studies excluded from the review of BNP and NT-proBNP for heart failure (continued)*

Reference	Reason for exclusion
Heidenreich *et al*., 2004	Cost-effectiveness study using data from Vasan *et al*., 2002[172]
Hetmanski *et al*., 2000	Provides ROC curves but not 2×2 data
Hirata *et al*., 2001	Case–control study
Hunt *et al*., 1997	Case–control study
Ingelsson *et al*., 2005	Assessment of the validity of a hospital discharge diagnosis of heart failure
Iwanaga *et al*., 2006	Correlation study (BNP and LVEDP, left ventricular end-diastolic wall stress)
Januzzi *et al*., 2006	Prognostic study for heart failure outcomes
Jefic *et al*., 2005	Inappropriate reference test (pulmonary arterial wedge pressure)
Joung *et al*., 2003	Case–control study
Kanda *et al*., 2005	Study to determine risk factors for high BNP levels
Knudsen *et al*., 2003	Subset of Maisel *et al*., 2002[104]
Knudsen *et al*., 2005	Study to determine risk factors for high BNP levels
Koulouri *et al*., 2004	Inappropriate population (children)
Kragelund *et al*., 2006	Inappropriate reference test (coronary atherosclerosis)
Kupari *et al*., 2004	Inappropriate reference test (PCWP > 14 mmHg)
Kuster *et al*., 2002	Correlation study (BNP with NYHA, LVEDP, LVEF and 6-minute walk test)
Lang *et al*., 1994	Case–control study
Lee *et al*., 2006	Correlation study (NT-proBNP and extracellular water)
Leuchte *et al*., 2004	Inappropriate reference test (disease severity in primary pulmonary hypertension)
Li *et al*., 2005	Review article
Lim *et al*., 2005	Comparison of BNP and diastolic function
Linden *et al*., 2006	Letter
Lubien *et al*., 2002	Inappropriate reference test (diastolic heart failure)
Luchner *et al*., 2005a	Same cohort as in Luchner *et al*., 2002[197] (effect of renal dysfunction on BNP and NT-proBNP levels)
Luchner *et al*., 2005b	Same cohort as in Luchner *et al*., 2002[197]
McClure *et al*., 1998	Cannot extract 2×2 data
McCullough *et al*., 2003	Subset of Maisel *et al*., 2002[104] (study of incremental increase in clinical diagnosis with BNP)
McDonagh *et al*., 2004	Pooled analysis of McDonagh *et al*., 1998,[165] Luchner *et al*., 2002[197] and Groenning *et al*., 2004[190]
Maisel *et al*., 2001	Subset of Krishnaswamy *et al*., 2001[176]
Maisel *et al*., 2003	Subset of Maisel *et al*., 2002[104]
Maisel *et al*., 2004	A trial designed to illustrate relationship between BNP levels, clinical decision-making and outcomes
Maisel *et al*., 2005	Review article
Mak *et al*., 2004	Inappropriate reference test (diastolic heart failure)
Maron *et al*., 2004	BNP levels in patients with hypertrophic cardiomyopathy
Mockel *et al*., 2005	Study to determine distributions of BNP in groups, factors influencing BNP and prognosis
Mottram *et al*., 2003	Correlation study (BNP and echocardiogram)
Mottram *et al*., 2003	Inappropriate reference test (diastolic heart failure)

continued

TABLE 64 *Studies excluded from the review of BNP and NT-proBNP for heart failure (continued)*

Reference	Reason for exclusion
Motwani *et al*., 1993	Case–control study
Muders *et al*., 1997	Provides ROC curves but not 2×2 data
Mueller *et al*., 2004	Randomised trial of BNP versus standard assessment for time to discharge and cost of treatment
Mueller *et al*., 2005	Inappropriate reference test (any structural cardiac disease)
Mueller *et al*., 2006	Cost-effectiveness study based on Mueller *et al*., 2004[67]
Nakae *et al*., 2005	Correlation study (BNP, echocardiogram and SPECT)
Nakamura *et al*., 2002	Inappropriate reference test (any cardiac abnormality)
Nakamura *et al*., 2003	Inappropriate reference test (LVH)
Nakamura *et al*., 2005	Inappropriate reference test (any heart disease)
Ng *et al*., 2002	Case–control study
Ng *et al*., 2004	Inappropriate index test (urinary BNP)
Nikolaou *et al*., 2005	Inappropriate reference test (myocardial ischaemia)
Norozi *et al*., 2005	Case–control study
O'Donoghue *et al*. 2005	Levels of BNP and NT-proBNP in systolic and preserved systolic heart failure from PRIDE data
Omland *et al*., 1996	Provides ROC curves but not 2×2 data
Omland *et al*., 2005	Review article (references checked)
Orlowska *et al*., 2005	Inappropriate reference test (left ventricular mass)
Pieralli *et al*., 2006	Inappropriate reference test (right ventricular dysfunction)
Post *et al*., 2004	Inappropriate reference test (cardiac cause for dyspnoea)
Pfister *et al*., 2004	Review article (references checked)
Puschita *et al*., 2005	Correlation study (NT-proBNP and heart failure)
Ray *et al*., 2005	Inappropriate reference test (pulmonary oedema)
Redfield *et al*., 2004	Inappropriate reference test (preclinical ventricular dysfunction)
Ribeiro *et al*., 2006	Comparison of conventional diagnosis with BNP + ECG strategy
Richards *et al*., 1999	Prognostic study for development of heart failure
Richards *et al*., 2004	Narrative review
Rutten *et al*., 2005	Prevalence of unrecognised heart failure in patients with COPD
Sakhuja *et al*., 2005	Substudy of PRIDE study of the diagnostic accuracy of combination of BNP and QRS duration
Seino *et al*., 2004	Case–control study
Shao *et al*., 2005a	Correlation study (BNP and echocardiogram)
Shao *et al*., 2005b	In Chinese
Sirithunyamont *et al*., 2003	Case–control study
Song *et al*., 2005	Inappropriate reference test (NYHA classes II–IV)
Steg *et al*., 2005	Subset of Maisel *et al*., 2002[104] (only those patients who had an echocardiogram)
Suzuki *et al*., 2000	Correlation study (BNP and echocardiogram)
Talwar *et al*., 2000a	Correlation study (BNP and LWMI)
Talwar *et al*., 2000b	Case–control study
Tang *et al*., 2003	Inappropriate population (all patients had heart failure)

TABLE 64 *Studies excluded from the review of BNP and NT-proBNP for heart failure (continued)*

Reference	Reason for exclusion
Tang *et al*., 2005	Case–control study
Thackray *et al*., 2006	Inappropriate reference standard (LVEF and NYHA classes II–IV)
Tjeerdsma *et al*., 2002	Case–control study
Troughton *et al*., 2004	Study of determinants of BNP levels in patients with systolic heart failure
Tschope *et al*., 2005	Inappropriate reference test (diastolic heart failure)
Vasan *et al*., 2002	Retrospective study of only patients with BNP and adequate echocardiogram
Waku *et al*., 2000	Not clear which patients had the reference test
Wei *et al*., 2005	Inappropriate reference test (diastolic heart failure)
Wei *et al*., 2005	Study of differences in BNP levels in heart failure patients with different aetiologies
Wieczorek *et al*., 2002	Case–control study
Williams *et al*., 2004	Correlation study (BNP and echocardiogram with peak VO_2 and exercise duration)
Wu *et al*., 2004	Study comparing readmissions for heart failure or pulmonary disease before and after BNP testing introduction
Wu *et al*., 2006	Prognostic study
Wyer *et al*., 2006	Commentary on other research
Yamada *et al*., 1997	Correlation study (BNP and echocardiogram)
Yu *et al*., 1996	Correlation study (BNP and transmitral flow velocity)
Zaninotto *et al*., 2005	Inappropriate reference test (various cardiac diseases)
Zhao *et al*., 2006	Case–control study

AUC, area under the curve; COPD, chronic obstructive pulmonary disease; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVSD, left ventricular systolic dysfunction; LWMI, left ventricular wall motion index; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; ROC, receiver operating characteristic; SPECT, single photon emission computerised tomography.

Appendix 6

Update of systematic review performed for the NICE heart failure clinical guideline

Pharmacological therapy

The question updated from the heart failure guideline[50] was: What licensed drug therapy can be used to modify the outcome of heart failure in terms of quality of life, morbidity and mortality (including acute decompensation or chronic heart failure)?

Any studies from September 2002 to 10 November 2006 were considered. Only relevant systematic reviews, meta-analyses and RCTs with sample sizes ≥ 30 participants were included. Other inclusion criteria were:

- *relevant drugs* – angiotensin receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, beta-blockers and spironolactone
- *relevant outcomes* – hospitalisation/rehospitalisation, mortality, quality of life and cost-effectiveness.

Data extraction was carried out for those studies that met the inclusion criteria. Any studies considering cost-effectiveness were not subjected to data extraction but kept aside for future reference. Furthermore, studies that could be indirectly related to the model construction were also kept aside. *Table 65* shows the number and types of studies retrieved for each of the drug groups for which data is included in the evidence tables.

Overall summary

Angiotensin receptor blockers

Although it was demonstrated that adding an ARB (namely candesartan) to an ACE inhibitor was effective in reducing cardiovascular mortality and morbidity in the CHARM-Added trial, pooled analysis of four similar trials (including CHARM-Added) showed that using an ARB alone or an ARB in conjunction with an ACE inhibitor had no effect on mortality. This is in line with a previously reported finding in the heart failure guideline. There were some benefits of ARB therapy in those taking an ACE inhibitor without a beta-blocker. The effects seen in CHARM-Added were present regardless of the background dose of ACE inhibitor therapy.

In CHARM-Alternative it was shown that, if an individual is intolerant to ACE inhibitor therapy, candesartan is not only tolerated well but is also beneficial in reducing heart failure hospitalisation.

In individuals with preserved LVEF (CHARM-Preserved), candesartan reduced hospitalisation but had no effect on mortality. On the other hand, subgroup analysis of patients with low LVEF demonstrated improvement in both mortality and hospitalisation rates for those taking candesartan compared with those taking placebo.

In terms of quality of life, improvement was more apparent in the candesartan group; however, the

TABLE 65 *Numbers and types of studies summarised in the evidence tables*

	Drug group			
	ARBs	**ACE inhibitors**	**Beta-blockers**	**Spironolactone**
Systematic reviews/meta-analyses	1	0	0	0
Randomised controlled trials	3	1	4	1
Relevant additional papers (i.e. post hoc analysis, etc.)	4	0	0	0

effects were not substantial (37.7% versus 33.5% improved in the candesartan and placebo groups respectively).

Overall, ARBs, especially candesartan (for which the dosage was titrated up to the maximally recommended dose of 32 mg/day in all of the studies), have been shown to have a more prominent benefit in reducing hospitalisation.

Angiotensin-converting enzyme inhibitors
Only one study was identified, in which use of quinapril did not result in any improvement in quality of life; however, the assessment tool used to detect any changes in this outcome was questionable.

Beta-blockers
Nebivolol therapy was considered in two RCTs of which one reported no effects on quality of life. The same trial reported no effects on mortality either but marginal improvements in both mortality and hospitalisation rates were established in the second trial. This drug, however, is licensed for use in hypertension and not heart failure.

Of those drugs that are licensed for use in heart failure, one trial found that carvedilol therapy resulted in a reduction in combined mortality and cardiovascular hospitalisation, regardless of whether administered at a low or high dose. Another trial found that, in comparison with metoprolol, carvedilol therapy was associated with fewer deaths – a finding that was not available in the earlier systematic review in the heart failure guideline.

Spironolactone
Only one study with a very small sample size of 30 participants was identified. This reported that spironolactone had no effect on quality of life. The earlier systematic review of aldosterone antagonists did not reveal any studies that considered quality of life as an outcome measure.

Although eplerenone was not one of the drugs being specifically considered for the purposes of this review and is not licensed for use in the UK, a large RCT was discovered that reported very favourable results for this drug over placebo. Both mortality and hospitalisation were significantly reduced in patients with left ventricular dysfunction. This trial was mentioned in the earlier systematic review but the findings were not available at that time.

Costing studies
Five potentially relevant studies were identified and have been referenced.

Evidence tables

Angiotensin receptor blockers

Reviews

Paper	Dimopoulos K, Salukhe T, Coats A, Mayet J, Piepoli M, Francis D. Meta-analyses of mortality and morbidity effects of an angiotensin receptor blocker in patients with chronic heart failure already receiving an ACE inhibitor (alone or with a β-blocker). *Int J Cardiol* 2004;**93**:105–11
Description	Meta-analysis
n	Four RCTs included, in which information was available on combined ARB and ACE inhibitor therapy vs ACE inhibitor and placebo alone; 40.5% were also on beta-blockers Age: 63.2 years; male: 79.8%; NYHA class II: 49.3%, class III: 48.3%, class IV: 2.3%; LVEF: 25.6%
Intervention	Interventions considered included three ARBs – losartan, valsartan and candesartan
Outcomes	Outcome measures reported include mortality and combined end point of mortality and morbidity. All studies had a follow-up duration of at least 6 months
Results	Three separate meta-analyses were performed: (1) all patients ($n = 7666$), (2) all patients on concomitant beta-blockers, (3) patients not on concomitant beta-blockers (1) $n = 3950$ in the combined ARB and ACE inhibitor group, $n = 3716$ in the no ARB, only ACE inhibitor and placebo group. Addition of ARB had no significant effect on all-cause mortality. Only slight improvement with ARB treatment on combined end point was established [overall odds ratio (OR) 0.89; 95% CI 0.81–0.98] and no heterogeneity was found with either end point (2) Of the 3163 patients on beta-blocker therapy, 1569 received ARB and demonstrated a mortality rate of 23.3%. For the 1594 on no ARB the mortality rate was 24.1%. No significant effects were seen between the two groups for either all-cause mortality or combined end point (3) In total, 4029 patients were not receiving beta-blocker therapy. Mortality was similar in those on ARB and those on no ARB. However, combined end point of mortality–morbidity was significantly reduced in those in the ARB group (overall OR 0.83; 95% CI 0.73–0.94)
Comments	Details on the dosages and duration of ARB therapy have not been reported in this review Relevant data regarding those with/without concomitant beta-blocker therapy was available for only two RCTs Only a small number of studies merited inclusion in this review Briefly states that the fixed-effects model was used in terms of the methodology for pooled analysis. In instances in which heterogeneity was evident, further analyses using a random-effects model confirmed initial findings The authors state that the combined mortality and morbidity end points varied in the studies Although patients with a variable degree of functional impairment were considered in this review, one of the larger trials included only those in the more severe range (i.e. NYHA of classes III–IV) ARB therapy was beneficial in those taking ACE inhibitor without a beta-blocker
Reference	1
Studies included	Hamroff, 1999; McKelvie, 1999 – the RESOLVD pilot study investigators; Cohn, 2001 – Val-HeFT; McMurray, 2003 – CHARM-Added

Experimental studies

Paper	Granger C, McMurray J, Yusuf S, Held P, Michelson E, Olofsson B, *et al*. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003;**362**:772–6
Description	RCT
n	*n* = 2028 (treatment = 1013, control = 1015) Treatment group: age: 66.3 years; male: 68.2%; ischaemic origin: 69.7%; LVEF: 29.8%; NYHA class II: 48.1%, class III: 48.4%, class IV: 3.6% 618 centres in 26 countries
Intervention	Use of candesartan in patients who were intolerant to ACE inhibitors [defined as previous discontinuation by a physician because of intolerance for a number of reasons primarily including cough (70%), hypotension (14%) and renal dysfunction (13%)] at doses of up to a target of 32 mg a day for a median duration of follow-up of 33.7 months vs placebo
Outcomes	Primary end point was cardiovascular death or chronic heart failure-related hospitalisation. Also individual analysis of each of these two outcomes
Results	Three patients were lost to follow-up, two in the candesartan group and one in the placebo group In total, 334 (33%) on candesartan vs 406 (40%) on placebo encountered cardiovascular death or hospitalisation for chronic heart failure [adjusted hazard ratio 0.70 (95% CI 0.60–0.81, $p < 0.0001$)] In relation to the individual outcomes, 219 (21.6%) and 252 (24.8%) experienced cardiovascular death in the candesartan and placebo groups, respectively [adjusted hazard ratio 0.80 (95% CI 0.66–0.96, $p = 0.02$)], and 207 (20.4%) vs 286 (28.2%), respectively, experienced hospitalisation [adjusted hazard ratio 0.61 (95% CI 0.51–0.73, $p < 0.0001$)] Discontinuation of medication because of any adverse event/abnormal laboratory investigation occurred in 218 (21.5%) vs 196 (19.3%) in the candesartan and placebo groups respectively. Renal dysfunction, hyperkalaemia and hypotension were the main reasons for discontinuing, more so for candesartan than for placebo, and this was more apparent in those presenting with a medical history of such events A 23% relative risk reduction in cardiovascular mortality or chronic heart failure hospitalisation with candesartan is reported, and the need to treat 14 patients with candesartan to prevent one patient from experiencing any of the two outcomes
Comments	This study demonstrated that individuals who were intolerant to ACE inhibitors tolerated candesartan well The need to monitor serum creatinine and potassium levels during candesartan administration is highly encouraged, especially in those individuals with a history of renal insufficiency and hyperkalaemia
Reference	2

Paper	McMurray J, Ostergren J, Swedberg K, Granger C, Held P, Michelson E, *et al*. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003;**362**:767–71
Description	RCT
n	*n* = 2548 (treatment = 1276, control = 1272) Treatment group: age: 64.0 years; male: 78.8%; ischaemic origin: 62.2%; LVEF: 28.0%; NYHA class II: 24.5%, class III: 73.0%, class IV: 2.6% 618 centres in 26 countries
Intervention	Use of candesartan in patients who were already being treated with ACE inhibitors. The dose of candesartan was up to a target 32 mg a day for a median duration of follow-up of 41 months vs placebo
Outcomes	Primary end point was cardiovascular death or chronic heart failure-related hospitalisation. Also individual analysis of each of these two outcomes
Results	Four patients were lost to follow-up, three in the candesartan group and one in the placebo group In total, 483 (37.9%) on candesartan vs 538 (42.3%) on placebo encountered cardiovascular death or hospitalisation for chronic heart failure [adjusted hazard ratio 0.85 (95% CI 0.75–0.96, $p < 0.01$)] In relation to the individual outcomes, 302 (23.7%) and 347 (27.3%) experienced cardiovascular death in the candesartan and placebo groups, respectively [adjusted hazard ratio 0.83 (95% CI 0.71–0.97, $p = 0.021$)], and 309 (24.2%) vs 356 (28.0%), respectively, experienced hospitalisation [adjusted hazard ratio 0.83 (95% CI 0.71–0.97, $p = 0.018$)] Whether or not the patients were receiving beta-blockers in addition to ACE inhibitor made no difference to the degree of benefit achieved with candesartan. Furthermore, treatment had a similar effect in those taking higher or lower doses of ACE inhibitor Discontinuation of medication because of any adverse event/abnormal laboratory investigation occurred in 309 (24.2%) vs 233 (18.3%) of the candesartan and placebo groups respectively. A twofold increase in creatinine level from baseline in the candesartan group compared with the placebo group was responsible for treatment discontinuation. Hypotension and hyperkalaemia were other reasons for discontinuation in both groups with the latter adverse event being more evident in those administered candesartan The need to treat 23 patients to prevent one first occurrence of either cardiovascular death or hospitalisation for chronic heart failure is reported, as well as a 15% relative risk reduction in cardiovascular mortality
Comments	The addition of candesartan to ACE inhibitors was shown to be beneficial in the reduction of cardiovascular mortality and morbidity The majority of the patients were at the moderate stage of heart failure (NYHA class III)
Reference	3

Paper	McMurray J, Young J, Dunlap M, Granger C, Hainer J, Michelson E, *et al*. Relationship of dose of background angiotensin-converting enzyme inhibitor to the benefits of candesartan on the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)-Added trial. *Am Heart J* 2006;**151**:985–91
Description	Post hoc subgroup analysis of patients in CHARM-Added trial
n	*n* = 529 on 'maximum dose' vs *n* = 2019 on 'not maximum dose' of background ACE inhibitor Maximum dose group: age: 64 years; male: 81%; ischaemic origin: 56%; LVEF: 30%; NYHA class II: 22%, class III: 76%, class IV: 2.5% Not maximum dose group: age: 64 years; male: 78%; ischaemic origin: 64%; LVEF: 30%; NYHA class II: 25%, class III: 72%, class IV: 3.2%
Intervention	As in CHARM-Added
Outcomes	As in CHARM-Added
Results	Candesartan effects on cardiovascular mortality and hospitalisation were not modified in relation to the background ACE inhibitor dose: maximum dose hazard ratio for mortality was 0.76 (95% CI 0.54–1.08) vs 0.86 (95% CI 0.73–1.03) for not maximum dose. Maximum dose hazard ratio for hospitalisation was 0.70 (95% CI 0.51–0.96) vs 0.87 (95% CI 0.73–1.03) for not maximum dose Rates of discontinuation of candesartan and placebo in those receiving maximum dose ACE inhibitor were 7.4% vs 8.1%, respectively, because of creatinine increase; 4.5% vs 3.1%, respectively, because of hypotension; and 4.1% vs 1.5%, respectively, because of hyperkalaemia
Comments	This post hoc analysis considered the effects of an ARB when added to either a maximum dose of ACE inhibitor or not a maximum dose of ACE inhibitor In total, 80% of the ACE inhibitors used were enalapril, lisinopril, captopril, ramipril and trandopril Beneficial effects with candesartan were achieved in patients taking both a high and a low dose of ACE inhibitor
Reference	4

Paper	Yusuf S, Pfeffer M, Swedberg K, Granger C, Held P, McMurray J, *et al.* Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved trial. *Lancet* 2003;**362**:777–81
Description	RCT
n	*n* = 3023 (treatment = 1514, control = 1509) Treatment group: age: 67.2 years, male: 60.8%, ischaemic origin: 56.4%, LVEF: 54.0%; NYHA class II: 61.5%, class III: 36.7%, class IV: 1.8% 618 centres in 26 countries
Intervention	Use of candesartan in patients who had preserved LVEF. The dose of candesartan was up to a target 32 mg a day for a median duration of follow-up of 36.6 months vs placebo
Outcomes	Primary end point was cardiovascular death or chronic heart failure-related hospitalisation. Also individual analysis of each of these two outcomes
Results	Three patients were lost to follow-up, two in the candesartan group and one in the placebo group In total, 333 (22.0%) on candesartan vs 366 (24.3%) on placebo encountered cardiovascular death or hospitalisation for chronic heart failure [adjusted hazard ratio 0.86 (95% CI 0.74–1.00, $p = 0.051$)] In relation to the individual outcomes, 170 (11.2%) and 170 (11.3%) experienced cardiovascular death in the candesartan and placebo groups, respectively [adjusted hazard ratio 0.95 (95% CI 0.76–1.18, $p = 0.635$)], and 241 (15.9%) vs 276 (18.3%), respectively, experienced hospitalisation [adjusted hazard ratio 0.84 (95% CI 0.70–1.00, $p = 0.047$)] Discontinuation of medication because of any adverse event/abnormal laboratory investigation occurred in 270 (17.8%) vs 204 (13.5%) in the candesartan and placebo groups respectively More patients in the candesartan than placebo group had raised creatinine (4.8% vs 2.4%, respectively) and potassium (1.5% vs 0.6%, respectively) levels. Hypotension was more apparent in the candesartan (2.4%) than placebo (1.1%) group A 14% relative risk reduction is reported
Comments	The main benefit of candesartan in this trial was on hospital admissions; mortality rates were similar in both groups All patients had an LVEF > 40% Although physicians were responsible for diagnosing heart failure at entry to the trial, it was noted that this study included more women, patients were older and two-thirds of patients had been previously hospitalised for heart failure and so probably had heart failure
Reference	5

Paper	Pfeffer M, Swedberg K, Granger C, Held P, McMurray J, Michelson E, *et al*. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet* 2003;**362**:759–66
Description	Combined overall analysis of the three CHARM trials
n	*n* = 7599 (treatment = 3803, control = 3796) Treatment group: age: 65.9 years; male: 68.8%; LVEF: 38.8%; NYHA class II: 45.5%, class III: 52.0%, class IV: 2.5% 618 centres in 26 countries
Intervention	Candesartan was administered up to a target dose of 32 mg a day for a median duration of follow-up of 37.7 months vs placebo
Outcomes	Primary end point was cardiovascular death or chronic heart failure-related hospitalisation. Also individual analysis of each of these two outcomes
Results	Altogether 10 patients were lost to follow-up, seven from the candesartan group and three from the placebo group In total, 1150 (30.2%) on candesartan vs 1310 (34.5%) on placebo encountered cardiovascular death or hospitalisation for chronic heart failure [adjusted hazard ratio 0.82 (95% CI 0.75–0.88, $p < 0.0001$)] In relation to the individual outcomes, 691 (18.2%) and 769 (20.3%) experienced cardiovascular death in the candesartan and placebo groups, respectively [adjusted hazard ratio 0.87 (95% CI 0.78–0.96, $p = 0.006$)], and 757 (19.9%) vs 918 (24.2%), respectively, experienced hospitalisation [adjusted hazard ratio 0.77 (95% CI 0.70–0.84, $p < 0.0001$)] Discontinuation because of any adverse event/abnormal laboratory investigation was more prominent in the candesartan group – 797 (21.0%) vs 633 (16.7%) for the candesartan and placebo groups respectively. The occurrence of hypotension, hyperkalaemia and increased creatinine values resulted in a greater discontinuation rate in the candesartan group Candesartan effectiveness was similar in patients with LVEF of > or < 40%
Comments	
Reference	6

Paper	Young J, Dunlap M, Pfeffer M, Probstfield J, Cohen-Solal A, Dietz R, *et al*. Mortality and morbidity reduction with candesartan in patients with chronic heart failure and left ventricular systolic dysfunction: results of the CHARM low-left ventricular ejection fraction trials. *Circulation* 2004;**110**:2618–26
Description	Pooled analysis of two RCTs – CHARM-Added and CHARM-Alternative
n	$n = 4576$ (treatment = 2289, control = 2287) Treatment group: age: 65.1 years; male: 74.1%; LVEF: 29%; NYHA class II: 34.9%, class III: 62.1%, class IV: 3.0% 618 centres in 26 countries
Intervention	Candesartan was administered up to a target dose of 32 mg a day for a median duration of follow-up of 40 months vs placebo
Outcomes	Primary end point was cardiovascular death or chronic heart failure-related hospitalisation. Also individual analysis of each of these two outcomes
Results	Seven patients were lost to follow-up, five in the candesartan group and two in the placebo group In total, 817 (35.7%) on candesartan vs 944 (41.3%) on placebo encountered cardiovascular death or hospitalisation for chronic heart failure [adjusted hazard ratio 0.82 (95% CI 0.74–0.90, $p < 0.001$)] In relation to the individual outcomes, 521 (22.8%) and 599 (26.2%) experienced cardiovascular death in the candesartan and placebo groups, respectively [adjusted hazard ratio 0.84 (95% CI 0.75–0.95, $p = 0.005$)], and 516 (22.5%) vs 642 (28.1%), respectively, experienced hospitalisation [adjusted hazard ratio 0.76 (95% CI 0.68–0.85, $p < 0.001$)] An adverse event or laboratory abnormality resulted in medication discontinuation in 528 (23.1%) in the candesartan group and 429 (18.8%) on placebo. Creatinine increase in 7.1% vs 3.5%, hypotension in 4.2% vs 2.1% and hyperkalaemia in 2.8% vs 0.5% were other causes of study medication discontinuation in the candesartan vs placebo groups respectively
Comments	Candesartan therapy proved beneficial regardless of whether patients were on an ACE inhibitor or not All patients had a mean LVEF ≤ 40% In total, 44% of the patients were not taking an ACE inhibitor
Reference	7

Paper	O'Meara E, Lewis E, Granger C, Dunlap M, McKelvie R, Probstfield J, *et al*. Patient perception of the effect of treatment with candesartan in heart failure. Results of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. *Eur J Heart Fail* 2005;**7**:650–6
Description	Secondary analysis of patients in the CHARM programme
n	*n* = 2498 Age: 65.4 years; male: 66.8%; LVEF: 0.40; NYHA class II: 37.1%, class III: 60.8%, class IV: 2.0%
Intervention	Candesartan was administered up to a target dose of 32 mg vs placebo
Outcomes	Quality of life: the McMaster Overall Treatment Evaluation (OTE) questionnaire was a secondary outcome measure in CHARM-Overall. On this, patients rated the perceived effect of treatment in terms of improvement in symptomatic well-being and functional capacity
Results	479 patients had died by the end of the study Scores on the OTE questionnaire for overall symptom improvement were more favourable for the patients in the candesartan group (37.7%) than for the patients in the placebo group (33.5%) Deterioration in OTE score was reported in 10.8% vs 12.0% on candesartan and placebo respectively The OTE score remained unchanged in 51.4% in the candesartan group and 54.4% in the placebo group
Comments	Only those patients in the trial from Canada and the USA (33% of the overall CHARM patients) completed the questionnaire A single subjective outcome measure is used
Reference	8

Angiotensin-converting enzyme inhibitors

Paper	Zi M, Carmichael N, Lye M. The effect of quinapril on functional status of elderly patients with diastolic heart failure. *Cardiovasc Drugs Ther* 2003;**17**:133–9
Description	RCT
n	*n* = 74 (treatment = 36, control = 38) Treatment group: age: 77 years; male: 38.9%; LVEF: ≥ 40%; NYHA class I: 5.5%, class II: 77.8%, class III: 16.7%
Intervention	Quinapril was titrated up to a target dose of 40 mg a day vs placebo for a period of 6 months
Outcomes	Quality of life was assessed by the McMaster quality of life (QoL) questionnaire
Results	There were no significant differences in the QoL scores for either group when compared with baseline scores The number of adverse events did not differ between groups, although there was a non-significant tendency for the quinapril group patients to have a lesser chance of worsened heart failure or being hospitalised
Comments	This study has a small sample size The authors report that the QoL questionnaire utilised in this study may not have been sensitive enough for detecting drug-related changes in QoL
Reference	9

Beta-blockers

Paper	Edes I, Gasior Z, Wita K. Effects of nebivolol on left ventricular function in elderly patients with chronic heart failure: results of the ENECA study. *Eur J Heart Fail* 2005;**7**:631–9
Description	RCT
n	*n* = 260 (treatment = 134, control = 126) Treatment group: age: 72 years; male: 70.2%; LVEF: 25.4%; NYHA class II: 52.2%, class III: 45.5%, class IV: 2.2%
Intervention	Nebivolol was titrated up to a maximum possible dose of 10 mg a day vs placebo for a period of 8 months
Outcomes	The Minnesota Living with Heart Failure questionnaire was used to assess quality of life Documented hospital visits determined the hospitalisation rate Mortality rate
Results	The total score on the quality of life questionnaire decreased by 9.13% vs 11.01% for the nebivolol and placebo groups respectively ($p = 0.34$) 1535 hospitalisations were recorded for those in the nebivolol group and 1411 for those in the placebo group The mortality rate was identical – seven patients died from each group Kaplan–Meier analysis revealed non-significant survival rates of 67.47% in the nebivolol group and 62.89% in the placebo group In total, 81 (60.45%) patients in the nebivolol group and 78 (61.9%) in the placebo group experienced at least one adverse event; there was no significant difference in safety parameters between the two groups
Comments	Nebivolol was well tolerated and reported to have a similar effect to other beta-blockers (metoprolol and carvedilol) considered in previous trials
Reference	10

Paper	Flather M, Shibata M, Coats A, Van Veldhuisen D, Parkhomenko A, Borbola J *et al*. Randomised trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J* 2005;**26**:215–25
Description	RCT
n	*n* = 2128 (treatment = 1067, control = 1061) Treatment group: age: 76.1 years; male: 61.6%; LVEF: 36%; NYHA class I: 3.0%, class II: 56.5%, class III: 38.7%, class IV: 1.8% Patients were enrolled from 11 different countries
Intervention	Nebivolol was titrated up to a target dose of 10 mg a day vs placebo for a maximum period of 16 weeks
Outcomes	Combined all-cause mortality or cardiovascular hospitalisation was used as the primary measure to determine the effect of treatment on quality of life and risk of death. Mortality and hospitalisation were also considered separately as secondary outcomes
Results	In total, 31.1% in the nebivolol group vs 35.3% in the placebo group experienced the primary outcome [adjusted hazard ratio 0.86 (95% CI 0.74–0.99, $p = 0.039$)] An absolute risk reduction of 4.2% suggested the need to treat 24 patients for 21 months to avoid one event In relation to the secondary outcomes, all-cause mortality occurred in 15.8% vs 18.1%, cardiovascular mortality in 11.5% vs 13.7%, cardiovascular hospitalisation in 24% vs 26% and all-cause hospitalisation in 33.6% vs 34.3% in the nebivolol vs placebo groups respectively The only differences between the two groups with regards to adverse events were more reports of bradycardia and decreased occurrence of angina pectoris and unstable angina in the nebivolol group Treatment discontinuation rates were similar in both groups
Comments	This trial was performed in patients with heart failure aged ≥ 70 years, regardless of ejection fraction, and demonstrated that beta-blockers are of benefit in the elderly Beneficial effects of nebivolol were seen after 6 months of treatment with continual treatment resulting in increased risk reduction
Reference	11

Paper	Hori M, Sasayama S, Kitabatake A, Toyo-oka T, Handa S, Yokoyama M, *et al*. Low-dose carvedilol improves left ventricular function and reduces cardiovascular hospitalisation in Japanese patients with chronic heart failure: the Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) trial. *Am Heart J* 2004;**147**:324–30
Description	RCT
n	*n* = 173 (treatment low dose = 47, high dose = 77, control = 49) Low-dose treatment group: age: 59 years; male: 77%; LVEF: 30%; NYHA class II: 81%, class III: 19% High-dose treatment group: age: 60 years; male: 74%; LVEF: 30%; NYHA class II: 75%, class III: 25%
Intervention	Low-dose carvedilol (5 mg) vs high-dose carvedilol (20 mg) for a maintenance therapy phase of 24–48 weeks vs placebo
Outcomes	Combined all-cause mortality or cardiovascular-related hospitalisation, cardiovascular hospitalisation and hospitalisation for worsening of heart failure were all relevant secondary outcome measures
Results	The death or cardiovascular hospitalisation rate was significantly lower in both the low- and high-dose carvedilol groups than in the placebo group. A 71% risk reduction was reported in the low-dose group and an 80% risk reduction in the high-dose group Risk reduction rates for cardiovascular hospitalisation were 86% and 85% for the low- and high-dose groups, respectively, as compared with placebo including worsening of heart failure-related hospitalisation risk reduction rates of 91% for the low-dose and 88% for the high-dose groups There were no significant differences in adverse events between the three groups
Comments	Dose-related improvements with carvedilol were established Improvement with the low dose was almost at the level of that achieved with the high dose The results of this study may be specific to a Japanese population as a similar study in the USA identified a recommended carvedilol dose of 12.5–50 mg a day rather than 5–20 mg as suggested in the present study
Reference	12

Paper	Poole-Wilson P, Swedberg K, Cleland J, Di Lenarda A, Hanrath P, Komajda M, *et al*. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet* 2003;**362**:7–13
Description	RCT
n	*n* = 3029 (carvedilol = 1511, metoprolol = 1518) Carvedilol group: age: 61.6 years; male: 79%; ischaemic origin: 51%; LVEF: 0.26; NYHA class II: 48%, class III: 48%, class IV: 3% Metoprolol group: age: 62.3 years; male: 80%; ischaemic origin: 54%; LVEF: 0.26; NYHA class II: 49%; class III: 47%, class IV: 4% Patients were enrolled from 341 centres in 15 European countries
Intervention	Carvedilol was administered up to a target dose of 25 mg twice a day vs metoprolol up to a target dose of 50 mg twice a day. The study duration was for an average of 58 (SD 6) months
Outcomes	All-cause mortality was the primary outcome measure. Combined all-cause mortality or all-cause hospitalisation was the secondary outcome measure
Results	In total, five patients were lost to follow-up from both groups and 28 withdrew consent; however, analysis was conducted on an intention to treat basis In relation to all-cause mortality the results were in favour of carvedilol with 512 (34%) deaths in this group and 600 (40%) in the metoprolol group [hazard ratio 0.83 (95% CI 0.74–0.93, $p = 0.002$)]. In total, 438 (29%) and 534 (35%) deaths were cardiovascular related in the carvedilol and metoprolol groups respectively [hazard ratio 0.80 (95% CI 0.70–0.90, $p = 0.0004$)] The secondary end point was experienced at a similar rate in both groups – 1116 (74%) patients in the carvedilol group and 1160 (76%) in the metoprolol group. For this, the hazard ratio for hospitalisation was 0.97 (95% CI 0.89–1.05, $p = 0.45$) Treatment discontinuation rates were similar in both the carvedilol (32%) and metoprolol (32%) groups In total, 94% of patients experienced at least one adverse event in the carvedilol group and 96% in the metoprolol group. Beta-blocker-related adverse events of bradycardia and hypotension occurred at a similar rate in both groups The yearly mortality rates were 8.3% and 10.0% for the carvedilol and metoprolol groups respectively
Comments	Carvedilol has been shown to be more beneficial than metoprolol
Reference	13

Spironolactone

Paper	Agostoni P, Magini A, Andreini D, Contini M, Apostolo A, Bussotti M, *et al*. Spironolactone improves lung diffusion in chronic heart failure. *Eur Heart J* 2005;**26**:159–64
Description	RCT
n	*n* = 30 (treatment = 15, control = 15) Treatment group: age: 60.3 years; male: 66.7%; LVEF: 40%
Intervention	Spironolactone 25 mg a day was administered vs placebo and the total follow-up period was 6 months
Outcomes	The Minnesota quality of life questionnaire was used to assess quality of life
Results	Quality of life was not significantly affected by spironolactone intervention
Comments	Inclusion criteria specified that only those patients within NYHA classes II and III were eligible for this study, although the number falling into each range is not mentioned A very small sample size is used
Reference	14

Eplerenone

Paper	Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, *et al*. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;**348**:1309–21
Description	RCT
n	*n* = 6642 (treatment = 3319, control = 3313) Treatment group: age: 64 years; male: 72%; LVEF: 33% Patients were enrolled from 674 centres in 37 countries
Intervention	Eplerenone increased up to a maximum dose of 50 mg a day was administered vs placebo and the mean duration of follow-up was 16 months (range 0–33 months)
Outcomes	All-cause mortality and cardiovascular-related mortality or hospitalisations were the primary outcomes All-cause mortality or any-cause hospitalisation was also analysed as a secondary outcome
Results	All-cause mortality occurred in 478 (14.4%) patients in the eplerenone group and 554 (16.7%) in the placebo group [0.85 relative risk reduction was reported (95% CI 0.75–0.96, $p = 0.008$)] Cardiovascular-related mortality or hospitalisation occurred in 885 (26.7%) in the eplerenone group and 993 (30.0%) in the placebo group [relative risk reduction 0.87 (95% CI 0.79–0.95, $p = 0.002$)] In total, 1730 and 1829 patients experienced the secondary outcome in the eplerenone and placebo groups respectively [relative risk reduction 0.92 (95% CI 0.86–0.98)] An estimated number of the need to treat of 50 patients to prevent one death per year and of 33 patients to prevent one cardiovascular related death or hospitalisation per year is reported
Comments	Left ventricular dysfunction determined by a LVEF of ≤ 40% and documented heart failure formed some of the inclusion criteria From each group, 90% showed symptoms of heart failure, and 14% in the treatment group and 15% in the placebo group had a medical history of heart failure The trial was designed to continue until 1012 deaths had occurred
Reference	15

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8. O'Meara E, Lewis E, Granger C, Dunlap M, McKelvie R, Probstfield J, *et al*. Patient perception of the effect of treatment with candesartan in heart failure. Results of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. *Eur J Heart Fail* 2005;**7**:650–6.

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Costing studies

Relevant post hoc analysis of previously included randomised controlled trials in the guideline

Stewart S, McMurray JJV, Hebborn A, Coats AJS, Packer M; the COPERNICUS Study Group. Carvedilol reduces the costs of medical care in severe heart failure: an economic analysis of the COPERNICUS study applied to the United Kingdom. *Int J Cardiol* 2005;**100**:143–9.

Other relevant costing studies/ economical evaluations

Cowper PA, DeLong ER, Whellan DJ, LaPointe NMA, Califf RM. Economic effects of beta-blocker therapy in patients with heart failure. Am J Me*d* 2004;**116**:104–11.

Inomata T, Izumi T, Kobayashi M. Cost-effectiveness analysis of carvedilol for the treatment of chronic heart failure in Japan. *Circulation J* 2004;**68**:35–40.

Shibata MC, Nilsson C, Hervas-Malo M, Jacobs P, Tsuyuki RT. Economic implications of treatment guidelines for congestive heart failure. *Can J Cardiol* 2005;**21**:1301–6.

Tilson L, McGowan B, Ryan M, Barry M. Cost-effectiveness of spironolactone in patients with severe heart failure. *Ir J Med Sci* 2003;**172**:70–2.

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Granger BB, Swedberg K, Ekman I, Granger CB, McMurray JJ, *et al*. Adherence to candesartan and placebo and outcomes in chronic heart failure in the CHARM programme: double-blind, randomised, controlled clinical trial. *Lancet*;2005;**366**: 2005–11.

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Solomon SD, Wang D, Finn P, Skali H, Zornoff L, McMurray JJ, *et al*. Effect of candesartan on cause-specific mortality in heart failure patients: the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) program. *Circulation* 2004;**110**:2180–3.

Rehabilitation and exercise training

The question updated from the heart failure guideline[50] was: What is the evidence for recommending rehabilitation and/or a period of exercise training for patients with chronic heart failure?

Any relevant studies from September 2002 to 19 November 2006 were searched. In total, nine RCTs met the inclusion criteria (same population and outcome measures as for the drugs therapy search) for this review; however, as the majority of them consisted of very small sample sizes (i.e. 30–46 participants in six studies) it was decided that an arbitrary cut-off of ≥ 50 participants would be the most appropriate way forward for practical reasons and for the purposes of obtaining meaningful data for model construction. *Table 66* shows the number of relevant papers for which data extraction was completed.

TABLE 66 *Number of relevant papers summarised in the evidence tables*

Systematic reviews/meta-analysis	3
RCTs	3

Overall summary

Since the previous findings on exercise and rehabilitation effectiveness were reported in the heart failure guideline, newer systematic review and meta-analysis evidence has emerged that reports on mortality rates. This evidence indicates that there has been only one study reporting reduced mortality, over a long-term period of 3.3 years. In the two new papers identified there were discrepancies in some of the included studies, as was the case with the results – those included in the systematic review showed that exercise training had no effect on mortality, whereas those pooled in the meta-analysis demonstrated lower mortality with exercise training over the control. Only one recent study was identified that considered this outcome, which reported that exercise training had no effect on mortality.

On the whole, the evidence suggests that, in patients with heart failure, exercise training can be extremely beneficial for improving quality of life. This point is reinforced by the fact that, in nearly all of the studies reviewed, quality of life improved in those undergoing exercise training but remained the same in those not exposed to this intervention. All studies included within the reviews were conducted either during or before 2002 and so it is unsurprising that similar results were previously reported in the heart failure guideline. Furthermore, pooled analyses of several trials showed that exercise training can be useful in lowering the incidence of hospital admissions.

Evidence tables
Reviews

Paper	Rees K, Taylor R, Singh S, Coats A, Ebrahim S. Exercise based rehabilitation for heart failure. *Cochrane Database Syst Rev* 2004;**3**:CD003331
Description	Systematic review
n	29 RCTs included on exercise-based interventions *n* = 1126 altogether; all patients were within NYHA classes II and III and had a LVEF of < 40% Mean age range: 51–77 years; with the exception of two studies, all other studies mostly recruited men
Intervention	Aerobic intervention was considered in 23 studies and resistance training of peripheral muscle groups in six studies
Outcomes	Outcome measures included all-cause mortality, hospital admissions/rehospitalisation and validated measures of health-related quality of life. Mean follow-up duration was 20 (SD 14) weeks (range 4–60 weeks); only one study had 3.3 years of follow-up
Results	The one study (*n* = 99) with 3.3 years of follow-up demonstrated a significant reduction in cardiac mortality [odds ratio (OR) 0.32 (95% CI 0.13–0.8)] and rehospitalisations for heart failure [OR 0.28 (95% CI 0.09–0.85)] Mortality was reported as the reason for 'dropouts' in eight studies; these deaths were not related to the study intervention. Pooled analysis of the data from these studies showed that there was no significant difference between intervention and control groups in terms of all-cause mortality Quality of life was reported as an outcome in nine studies; seven reported improvement with intervention compared with control. Four out of five studies that utilised the Minnesota Living with Heart Failure questionnaire found significant short-term improvements in the intervention group; of these five studies, one also showed that the beneficial effects of the intervention were maintained at 12 months of follow-up
Comments	'Usual medical care' or an 'attention placebo' formed the control group In total, 23 of the studies were of a parallel group design and six were crossover trials. With crossover designs only the data from the first arm of the study was used, unless combined data from the two arms was presented, in which case these were included as long as there were no reports of carryover effects or there was a washout period Authors have mentioned that included studies were largely of small sample size and poor methodology. Furthermore, the findings of this review can be applied only to those with stable chronic heart failure It appears that not many women were recruited into such exercise-based interventional programmes Only studies up to the year 2001 were searched
Reference	1
Studies included	Belardinelli, 1992; Belardinelli, 1995; Belardinelli, 1999; Cider, 1997; Coats, 1990; Coats, 1992; Dubach *et al.*; Gottlieb, 1999; Hambrecht, 1995; Hambrecht, 1998; Hambrecht, 2000; Jette, 1991; Keteyian, 1996; Kiilavuori, 1996; Maiorana, 2000; Meyer, 1996; Oka, 2000; Owen, 2000; Parnell, 2002; Ponikowski, 1997; Pu, 2001; Quittan, 1999; Teo, 1995, EXERT; Tyni-Lenne, 1997; Tyni-Lenne, 2001; Tyni-Lenne/Gordon, 1996; Wielenga, 1998; Wielenga, 1999, CHANGE; Willenheimer, 1998

Paper	Smart N, Marwick T. Exercise training for patients with heart failure: a systematic review of factors that improve mortality and morbidity. *Am J Med* 2004;**116**:693–706
Description	Systematic review
Results/ comments	This systematic review also reports on mortality rates following exercise training in heart failure patients. The studies included within this review are very similar to those already included in the Cochrane systematic review (Rees *et al*., 2004) for which data extraction has been completed. The main difference between the reviews is that this review considers all study designs whereas Rees *et al*. considers only RCTs. As with Rees *et al*., this review also reported that there were no deaths directly related to the intervention. In the RCTs ($n = 30$ trials) the mortality rates were 4.2% and 7.1% for the exercise and control groups respectively. Death during the activity or follow-up period was associated with an odds ratio of 0.71 (95% CI 0.37–1.02, $p = 0.06$) for exercise vs control patients
Reference	2

Paper	Piepoli M, Davos C, Francis D, Coats A, ExTraMATCH Collaborative. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *BMJ* 2004;**328**:189
Description	Meta-analysis
n	Nine RCTs were included in which patients had undergone at least 8 weeks of exercise training and for which individual patient follow-up data on survival for at least 3 months were available $n = 801$ (exercise training = 395, control = 406) Exercise group: age: 60.5 years; male: 88.4%; mean NYHA class: 2.6; LVEF: 27.9%
Intervention	Exercise training programme
Outcomes	All-cause mortality was the primary outcome. Mortality or first hospitalisation was the secondary end point
Results	88 (22%) deaths vs 105 (26%) deaths were reported in the exercise and control groups, respectively, and so there was a significantly lower mortality rate in the exercise group (log-rank $\chi^2 = 5.9$, $p = 0.015$); hazard ratio for mortality = 0.65 (95% CI 0.46–0.92). The need to treat 17 patients to prevent one death in 2 years is reported The incidence of hospital admissions was also significantly lower in the exercise group, with 127 experiencing the secondary end point in the exercise group and 173 in the control group (log-rank $\chi^2 = 6.4$, $p = 0.011$); hazard ratio for combined end point = 0.72 (95% CI 0.56–0.93)
Comments	
Reference	3
Studies included	Belardinelli, 1999; Dubach, 1997; Giannuzzi, 1997; Hambrecht, 1995; Kiilavuori, 2000; McKelvie, 2002; Zanelli, 1997; Wielenga, 1999; Willenheimer, 1998

Experimental studies

Paper	Austin J, Williams R, Ross L, Moseley L, Hutchison S. Randomised controlled trial of cardiac rehabilitation in elderly patients with heart failure. *Eur J Heart Fail* 2005;**7**:411–17
Description	RCT
n	*n* = 200 (exercise = 100, control = 100) Exercise group: age: 71.9 years; male: 44%; 15% had LVEF of ≤ 40–35%, 49% LVEF < 35–30%, 36% LVEF < 30%; NYHA class II: 56%, class III: 44%
Intervention	The exercise training group underwent an 8-week cardiac rehabilitation programme in which patients were required to attend two 2.5-hour classes weekly. Patients then went on to a 16-week community-based exercise regimen, which involved 1-hour weekly sessions. Aerobic, low resistance and high repetitive muscular strength training made up the exercise programme
Outcomes	Health-related quality of life was assessed by the Minnesota Living with Heart Failure and EuroQol questionnaires Hospital admissions and mortality, although not included as outcome measures, were also recorded
Results	Scores on both of the quality of life instruments were significantly better at 24 weeks than at baseline for the experimental group compared with the control group Total hospital admissions were significantly fewer in the experimental group (10.6%) than in the control group (20.2%) ($p < 0.01$) The mortality rate was similar in both groups
Comments	Beneficial effects of exercise training were seen as early as 8 weeks when the patients were undergoing the most intense phase of the programme The authors suggest that the increased contact of patients with the rehabilitation team may have been responsible for the improved quality of life and lower incidence of hospitalisation in the exercise group
Reference	4

Paper	Giannuzzi P, Temporelli P, Corra U, Tavazzi L. Antiremodeling effect of long-term exercise training in patients with stable chronic heart failure: results of the Exercise in Left Ventricular Dysfunction and Chronic Heart Failure (ELVD-CHF) trial. *Circulation* 2003;**108**:554–9
Description	RCT
n	*n* = 90 (exercise = 45, control = 45) Exercise group: age: 60 years; patients were 'predominantly male'; LVEF: 25%; NYHA class II: 62%, class III: 38% Patients were enrolled from 15 unselected cardiac rehabilitation centres throughout Italy
Intervention	Those in the exercise training group underwent 30 minutes of bicycle training 3–5 times a week for an overall period of 6 months. Additionally, patients were advised to take > 30 minutes of brisk walks daily and undertake intermittent 30 minutes of callisthenics as part of their home-based programme
Outcomes	Modified 6-point Likert symptom questionnaires were used to assess quality of life. These considered symptoms relating to breathlessness, tiredness, chest pain, daily activity and emotional status
Results	The perceived symptoms score on the quality of life questionnaires significantly improved from a mean of 13.4 at baseline to 10.9 at 6 months' follow-up in the exercise training group ($p < 0.05$). This score remained unchanged in the control group There was one sudden cardiac death in the control group but none in the exercise training group Two patients in the exercise training group were admitted to hospital because of temporarily worsening dyspnoea and congestion at 3 and 4 months into the study, compared with one patient in the control group
Comments	The exercise training programme in this study was considered as moderately intensive Not much detail has been provided about the quality of life outcome measures and so it is uncertain whether these were validated assessment tools
Reference	5

Paper	Passino C, Severino S, Poletti R, Piepoli M, Mammini C, Clerico A, *et al*. Aerobic training decreases B-type natriuretic peptide expression and adrenergic activation in patients with heart failure. *J Am Coll Cardiol* 2006;**47**:1835–9
Description	RCT
n	*n* = 85 (exercise = 44, control = 41) Exercise group: age: 60 years; male: 89%; LVEF: 35.3%; NYHA class I: 13.6%, class II: 63.6%, class III: 22.7%
Intervention	The exercise group underwent a 9-month home-based physical training programme, which included cycling on a bike for at least three times a week for 30 minutes each time
Outcomes	The Minnesota Living with Heart Failure questionnaire was used to assess quality of life at baseline and on completion of the study
Results	The quality of life score significantly improved in the exercise group from a mean of 54 at baseline to 32 at 9 months' follow-up ($p < 0.01$), but patients in the control group showed no change
Comments	Initially, 95 patients were recruited for this study, of whom 85 completed and were included in the analysis
Reference	6

References

1. Rees K, Taylor R, Singh S, Coats A, Ebrahim S. Exercise based rehabilitation for heart failure. *Cochrane Database Syst Rev* 2004;**3**:CD003331.

2. Smart N, Marwick T. Exercise training for patients with heart failure: a systematic review of factors that improve mortality and morbidity. *Am J Med* 2004;**116**:693–706.

3. Piepoli M, Davos C, Francis D, Coats A, ExTraMATCH Collaborative. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *BMJ* 2004;**328**:189.

4. Austin J, Williams R, Ross L, Moseley L, Hutchison S. Randomised controlled trial of cardiac rehabilitation in elderly patients with heart failure. *Eur J Heart Fail* 2005;**7**:411–17.

5. Giannuzzi P, Temporelli P, Corra U, Tavazzi L. Antiremodeling effect of long-term exercise training in patients with stable chronic heart failure: results of the Exercise in Left Ventricular Dysfunction and Chronic Heart Failure (ELVD-CHF) trial. *Circulation* 2003;**108**:554–9.

6. Passino C, Severino S, Poletti R, Piepoli M, Mammini C, Clerico A, *et al*. Aerobic training decreases B-type natriuretic peptide expression and adrenergic activation in patients with heart failure. *J Am Coll Cardiol* 2006;**47**:1835–9.

Relevant studies with a sample size ≤ 50

Dall'Ago P, Chiappa GRS, Guths H, Stein R, Ribeiro JP. Inspiratory muscle training in patients with heart failure and inspiratory muscle weakness: a randomized trial. *J Am Coll Cardiol* 2006;**47**:757–63.

Gary RA, Sueta CA, Dougherty M, Rosenberg B, Cheek D, Preisser J, *et al*. Home-based exercise improves functional performance and quality of life in women with diastolic heart failure. *Heart Lung* 2004;**33**: 210–18.

Harris S, LeMaitre JP, Mackenzie G, Fox KA, Denvir MA. A randomised study of home-based electrical stimulation of the legs and conventional bicycle exercise training for patients with chronic heart failure. *Eur Heart J* 2003;**24**:871–8.

Jónsdóttir S, Andersen KK, Sigurôsson AF, Sigurôsson SB. The effect of physical training in chronic heart failure. *Eur J Heart Fail* 2006;**8**: 97–101.

van den Berg-Emons R, Balk A, Balk A, Bussmann H, Stam H. Does aerobic training lead to a more active lifestyle and improved quality of life in patients with chronic heart failure? *Eur J Heart Fail* 2004;**6**:95–100.

Yeh GY, Wood MJ, Lovell BH, Stevenson LW, Eisenberg DM, Wayne PM, *et al*. Effects of tai chi mind-body movement therapy on functional status and exercise capacity in patients with chronic heart failure: a randomized controlled trial. *Am J Med* 2004;**117**:541–8.

Multidisciplinary working

The question updated from the heart failure guideline[50] was: What evidence is there that a dedicated multidisciplinary team improves care of those diagnosed with heart failure above the standard approach?

Any relevant studies from September 2002 to 12 January 2007 were searched. The inclusion criterion in relation to the population and outcome measures was the same as for the drugs therapy search. Because of the large number of papers that appeared to be of relevance on abstract scrutiny, it was decided that certain limitations should be applied to study selection at this stage for practical reasons. Therefore, close inspection of the abstracts led to excluding studies that were based on the following:

- a 'post discharge' population, as it was contemplated that such patients would not be of relevance to the model
- studies relating to adherence to medication
- interventions of a 'telenursing' nature as these are not common in the UK
- studies with a sample size < 30.

Table 67 shows the number of relevant papers for which data extraction was completed. Any relevant costing studies were not subjected to data extraction but kept aside for future reference.

TABLE 67 *The number of relevant papers summarised in the evidence tables*

	Intervention	
	Nurse-led	**Overall MC**
Systematic review/ meta-analysis	1	6
RCTs	3	1

MC, multidisciplinary care in general as opposed to specific nurse-led intervention.

Overall summary

All of the evidence gathered in this update revealed similar findings to those reported previously in the heart failure guideline.

Studies on both nurse-led and overall multidisciplinary care interventions suggested that there was no real benefit of either approach on mortality rates unless specialised follow-up or discharge planning was incorporated within the care programme.

Not many studies looked into quality of life as a primary outcome. In general, this outcome was improved, but more studies are needed to establish any definite effects.

There was a vast amount of evidence indicating that both nurse-led and overall multidisciplinary care approaches reduce the incidence of hospitalisation. It should, however, be noted that any improvements in this outcome were largely apparent during the intervention period and any effects were generally absent post intervention.

The evidence tended to indicate that these interventions were cost-effective.

Evidence tables
Nurse-led interventions
Reviews

Paper	Phillips C, Singa R, Rubin H, Jaarsma T. Complexity of programme and clinical outcomes of heart failure disease management incorporating specialist nurse-led heart failure clinics. A meta-regression analysis. *Eur J Heart Fail* 2005;**7**:333–41
Description	Meta-analysis
n	Six RCTs were included *n* = 949 [intervention = 464, usual care (control) = 485] Pooled data: age:73 years; male:58%; LVEF: 34%; NYHA class II: < 5%, class III: 70%, class IV: 25%
Intervention	Specialist nurse-led heart failure clinics; the programmes largely consisted of the following across trials – chronic heart failure education for patients and carers to enhance self-care, medication review, counselling, telephone contact, a home visit, follow-up at nurse-led heart failure clinic and discharge planning The average follow-up period was 8.5 months
Outcomes	Relevant outcomes included rehospitalisation, mortality, combined end point of mortality and hospitalisation, heart failure hospitalisation, number of hospital days utilised per patient during follow-up, quality of life and medical costs
Results	Overall relative risk for rehospitalisation was 0.91 (95% CI 0.72–1.16) for intervention vs usual care. The point estimate for rehospitalisation was 1.00 (0.86–1.17) for programmes with fewer components (i.e. without any hospital discharge planning) vs 0.30 (0.04–2.60) for programmes with more components (i.e. containing discharge planning). These values were 0.65 (0.43–1.00) vs 0.09 (0.10–0.65) for heart failure hospitalisation and 0.09 (–1.17 to 1.34) vs –0.26 (–0.49 to –0.02) for the number of hospital days utilised, for fewer vs more component programmes respectively The overall relative risk for mortality was 0.80 (0.57–1.13). The estimates were 0.75 (0.55–1.03) for fewer component programmes vs 0.96 (0.63–1.47) for more component programmes Results for the combined mortality and hospitalisation end point were 0.91 (0.80–1.03) for fewer component programmes vs 0.61 (0.18–2.02) for more component programmes Quality of life scores were available for five out of six studies, which demonstrated a greater percentage improvement in the intervention group (30 ± 20.7%) than in the control group (19.3 ± 12.6%; $p = 0.13$) The savings for medical costs per patient per month were not significantly different between groups ($n = 3$ trials), although it appeared that utilising the intervention approach could save more than usual care
Comments	More complex programmes were defined as comprising more components Random allocation of at least 100 patients was one of the criteria for inclusion of studies into this review; hence, only six studies were reviewed The authors mention that the very few studies included in this review were not powered to detect changes in the range of outcomes evaluated Although discharge planning appears to have played a significant role in improvements seen in those with this aspect of care within their management programme, it is not clear how much the other aspects of the programmes (i.e. patient education, specific nurse-led clinic visits) may have contributed to any benefits None of the included trials was conducted in the UK
Reference	1
Studies included	Cline, 1998; Ekman, 1998; McDonald, 2002/Ledwidge, 2003; Doughty, 2002; Kasper, 2002; Stromberg, 2003

Experimental studies

Paper	Kimmelstiel C, Levine D, Perry K, Patel A, Sadaniantz A, Gorham M, *et al*. Randomized controlled evaluation of short- and long-term benefits of heart failure disease management within a diverse provider network: the SPAN-CHF trial. *Circulation* 2004;**110**:1450–5
Description	RCT
n	*n* = 200 (intervention = 97, control = 103) Intervention group: age: 70.3 years; male: 57.7%; LVEF: 0.30; NYHA class II: 50.5%, class III: 49.5% Patients were enrolled from six diverse sites including academic/medical centres, community hospitals/ cardiology practices
Intervention	A 3-month nurse-driven heart failure disease management programme – specialised and networked care in heart failure (SPAN-HF) The nurses held an initial meeting with the patients and their families in which issues such as diet, weight and self-monitoring were discussed. Patients were also provided with a teaching handbook that informed them of further details such as clinical signs and symptoms that would prompt a call to the nurse or their GP. The meetings lasted 45–90 minutes and were followed up by weekly/biweekly telephone calls from the nurse managers; the total study period lasted for 90 days
Outcomes	Data on hospitalisations was extracted from patient medical records. Data collection was carried out at 3 (90-day short-term follow-up) and 12 months (long term)
Results	Four deaths in the intervention group and five in the control group occurred during the 90-day study period. Also during the 90 days of intervention, significantly fewer heart failure hospitalisations were recorded for the intervention group than for the control group [relative risk (RR) 0.48, $p = 0.027$]. The mortality or hospitalisation rates for heart failure were 16% and 23% for the intervention and control groups respectively [RR 0.66, $p = 0.16$]. The number of days in hospital for heart failure was significantly reduced in the intervention group compared with the control group [RR 0.54, $p < 0.001$]. Hospitalised days for cardiovascular causes were also reduced for the intervention group Over the long-term follow-up period the mortality rates were 11.3% and 13.6% for the intervention and control groups respectively. Only the significant reduction in days in hospital for cardiac causes was apparent in the long term; all other benefits seen in the short-term follow-up were no longer evident
Comments	This was a multicentre study The benefits of the intervention were only short-lived; discontinuation of the intervention had a substantial impact on hospitalisation. The authors therefore suggest that more active chronic intervention is required for sustained benefit in the present population
Reference	2

Paper	Mårtensson J, Stromberg A, Dahlstrom U, Karlsson J, Fridlund B. Patients with heart failure in primary health care: effects of a nurse-led intervention on health-related quality of life and depression. *Eur J Heart Fail* 2005;**7**:393–403
Description	RCT
n	*n* = 153 [intervention = 78, usual care (control) = 75] Intervention group: age:79 years; male: 54%; NYHA class II: 38%, class III: 51%, class IV: 10% Patients were enrolled from eight primary health-care centres in Sweden
Intervention	Following a short heart failure education course for primary health-care nurses and physicians during which the study intervention was discussed, the nurse-led intervention was initiated. This consisted of a single 2-hour home-based session in which the patient and their family were educated and counselled in relation to heart failure management in an attempt to improve health-related quality of life. Nurses followed this visit up 12 months later by telephone interview
Outcomes	Both generic (SF-36 health survey) and disease-specific (Minnesota Living with Heart Failure questionnaire) instruments were used to evaluate health-related quality of life. These questionnaires were completed at the start of the study and then at 3 and 12 months' follow-up
Results	At the 12-month telephone follow-up there were 10 (13%) deaths in the intervention group and three (4%) in the control group Neither group showed any significant improvement in any of the dimensions of the SF-36 health survey. Quality of life remained the same in the intervention group, whereas significant deterioration in 'role functioning', 'vitality' and the 'mental component summary' dimensions was seen in the control group. There was a tendency towards significant improvement in role functioning due to physical limitations, vitality and social functioning at 3 months in the intervention group; however, no such development was apparent at 12 months There was no significant improvement for either group on the Minnesota Living with Heart Failure questionnaire
Comments	Study was conducted in a primary health-care setting, therefore very relevant population The main benefit of the nurse-led intervention was that it appeared to prevent patients' quality of life from getting any worse The nurse-led intervention itself appears brief with minimal follow-up contact. Perhaps nurse contact in person would have been a more appropriate means of follow-up at 12 months than telephone-based interviewing It has been suggested that the higher mortality rate in the intervention group may have been because these patients had more severe heart failure (6 of 10 patients were within NYHA class IV) than those in the control group
Reference	3

Paper	Sisk J, Hebert P, Horowitz C, McLaughlin M, Wang J, Chassin M. Effects of nurse management on the quality of heart failure care in minority communities: a randomised trial. *Ann Intern Med* 2006;**145**:273–83
Description	RCT
n	*n* = 406 [intervention = 203, usual care (control) = 203] Intervention group: age: 59.6 years; male: 55.2%; LVEF < 40% in all patients; NYHA class I: 17.7%, class II: 24.6%, class III: 16.3%, class IV: 41.4% Patients were enrolled from four hospitals in Harlem, New York
Intervention	The nurse-led intervention involved an initial appointment with the patient in which heart failure education and counselling were provided. The nurses then followed-up the patients by telephone contact in which heart failure management progress was monitored. Subsequent to each visit the nurses liaised with the patients' clinicians to discuss any examinations and prescription changes. The overall trial period was 12 months. A subset of patients (127 patients from each group) was also followed-up for a further 6-month period after the trial
Outcomes	Data regarding any hospital admissions during the trial period were obtained from the participating hospitals The Minnesota Living with Heart Failure questionnaire was administered at quarterly interviews Mortality was determined through deaths recorded in the National Death Index and reports from patients' families
Results	Hospital admissions were fewer in the intervention group (*n* = 143 total hospitalisations) than in the control group (*n* = 180) by the end of the trial [adjusted difference –0.13 hospitalisations/person-year* (95% CI –0.25 to –0.001)]. There were 55 fewer cumulative hospitalisations in the intervention group than in the control group at 18 months' follow-up [adjusted difference –0.23 hospitalisations/person-year (95% CI –0.39 to –0.07)]. The probability of being hospitalised at least once during the 12-month period was similar in both groups 'Better functioning' at 12 months' follow-up was apparent for the intervention group compared with the control group, as assessed on the Minnesota Living with Heart Failure questionnaire; scores for each group were 38.6 vs 47.3 respectively [difference –8.8 (95% CI –15.3 to –2.2)] In total, 22 deaths occurred in each group during the 12-month trial period, with three fewer deaths in the intervention group at 18 months (risk ratio 0.88, 95% CI 0.48–1.61)
Comments	All patients had to be community dwelling on entry to the study *The number of cumulative hospitalisations per person-year was calculated whereby 'a person-year' was equivalent to the number of days that each person survived during the trial/post-trial period divided by 365 days This trial supports the use of nurse-led interventions in minority communities; however, the authors were unable to establish the exact aspects of the intervention programme that were accountable for the improvements
Reference	4

Multidisciplinary care in general

Reviews

Paper	Gonseth J, Guallar-Castillon P, Banegas J, Rodriguez-Artalejo F. The effectiveness of disease management programmes in reducing hospital re-admission in older patients with heart failure: a systematic review and meta-analysis of published reports. *Eur Heart J* 2004;**25**:1570–95
Description	Systematic review and meta-analysis
n	27 RCTs on disease management (DM) programmes, 13 of which were carried out in the USA Sample size in the studies ranges from 34 to 1966 Mean age: 70 years in most studies; LVEF < 40% in 13 studies
Intervention	The definition used to select studies with relevant DM programmes was 'an intervention designed to manage heart failure and reduce hospital readmissions using a systematic approach to care and potentially employing multiple treatment modalities' Typically, interventions included the following components: patient education, counselling, telephone calls and nurse involvement. Intervention duration varied from a single home visit to 12 months
Outcomes	Heart failure/other cardiovascular disease hospital readmission, all-cause readmission, and combined readmission or death
Results	Six of the 11 studies eligible for meta-analysis showed a homogeneous and significant reduction in readmission for heart failure or cardiovascular disease. Relative risk (RR) reduction based on a total of 3160 patients across the 11 studies was 0.70 (95% CI 0.62–0.79, $p < 0.0001$), suggesting a 30% reduction in frequency of readmission Of 16 studies, only three reported a significant reduction in all-cause readmission. On the basis of 4440 patients included in a random-effects model, a 12% reduction in all-cause admission is reported (pooled RR 0.88, 95% CI 0.79–0.97, $p = 0.01$). Four out of 10 studies reported a statistically significant reduction in combined readmission or death. With the inclusion of a total of 2985 patients, an 18% reduction in this combined end point is reported (pooled RR 0.82, 95% CI 0.72–0.94, $p = 0.004$). Only one study looked into long-term mortality effects over a period of 4.2 years; this showed a marginally significant reduction ($p = 0.06$) for the DM programme group (56%) vs usual care (65%) In total, 13 of the 27 studies explored the cost of the DM intervention vs the cost of usual care, of which 10 estimated reduced costs with the former strategy and one reported similar costs in both groups
Comments	Included RCTs spanned the years from 1993 to August 2003 Only 11 of the included studies scored 3/5 on JADAD quality assessment
Reference	5
Studies included	DIAL, 2003; Laramee, 2003; Stromberg, 2003; Doughty, 2002; Harrison, 2002; Kasper, 2002; Krumholz, 2002; McDonald, 2002; Riegel, 2002; Stewart, 2002; Blue, 2001; Jerant, 2001; McDonald, 2001; Hughes, 2000; Philbin, 2000; Jaarsma, 1999; Naylor, 1999; Rainville, 1999; Stewart, 1999a; Stewart, 1999b; Cline, 1998; Ekman, 1998; Serxner, 1998; Stewart, 1998; Weinberger, 1996; Rich, 1995; Rich, 1993

Other systematic reviews/meta-analyses

Paper	Reference no.	No. of RCTs included	Outcomes/comments
Gwadry-Sridhar *et al*., 2004	6	8 RCTs[a]	Outcomes included readmission and mortality rates. As this review is very similar to that of Gonseth *et al*. the results are not reported here. Furthermore, fewer studies are included in this review than in that by Gonseth *et al*. because in this review searches were carried out only up to the year 2000 whereas in Gonseth *et al*. the search was extended to 2003
McAlister *et al*., 2004	7	29 identified but not pooled because of significant heterogeneity; any additional trials included in this review that were not in the review of Gonseth *et al*. are of post-discharge patients and so not relevant population	All-cause mortality: Two trials found a significant difference between the intervention and control groups. Summary risk ratio (RR) for all 22 trials reporting mortality end point (3781 patients) is 0.83 (95% CI 0.70–0.99); however, heterogeneity testing was not significant ($p = 0.15$). Significant mortality reduction was primarily apparent for multidisciplinary teams providing specialised follow-up (RR 0.75, 95% CI 0.59–0.96) – number needed to treat (NNT) = 17. Telephone follow-up or self-care approaches were not as effective All-cause hospitalisation: Of 23 trials reporting this outcome, only three reported a reduction in hospitalisation. Summary RR for 23 trials (4313 patients) is 0.84 (95% CI 0.75–0.93); there was, however, significant heterogeneity in the results ($p < 0.01$) Heart failure hospitalisation: Six out of 19 trials reported significant reductions in the need for at least one hospitalisation with the intervention; pooled effect estimate of 19 trials: RR 0.73 (95% CI 0.66–0.82, $p = 0.36$ for heterogeneity), NNT = 11 to prevent one heart failure hospitalisation Total number of hospitalisations: Of 21 trials, 11 reported that the intervention arm of the trial was associated with fewer hospitalisations. Pooled effect estimate of 21 trials: RR 0.70 (95% CI 0.62–0.80) Total heart failure hospitalisations: This outcome was markedly reduced as established in 20 trials: RR 0.57 (95% CI 0.49–0.67) Quality of life: Nine out of 18 trials reported significantly better quality of life with the intervention Cost-effectiveness: 15 out of 18 trials reported that the intervention was more cost-effective than usual care
Taylor *et al*., 2005	8	16 RCTs[a]	The searches were conducted up to July 2003 Similar outcomes to those of previous reviews of readmission and mortality rates were reported. Secondary outcomes not fully considered in previous reviews were health-related quality of life and cost analyses Eight studies reported on quality of life of which four reported significant improvement with the intervention and four reported no change Of all seven studies that reported some sort of cost analysis, none reported significant differences between the intervention and control
Whellan *et al*., 2005	9	19 RCTs[a]	The search was conducted up to June 2003 A significant decrease in all-cause hospitalisation with the intervention is reported
Windham *et al*., 2003	10	15 RCTs[a]	The search was conducted up to March 2002 No new outcomes are reported, although results are analysed for RCTs and non-randomised studies overall

a All RCTs included in these reviews have already been covered in the review by Gonseth *et al*.

Experimental studies

Paper	Smith B, Forkner E, Zaslow B, Krasuski R, Stajduhar K, Kwan M, *et al*. Disease management produces limited quality-of-life improvements in patients with congestive heart failure: evidence from a randomised trial in community-dwelling patients. *Am J Manag Care* 2005;**11**:701–13
Description	RCT
n	*n* = 1069 [disease management (DM) = 356, augmented disease management (ADM) = 354, control = 359] DM group: age: 70.6 years; male: 71.6%; LVEF: 61.9% (diastolic heart failure), 35.8% (systolic heart failure); NYHA class I: 20.8%, class II: 57.9%, class III: 20.2%, class IV: 1.1% ADM group: age: 71.4 years; male: 69.8%; LVEF: 62.4% (diastolic heart failure), 34.6% (systolic heart failure); NYHA class I: 15.5%, class II: 58.8%, class III: 21.5%, class IV: 4.2% Patients were enrolled from six diverse sites including academic/medical centres, community hospitals/ cardiology practices
Intervention	Patients were randomised to one of three groups: usual care (control), DM and ADM Those in the DM group were assigned a disease manager and specialist cardiac nurse who provided patient education and medication management via telephone contact. This was carried out in conjunction with the patient's primary care provider Those in the ADM group experienced a similar intervention but were also given a blood pressure cuff, a finger pulse oximeter and an activity monitor for additional data exploration purposes
Outcomes	Health-related quality of life was measured with the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36); this was completed at baseline and then at 6-month intervals over the 18-month trial period (hence four data collection points)
Results	In total, 349 (32.6%) patients did not complete the study for various reasons There was no statistical difference in quality of life at baseline as expected At 6 months, 34.6% in the DM group and 25.6% in the control group reported improvement ($p = 0.04$). At 12 months, 36.9% in the ADM group and 26.8% in the control group reported improvement ($p = 0.004$). At 18 months, 36.9% in the ADM group, 29.9% in the DM group and 30.2% in the control group reported at least some improvement
Comments	This was a single-centre study Patients and staff were not blinded to the identity of the group to which patients were randomised and this could have potentially confounded the results, e.g. any short-term benefits claimed by the patients in the experimental group may have been because they were aware of being in the experimental group and so probably expected to improve Both interventions in this study failed to show any long-term major benefits in health-related quality of life. It should, however, be noted that, even though the SF-36 is deemed to be a valid and reliable instrument, a single self-administered tool was used for the purposes of assessing this outcome
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Feedback

The HTA programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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