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NICE Clinical Guideline No 108

# CHRONIC HEART FAILURE

National clinical guideline for diagnosis and management in primary and secondary care

August 2010

Royal College of Physicians

Setting higher medical standards

## National Clinical Guideline Centre for Acute and Chronic Conditions

The National Clinical Guideline Centre for Acute and Chronic Conditions (NCGC) was formed on the 1st April 2009 following the merger of the National Collaborating Centre for Acute Conditions, National Collaborating Centre for Chronic Conditions, National Collaborating Centre for Nursing and National Collaborating Centre for Primary Care. The NCGC, funded by NICE and hosted by the Royal College of Physicians of London, is the largest centre in the UK developing clinical guidelines to describe care for long term conditions delivered across primary and secondary care. The NCGC involves the following partners: Royal College of General Practitioners, Royal College of Nursing, Royal College of Physicians London, and Royal College of Surgeons; with Management Board representation from Cochrane UK, SW Strategic Health Authority, and the RCP Patient & Carer Network.

## Acknowledgements

The Guideline Development Group would like to thank Martin Cowie (Professor of Cardiology (Health Services Research) at the Imperial College-London), Jill Parnham (Operations Director NCGC), Bernard Higgins (Clinical Director NCGC), Norma O'Flynn (Clinical Director NCGC), David Wonderling (Health Economics Lead NCGC),Susan Latchem and Sarah Dunsdon (Guideline Commissioning Managers, NICE) for their support and help.

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The NCGC would like to thank Dr Paul Collinson (Consultant Pathologist) and Ms Ainsley Cowie (Cardiac Rehabilitation Physiotherapist) for their advice and help in developing this update.

Published by the National Clinical Guideline Centre at The Royal College of Physicians, 11 St Andrew's Place, Regent's Park, London, NW1 4LE

First published 2010



This guideline should be cited as: National Clinical Guideline Centre. (2010) Chronic heart failure: the management of chronic heart failure in adults in primary and secondary care. London: National Clinical Guideline Centre. Available from: http://guidance.nice.org.uk/CG108/Guidance/pdf/English

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# Contents

# Glossary

| Acronym/Term | Description |
|---|---|
| 6MWT | 6 minute walk test – an evaluation of exercise capacity |
| ACEI | Angiotensin-converting enzyme inhibitors (treatment for high blood pressure and heart failure). |
| AF | Atrial fibrillation (irregularly irregular rhythm of the heart). |
| AMI | Acute myocardial infarction (damage to the heart muscle usually due to blockage of a blood vessel supplying it) |
| Applicability | The degree to which the results of an observation, study or review are likely to hold true in a particular clinical practice setting. |
| ARB | Angiotensin receptor blocker (treatment for high blood pressure and heart failure) |
| Arm (of a clinical study) | Sub-section of individuals within a study who receive one particular intervention, for example placebo arm |
| Base case analysis | In a modelling, the base case is the primary analysis based on the best estimates of each model input. (c.f. sensitivity analysis) |
| Baseline | The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared. |
| Baseline risk | The probability of an event (e.g. death) occurring in the comparator arm. This is a term used in modelling, where the baseline risk from one data source might be combined with a risk ratio from another source to estimate the probability of an event occurring for patients receiving a different intervention. |
| BB | Beta blocker (treatment for heart rhythm, angina and heart attacks, high blood pressure and heart failure) |
| BNF | British national formulary |
| BNP | B-type natriuretic peptide (a protein substance secreted from the heart wall especially when stretched or when the pressure within it has risen) |
| BP | Blood pressure |
| CABG | Coronary artery bypass grafting. |
| CHD | Coronary heart disease. |
| CHF | Chronic heart failure. |
| CI | Confidence interval. A measure of the uncertainty around the main finding of a statistical analysis. |
| CM | Cardiomyopathy (A condition that has several forms. They are characterised by disease processes that primarily affect the heart muscle) |

| Acronym/Term | Description |
|---|---|
| Confidence interval (CI) | A range of values for an unknown population parameter with a stated 'confidence' (conventionally 95%) that it contains the true value. The interval is calculated from sample data, and generally straddles the sample estimate. The 'confidence' value means that if the method used to calculate the interval is repeated many times, then that proportion of intervals will actually contain the true value. |
| Conservative assumption | Where there is uncertainty modellers may have a choice of which value to give to a model input. A conservative assumption is where the modeller chooses the parameter in such a way that it cannot bias in favour of the new treatment (and is likely to be biasing in favour of the standard treatment). |
| COPD | Chronic obstructive pulmonary disease (A condition that affects the lungs and the airways, characterised by breathlessness, wheeze and cough) |
| Cost of illness analysis | A non-comparative study which estimates the cost per year associated with a particular disease. Such an analysis might include the cost of time off work as well as direct medical costs. |
| Cost-effective | Good value for money - that is sufficient additional (health) gains achieved relative to the additional cost incurred |
| Cost-effectiveness analysis (CEA) | An economic study design in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (For example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness. |
| Cost-effectiveness model | An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources to estimate costs and health outcomes. |
| Cost-effectiveness model | An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes. |
| Cost-effectiveness plane | A graph used to present results of cost-effectiveness analyses where incremental costs are plotted against incremental health effects (e.g. QALYs gained). |
| Cost-utility analysis (CUA) | A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs). |
| CRT | Cardiac resynchronisation therapy (A form of pacing of the heart, whereby both pumping chambers as well as the right filling chamber are paced. This improves the timing and efficiency of the pumping by the heart) |
| CV mortality | Cardiovascular mortality (Death caused by disease of the heart and the blood vessels) |

| Acronym/Term | Description |
|---|---|
| Decision analysis | An explicit quantitative approach to decision making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes. |
| Discount rate | The rate per year at which future costs and outcomes are discounted – see discounting. This has been set by the Treasury at 3.5% for economic evaluations, reflecting long-term interest rates. So a cost of £103.50 next year is valued today at £100. |
| Discounting | Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present. |
| Disutility | The reduction in utility attributed to experiencing a clinical event or health state. |
| DM | Diabetes mellitus |
| Dominance | An intervention is said to be dominated if there is an alternative intervention that is both less costly and more effective. |
| ECG | Electrocardiogram (Recording of the electrical activity of the heart) |
| Economic evaluation | Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and consequences. |
| eGFR | Estimated glomerular filtration rate (a measure of the function of the kidneys, reflecting the volume of blood that is liable to be cleared by the kidney per minute. The lower the number the worse is the function of the kidneys) |
| EQ-5D (EuroQol-5D) | A standardised instrument used to measure a health outcome. It provides a single index value for health status. |
| ER | Emergency room |
| ESC | European society of cardiology |
| Extended dominance | If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore more efficient and should be preferred, other things remaining equal. |
| Extrapolation | In data analysis, predicting the value of a parameter outside the range of observed values. |

| Acronym/Term | Description |
|---|---|
| Follow-up | Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables. |
| GDG | Guideline development group. Multiprofessional group responsible for developing this guideline |
| Generalisability | The extent to which the results of a study based on measurement in a particular patient population and/or a specific context hold true for another population and/or in a different context. In this instance, this is the degree to which the guideline recommendation is applicable across both geographical and contextual settings. For instance, guidelines that suggest substituting one form of labour for another should acknowledge that these costs might vary across the country. |
| GP | General practitioner. |
| GPP | Good practice point. |
| GRADE | Grading of Recommendations assessment, development and evaluation. The GRADE approach is a sequential process for preparing evidence profiles (summaries) and developing evidence-based recommendations. |
| Haemodynamic | Relating to the circulation of the blood, usually describes the mechanical effects of the circulatory system such as the pressure in a chamber or vessel. |
| Health economics | The study of the allocation of scarce resources among alternative healthcare treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of health. |
| Health-related quality of life (HRQoL) | A combination of an individual's physical, mental and social well-being; not merely the absence of disease. |
| HF | Heart failure. |
| HFPEF | Heart failure with preserved ejection fraction (a form of heart failure associated with preserved [good] contraction of the heart muscle) |
| HRQoL | Health-related quality of life |
| HTA | Health Technology Assessment. An evaluation exploring clinical and cost effectiveness and other related issues, for example organisational implications, of a health technology (e.g., drug, medical device, clinical or surgical procedure) |
| Hypertrophic cardiomyopathy | A form of heart muscle abnormality, frequently characterised by an unexplained increase in the thickness of the heart muscle due to a genetic abnormality. |

| Acronym/Term | Description |
|---|---|
| ICD | Implantable cardioverter defibrillator (A type of pacemaker capable of delivering an electrical shock inside the heart, to stop a lethal rhythm abnormality) |
| ICER | Incremental cost-effectiveness ratio.<br>The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another. |
| IHD | Ischaemic heart disease (Disease of the heart caused by insufficient blood supply to the heart) |
| Incremental analysis | The analysis of additional costs and additional clinical outcomes with different interventions. |
| Incremental cost | The mean cost per patient associated with an intervention minus the mean cost per patient associated with a comparator intervention. |
| Incremental net monetary benefit | The value, in monetary terms, of an intervention net of its cost compared with a comparator intervention. The INMB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INMB is calculated as: (£20,000 x QALYs gained) – Incremental cost. |
| INMB | Incremental net monetary benefit |
| INR | International normalised ratio (A measure of how thinned the blood is, in comparison to normal, as a result of blood thinning medication) |
| Intervention | Healthcare action intended to benefit the patient, for example, drug treatment, surgical procedure, psychological therapy. |
| IQR | Inter-quartile range |
| Ischaemia | Insufficient blood supply to an organ or tissue. |
| ISDN+Hyd | Isosorbide dinitrate and hydralazine. |
| ISWT | Incremental Shuttle Walk Test. A field test of functional capacity or exercise tolerance |
| IVRT | Isovolumic relaxation time (a short period in the cycle of the heart where the heart muscle is relaxing, but the amount of blood in the pumping chamber is not changing) |
| JVP | Jugular venous pressure (a measure of the pressure in the neck veins, assessed by the height of distended vein in the neck of the patient who is propped up at 45 degrees) |
| K+ | Potassium (One of the essential salts for the function of the body) |
| Length of stay | The total number of days a participant stays in hospital. |
| Life-years | The average years of remaining life expectancy. The life-years gained are the extra years of life attributable to one treatment compared with an alternative. |

| Acronym/Term | Description |
|---|---|
| LV | Left ventricular (Refers to the left pumping chamber of the heart) |
| LVADs | Left ventricular assist devices (Sophisticated device, implanted surgically to help a badly failing heart, to pump blood into the circulation) |
| LVEF | Left ventricular ejection fraction (the percentage of the volume of the blood that leaves the heart with each beat, this is a measure of the pumping function of the left pumping chamber of the heart) |
| LVSD | Left ventricular systolic dysfunction (The condition where the left pumping chamber's ability to pump is impaired. This is characterised by low left ventricular ejection fraction, and leads to heart failure) |
| LYG | Life year gained |
| Markov model | A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle). |
| Meta-analysis | A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials. |
| MI | Myocardial infarction (Heart attack) |
| MICE | Male, history of myocardial infarction, crepitations, ankle oedema |
| MID | Minimal important difference. The smallest difference in score in the outcome of interest that informed patients or informed proxies perceive as important, either beneficial or harmful, and that would lead the patient or clinician to consider a change in the management. |
| MLHF/MLWHFQ | Minnesota living with heart failure questionnaire. Measures the effect of heart failure and treatment for heart failure on an individual's quality of life. |
| Model | A model represents the essential aspects of a complex system in a usable form. Modelling is usually conducted when simply observing the outcomes in a controlled setting is not feasible. A decision model uses data often from different sources to quantify specific outcomes with one course of action compared with another. |
| NCC-CC | National Collaborating Centre for Chronic Conditions. |
| NCGC or NCGC-ACC | National Clinical Guideline Centre for Acute and Chronic Conditions |
| NHS | National Health Service |
| NICE | National Institute for Health and Clinical Excellence. |

| Acronym/Term | Description |
|---|---|
| NP | Natriuretic peptide (A protein substance secreted by the wall of the heart when it is stretched or under increased pressure. It has several forms) |
| NR | Not reported |
| NSF | National Service Framework. Policies set out by the National Health Service to clearly define standards of care for major medical issues |
| NTproBNP | N-terminal pro-B-type natriuretic peptide (One of the natriuretic peptides, protein substances secreted by the wall of the heart when it is stretched or under increased pressure. It has several forms) |
| NYHA | New York Heart Association (functional classification): (These allow an assessment of the patient's ability to carry out exercise before they develop their symptoms) |
| Observational study | Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups; for example, cohort studies and case–control studies. |
| PCT | Primary Care Trust. |
| Perspective | In economic evaluation the perspective is the body, whose costs and outcomes are accounted for in the model. In NICE guidelines, costs are measured from an NHS and personal social services perspective. Alternatively, some studies take a broader societal perspective, taking all costs into account. |
| PICO | Population, Intervention, Comparison and Outcome |
| Placebo | An inactive and physically identical medication or procedure used as a comparator in controlled clinical trials. |
| PND | Paroxysmal nocturnal dyspnoea (episodes of waking up suddenly with breathlessness) |
| PPIP | Patient and Public Involvement Programme |
| PPP | Purchasing Power Parity |
| Primary care | Healthcare delivered to patients outside hospitals. Primary care covers a range of services provided by general practitioners, nurses, dentists, pharmacists, opticians and other healthcare professionals. |
| Primary outcome | The outcome of greatest importance, usually the one in a study that the power calculation is based on. |
| Probabilistic analysis | In modelling, this is where distributions are applied to each model parameter instead of point estimates. This allows us to consider the uncertainty around the model results. This is also known as |
| Probabilistic sensitivity analysis | See probabilistic analysis |
| Product licence | An authorisation from the MHRA to market a medicinal product. |

| Acronym/Term | Description |
|---|---|
| Prognosis | A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes. |
| Purchasing Power Parity | Rate of currency conversion that reflects the prices of the same good or service in different countries |
| P-value | The probability that an observed difference could have occurred by chance, assuming that there is in fact no underlying difference between the means of the observations. If the probability is less than 1 in 20, the P value is less than 0.05; a result with a P value of less than 0.05 is conventionally considered to be 'statistically significant'. |
| PWD | Pulsed wave Doppler (one of the tools to assess the speed of movement by ultrasound. It has important applications in the assessment of the heart valves and heart muscle function) |
| QALY | Quality adjusted life year |
| QoL | Quality of Life. See also 'health-related quality of life' |
| QUADAS | Quality Assessment of Diagnostic Studies. A 14-item tool used to assess the quality of diagnostic accuracy studies. |
| Quality of life | See 'Health-related quality of life'. |
| Quality-adjusted life year (QALY) | An index of survival that is adjusted to account for the patient's quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost-utility analysis. The QALYs gained are the mean QALYs associated with one treatment minus the mean QALYs associated with an alternative treatment. |
| Randomised controlled trial (RCT) | A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups. |
| Reference standard | The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice. |
| Rehabilitation | Process to assist patients to achieve optimal function. May include a period of exercise training. |
| Relative risk (RR) | The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A/the risk of the event in group B). |
| Risk ratio | See Relative risk |
| RR | Relative risk (also known as risk ratio) |
| RRR | Relative risk reduction. The proportional reduction in risk in one treatment group compared to another. It is one minus the risk ratio. |

| Acronym/Term | Description |
|---|---|
| SD | Standard deviation |
| SE | Standard error |
| Sensitivity | Sensitivity or recall rate is the proportion of true positives which are correctly identified as such. For example in diagnostic testing it is the proportion of true cases that the test detects.<br><br>See the related term 'Specificity' |
| Sensitivity analysis | A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results.<br><br>One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study.<br><br>Multi-way simple sensitivity analysis (scenario analysis): two or more parameters are varied at the same time and the overall effect on the results is evaluated.<br><br>Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified.<br><br>Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (For example, Monte Carlo simulation). |
| Significance (statistical) | A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p < 0.05$). |
| SMR | Standardised mortality ratio |
| Specificity | The proportion of true negatives that a correctly identified as such. For example in diagnostic testing the specificity is the proportion of non-cases incorrectly diagnosed as cases.<br><br>See related term 'Sensitivity'<br><br>In terms of literature searching, a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers. |
| SR | Systematic review. A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. |

| Acronym/Term | Description |
|---|---|
| Systematic review | Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis. |
| Tariff price | The unadjusted price paid to NHS trusts for supplying an episode of care. These vary by broad categories of similar interventions. Although generally based on average costs, sometimes they are given additional weight to increase output (e.g. day cases compared with inpatient operations). |
| TDI | Tissue Doppler imaging (An ultrasound technique, where the speed of movement of the heart muscle can be measured at different times of the heart cycle, allowing the diagnosis of different types of abnormalities of the heart) |
| Time horizon | The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation. |
| Titration | The administration of small incremental doses of a drug until either the target dose or the maximum tolerated dose had been reached |
| UK | United Kingdom |
| Utility | A measure of the strength of an individual's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value. |
| Ventricular fibrillation | A type of serious heart rhythm characterized by very rapid, irregular, uncoordinated electrical activity of the pumping chambers with no pumping effect, it is fatal if not corrected immediately |
| VT | Ventricular tachycardia - A type of serious heart rhythm problem arising in the ventricles resulting in (usually) very rapid contraction of the ventricles. |
| WTP | Willingness to pay<br><br>How much a group of people or institution would be prepared to pay to receive a certain outcome. For example, we sometimes consider the theoretical willingness to pay for a QALY to be between £20,000 |

# 1 Introduction

## 1.1 Definition of chronic heart failure

Heart failure is a complex clinical syndrome of symptoms and signs that suggest impairment of the heart as a pump supporting physiological circulation. It is caused by structural or functional abnormalities of the heart. The demonstration of objective evidence of these cardiac abnormalities is necessary for the diagnosis of heart failure to be made.

The symptoms most commonly encountered are breathlessness (exertional dyspnoea, orthopnoea and paroxysmal nocturnal dyspnoea) fatigue and ankle swelling.

Signs in heart failure could be due to pulmonary and systemic congestion, the structural abnormalities causing heart failure, the structural abnormalities resulting from heart failure, or from complications of therapy.

Initially, research into heart failure concentrated on patients with heart failure and reduced contraction of the left ventricle. Consequently, therapeutic interventions were tested in this group of patients. The agreed description of this group of patients is heart failure with left ventricular systolic dysfunction (LVSD).

Over the last 10 years it has become evident that almost half the patients with heart failure syndrome do not have LVSD. This group have had several definitions and names given to their condition. Since patients with LVSD are defined on the basis of their reduced left ventricular ejection fraction, the Guideline Development Group (GDG) elected to adopt the term heart failure with preserved ejection fraction (HFPEF) to describe patients with heart failure and no evidence of LVSD.

The GDG recognises that the two terms LVSD and HFPEF have several limitations. These include the variability of the left ventricular ejection fraction measured by different imaging modalities, and the lack of universal agreement on the threshold of ejection fraction at which LVSD and preserved ejection fraction are defined. Some assert that even in patients with HFPEF, there is an impairment of the contraction of the long axis of the left ventricle. Others claim that HFPEF is synonymous with diastolic heart failure. The latter is a controversial term. It does not have a universally accepted definition, it lacks an agreed detection method(s) and is challenged by those who believe it co-exists with an un-detected impairment of systolic function. Some authorities use the term heart failure with normal ejection fraction (HFNEF). Both HFNEF and HFPEF suffer similar limitations, and neither of them accurately describes an underlying unifying pathological feature beyond the absence of evident LVSD.

There is no single diagnostic test for heart failure, and diagnosis relies on clinical judgement based on a combination of history, physical examination and appropriate investigations. These are discussed in more detail in Chapter 4 – Diagnosing heart failure.

## 1.2 Definition of a specialist

The term ‘specialist’ is applicable to a wide range of healthcare professionals; however within the context of this guideline, the term specialist is used in relation to establishing the diagnosis of heart failure through non-invasive procedures and to taking the decisions on the management of the heart failure syndrome and its multiple causes.

Throughout this guideline the term “specialist” denotes a physician with sub-specialty interest in heart failure (often a consultant cardiologist) who leads a specialist multidisciplinary heart failure team of professionals with appropriate competencies from primary and secondary care. The team will involve, where necessary, other services (such as rehabilitation, tertiary care and palliative care) in the care of individual patients.

Unless otherwise specified, within this guideline specialist assessment or management refers to assessment or management by this specialist multidisciplinary heart failure team. The team will decide who is the most appropriate team member to address a particular clinical problem.

## 1.3 Clinical context

Around 900,000 people in the UK today have heart failure – with almost as many with damaged hearts but, as yet, no symptoms of heart failure.[1] Both the incidence and prevalence of heart failure increase steeply with age, with the average age at first diagnosis being 76 years.[2] While around 1 in 35 people aged 65–74 years has heart failure, this increases to about 1 in 15 of those aged 75–84 years, and to just over 1 in 7 in those aged 85 years and above.[3] The Olmstead County, Minnesota, USA study established the prevalence of heart failure in the over 45 year old population to be 2.2% [4]. The prevalence of heart failure is expected to rise through a combination of improved survival of people with ischaemic heart disease, more effective treatments for heart failure, and the effects of population ageing.[5] The recent rise in the prevalence of heart failure with preserved left ventricular ejection fraction seems to mirror the rise in the prevalence of hypertension, diabetes mellitus, atrial fibrillation and obesity. The risk of heart failure is higher in men than in women in all age groups, but there are more women than men with heart failure due to population demographics'.[1]

The most common cause of heart failure in the UK is coronary artery disease – with many patients having suffered a myocardial infarction in the past.[1] A history of hypertension is also common[6], as is atrial fibrillation. Heart damage of unknown cause – such as dilated cardiomyopathy – accounts for just under 15% of cases under the age of 75.[7] There are few reliable data for different ethnic groups; it is likely that people of African or Afro-Caribbean origin are more likely to develop heart failure due to hypertension rather than coronary artery disease[8], whereas those of Asian origin have a greater risk of developing heart failure due to coronary artery disease – often accompanied by obesity and diabetes mellitus.

Heart failure has a poor prognosis: 30-40% of patients diagnosed with heart failure die within a year – but thereafter the mortality is less than 10% per year.[9,10] Survival rates are similar to those from cancer of the colon, and worse than those from cancer of the breast or prostate.[11] There is evidence of a trend of improved heart failure prognosis in the last 10 years. The 6 month mortality rate decreased from 26% in 1995 to 14% in 2005 (Improving survival in the six months after diagnosis of heart failure in the past decade: population-based data from the UK. [12]. The recent National UK Heart Failure audit suggests an in-patient mortality of 12% in 2009. The latter represents a trend of improvement compared to the findings of the Health Commission heart failure survey of 15% in-patient mortality [13] and coincided with improved uptake of heart failure therapy. Younger patients do better, as do patients with no other medical problems.[9],[10] Heart failure has a major impact on quality of life,[14] and is associated with mood disorders.[15]

Patients on general practitioner heart failure registers, representing prevalent cases of heart failure, continue to be at significant mortality risk, with a five year survival of 58% as compared to 93% in the age- and sex- matched general population.[10] On average, a general practitioner will look after 30 patients with heart failure, and suspect a new diagnosis of heart failure in perhaps 10 patients annually. Those who work in more deprived areas are likely to have more cases. The cost of general practitioner consultations has been estimated at £45 million per year, with an additional £35 million for GP referrals to outpatient clinics. In addition, community-based drug therapy costs the NHS around £129 million per year[16].

Heart failure accounts for a total of 1 million inpatient bed days – 2% of all NHS inpatient bed-days – and 5% of all emergency medical admissions to hospital. Hospital admissions due to heart failure are projected to rise by 50% over the next

25 years – largely due to the ageing of the population. This is despite a progressive decline of the age adjusted hospitalisation rate at 1-1.5% per annum since 1992-1993.[17] It is estimated that the total annual cost of heart failure to the NHS is around 2% of the total NHS budget: approximately 70% of this total is due to the costs of hospitalisation.[1,16] Admissions tend to be protracted: The median length of stay is 7-8 days, with 99% of patients discharged within 10 days.[13] Readmissions are common: about 1 in 4 patients are readmitted in three months[18]. Associated co-morbidity accounts for a substantial proportion of admissions of people with a diagnosis of heart failure.[19] The costs increase with disease severity, with the healthcare costs for patients with the most severe symptoms between 8 and 30 times greater than those with mild symptoms.[20]

As well as NHS costs, heart failure also places a burden on other agencies such as social services and the benefits system, and of course on the patients with heart failure and their families and caregivers.

For patients and their carers, the costs are more difficult to quantify, but the burden is both financial and via adverse effects on their quality of life. The financial costs of heart failure to the patient and family arise from prescription charges (in patients under the age of 60), attendance at GP surgeries and outpatient clinics, hospital stays, modifications to the home and loss of earnings due to absence from work or loss of employment (although given that heart failure is more common in older people, productivity losses nationally may not be as great as for other chronic conditions).

Quality of life is affected by the physical limitations imposed by the disease, and also by the social limitations that follow from this and the emotional problems that may also arise. These symptoms can be caused by the disease itself, by co-morbidities, or can result from the side effects of treatment. There is, however, evidence that both pharmacological and non-pharmacological treatments can improve patient quality of life, both in terms of physical functioning and well-being[21].

As was identified in the 2003 NICE guideline, there is a substantive evidence base for treatments to improve the prognosis of heart failure. Nevertheless, many patients remain sub-optimally treated.[13]

## 1.4 Rationale for the update

This guideline is a partial update of NICE Guideline No 5: Chronic Heart Failure - national clinical guideline for diagnosis and management in primary and secondary care (2003) .[22] The aim of the 2003 guideline was to offer best practice advice on the care of adult patients (aged 18 years or older) who have symptoms or a diagnosis of chronic heart failure. It defined the most effective combination of symptoms, signs and investigations required to establish a diagnosis of heart failure, and those which would influence therapy or provide important prognostic information. It also gave guidance on the treatment, monitoring and support of patients with heart failure.

Since 2003, European and North American guidelines, based on new high-quality evidence from randomised controlled trials in diagnosis, treatment and monitoring have been published. A partial update of the existing NICE guideline is necessary to ensure that the recommendations take into account the new evidence available.

## 1.5 Audience

The guideline update is intended for use by the following people or organisations:

- All healthcare professionals

- People with chronic heart failure and their carers
- Patient support groups
- Commissioning organisations
- Service providers

Separate, short versions of this document are also available for clinical staff and the public. These summarise the recommendations without full details of the supporting evidence:

- NICE Guidance
- Quick Reference Guide
- Understanding NICE Guidance (for patients and carers)

They are available from the NICE website (**www.nice.org.uk**) or, within the UK, from NICE publications (0845 003 7783) or email publications@nice.org.uk.

## 1.6 Principles for guideline development

The main principles behind the development of this guideline update were that it should:

- Consider all issues within an agreed scope that are important in the management of patients with chronic heart failure
- Use published evidence wherever this is available
- Be useful and usable to all professionals
- Take full account of the perspective of the person with heart failure and their carers
- Indicate areas of uncertainty or controversy needing further research.
- Provide a choice of guideline versions for different audiences.

## 1.7 Scope of update

The guideline update was developed in accordance with the scope, which detailed the remit of the guideline originating from the Department of Health, and specified those aspects of chronic heart failure care to be included and excluded.

Prior to the commencement of the guideline development, the scope was subjected to stakeholder consultation in accordance with processes established by NICE in the guideline manual [23]. The scope for the update is included in Appendix A and is summarised below:

### *Inclusions*

- Adults with symptoms or a diagnosis of chronic heart failure (including diastolic dysfunction).
- Diagnosing heart failure:
  - symptoms and signs
  - use of B-type natriuretic peptides (BNP and NT-proBNP)
  - echocardiography.
- Pharmacological treatment of heart failure, for example:
  - aldosterone antagonists
  - angiotensin II receptor antagonists.
- Invasive procedures:
  - cardiac resynchronisation therapy (incorporating relevant recommendations from NICE technology appraisal guidance 120)
  - implantable cardioverter defibrillators (incorporating relevant recommendations from NICE technology appraisal guidance 95)
- Disease monitoring in chronic heart failure:
  - serial measurement of circulating natriuretic peptide concentration

  - monitoring at home.

- Cardiac rehabilitation for heart failure.

### *Exclusions*

- Patients with right heart failure as a consequence of respiratory disease.
- Pregnant women

## 1.8 Other relevant NICE guidance

Since the publication of the 2003 CHF guideline, NICE has published other guidance which is relevant to the management of chronic heart failure. These publications are cross referenced where applicable.

1. Atrial fibrillation: the management of atrial fibrillation. NICE clinical guideline 36 (2006). Available from www.nice.org.uk/guidance/CG36
2. Cardiac resynchronisation therapy for the treatment of heart failure (NICE Technology appraisal 120 (2007). Available from www.nice.org.uk/guidance/TA120
3. Chronic kidney disease: Early identification and management of chronic kidney disease in adults in primary and secondary care. NICE clinical guideline 73 (2008). Available from www.nice.org.uk/guidance/CG73
4. Depression: the treatment and management of depression in adults (partial update) NICE clinical guideline 90 (2009). Available from: www.nice.org.uk/guidance/CG90
5. Depression in adults with a chronic physical health problem: treatment and management. NICE clinical guideline 91 (2009). Available from www.nice.org.uk/guidance/CG91
6. Hypertension: management of hypertension in adults in primary care .NICE clinical guideline 34 (2006). Available from www.nice.org.uk/guidance/CG34
7. Implantable cardioverter defibrillators (ICDs) for the treatment of arrhythmias (review of TA11) (NICE Technology appraisal 95 (2006). Available from www.nice.org.uk/guidance/TA95
8. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. NICE clinical guideline 67 (2008). Available from www.nice.org.uk/guidance/CG67
9. Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence. NICE clinical guideline 76 (2009). Available from www.nice.org.uk/guidance/CG76
10. MI secondary prevention: secondary prevention in primary and secondary care for patients following a myocardial infarction. NICE clinical guideline 48 (2007). Available from www.nice.org.uk/guidance/CG48
11. Short term circulatory support with left ventricular assist devices as a bridge to cardiac transplantation or recovery. NICE interventional procedure guidance 177 (2006). Available from www.nice.org.uk/guidance/IPG177
12. Smoking cessation services in primary care, pharmacies, local authorities and work places, particularly for manual working groups, pregnant women and hard to reach communities. NICE public health guidance 10 (2008). Available from www.nice.org.uk/guidance/PH10
13. Brief interventions and referral for smoking cessation in primary care and other settings. NICE public health intervention guidance 1 (2006). Available from www.nice.org.uk/guidance/PH1

14. Type 2 diabetes: the management of type 2 diabetes (partial update). NICE clinical guideline 87 (2009). Available from www.nice.org.uk/guidance/CG87

15. Varenicline for smoking cessation. NICE technology appraisal guidance 123 (2007). Available from www.nice.org.uk/guidance/TA123

## 1.9 Guideline limitations

These include:

- NICE clinical guidelines usually do not cover issues of service delivery, organisation or provision (unless specified in the remit from the Department of Health).
- NICE is primarily concerned with Health Services and so recommendations are not provided for Social Services and the voluntary sector. However, the guideline may address important issues related to the interface of NHS clinicians with these sectors.
- Generally, the guideline does not cover rare, complex, complicated or unusual conditions.
- It is not possible in the development of a clinical guideline to complete extensive systematic literature reviews of all pharmacological toxicity. NICE expect the guidelines to be read alongside the Summaries of Product Characteristics.
- The guideline usually makes recommendations within medication licence indications. Exceptionally, where there was clear supporting evidence, recommendations outside the licensed indications have been included. As far as possible where this is the case, it is indicated.

## 1.10 Plans for guideline revision

Further updates will take place in accordance with the specifications outlined in the NICE guideline manual[24].

## 1.11 Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide, and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The NCGC-ACC disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

## 1.12 Funding

The NCGC-ACC was commissioned by NICE to undertake the work on this guideline.

# 2 Methods

## 2.1 Introduction

This chapter describes the people and techniques used to derive the clinical recommendations that follow in later chapters. The preliminary scoping phase of the development followed the methods described in the NICE Guideline manual 2007 [23]. The rest of the guideline development followed the methods of the NICE Guideline manual 2009[24]

## 2.2 The Developers

### *2.2.1 The National Clinical Guideline Centre*

NICE commissioned the former National Collaborating Centre for Chronic Conditions (NCC-CC) in 2008 to develop this partial update. This merged with other collaborating centres to form the National Clinical Guideline Centre (NCGC) during the development of this guideline.

### *2.2.2 Guideline Development Group*

The guideline development group (GDG) comprised a multidisciplinary team of health professionals and two people with heart failure. The GDG was recruited following an application process as specified in the NICE Guideline manual [23]. Membership details of the GDG are included at the front of this guideline. Members of the GDG declared any potential conflicts of interest in accordance with NICE policy. These are listed in Appendix L. The GDG met approximately monthly from January 2009 – June 2010. The GDG was supported by the technical team.

### *2.2.3 The technical team*

The technical team met approximately two weeks before each GDG meeting and comprised the following members: GDG chair, GDG clinical advisor, Information Scientist, Research Fellow, Health Economist, Project Manager and Operations Director.

### *2.2.4 Involvement of people with chronic heart failure (CHF)*

The NCGC was keen to ensure the views and preferences of people with CHF and their carers informed all stages of the guideline. This was achieved by:

- having two people with CHF as a patient representative on the guideline development group (GDG)
- consulting with the Patient and Public Involvement Programme (PPIP) housed within NICE during the pre-development (scoping) and final validation stages of the guideline.
- inclusion of patient groups as registered stakeholders for the guideline.

## 2.3 The process of guideline development

The basic steps in the process of producing a guideline update are:

- Identifying areas of existing guidance that need updating
- Developing clinical questions
- Developing the review protocol
- Systematically searching for the evidence

- Critically appraising the evidence
- Undertaking new health economic analysis
- Distilling and synthesising the evidence and writing recommendations
- Agreeing the recommendations
- Structuring and writing the guideline
- Updating the guideline.

### *2.3.1 Identifying areas of existing guidance that need updating*

The NCGC conducted a preliminary search for new evidence using the search strategies from the original guideline. The views of healthcare professionals and patients were also sought to identify any change in practice or additional relevant published evidence. Key areas that would directly result in changes to recommendations were highlighted for updating.

### *2.3.2 Developing evidence based questions*

The technical team drafted a series of clinical questions that covered the guideline scope. The GDG refined and approved these questions, which are shown in Appendix B.

### *2.3.3 Developing the review protocol*

For each clinical question, the Information Scientist and the Research Fellow (with input from the technical team) prepared a review protocol. This protocol explained how the review was to be carried out and the different stages involved. The protocol also limited the introduction of bias, and should enable the review to be reproduced in the future. A health economic literature review protocol was also developed. All review protocols can be found in Appendix C.

**Table 2.1:** Components of the review protocol

| Component | Description |
|---|---|
| Review question | The review question as agreed by the GDG. |
| Objectives | Short description; for example 'To estimate the effects and cost effectiveness of…' or 'To estimate the diagnostic accuracy of…'. |
| Criteria for considering studies for the review | Using the PICO (population, intervention, comparison and outcome) framework. Including the study designs selected. |
| How the information will be searched | The sources to be searched and any limits that will be applied to the search strategies; for example, publication date, study design, language. (Searches should not necessarily be restricted to RCTs.) |
| The review strategy | The methods that will be used to review the evidence, outlining exceptions and subgroups. Indicate if meta-analysis will be used. |

### *2.3.4 Searching for the evidence*

The Information Scientist developed a search strategy for each question. Key words for the search were identified by the GDG. A separate health economic search strategy was developed looking for economic studies in chronic heart failure. Papers that were published in peer-reviewed journals (including e-publications ahead of print versions where identified) were considered as evidence by the GDG. Conference paper abstracts and non-English language papers were excluded from the searches.

The dates to be searched for each question were agreed with the GDG before the review was undertaken. See Appendix D for the search strategies.

**Types of study**

Each clinical question dictated the appropriate study design that was prioritised in the search strategy, however the strategy was not limited solely to these study types. For intervention studies, randomised controlled trials (RCTs) were the preferred sources of evidence. Cohort studies and lower levels of evidence were only considered if RCTs data was not available.

The evidence was restricted to meta-analysis or systematic reviews for the following question:

- What is the diagnostic accuracy of a collection of symptoms and signs, or a scoring system vs gold standard in the diagnosis of heart failure?

For the remaining diagnostic reviews, cross-sectional studies were preferred or case control data if these were not available.

From a health economic perspective, full economic evaluations (cost-effectiveness, cost-utility and cost-benefit analyses), cost-consequence analyses and comparative costing studies that addressed the clinical question were included. Studies were prioritised for inclusion if they were from a UK perspective and based intervention effectiveness on data from one or more RCT. A judgement was made on a question by question basis regarding whether to include studies from a non-UK perspective or that used observational evidence, depending on the availability and quality of the other evidence.

The research fellow or health economist identified relevant titles and abstracts for each clinical question from the search results and full papers were obtained. Exclusion lists were generated for each question together with the rationale for the exclusion. The exclusion lists were presented to the GDG. See Appendices C and D for review protocols and literature search details.

### *2.3.5 Re-run evidence*

Literature searches were repeated for all of the evidence-based questions at the end of the GDG development process allowing any relevant papers published up until 9 October 2009 to be considered. Future guideline updates will consider new evidence published after this date.

### *2.3.6 Appraising the evidence*

The research fellow or health economist, as appropriate, critically appraised the full papers and undertook data extraction. Critical appraisal checklists were compiled for each full paper. The evidence was considered carefully by the GDG for accuracy and completeness.

All procedures are fully compliant with the NICE methodology as detailed in the 'Guideline Development Methods – Information for National Collaborating Centres and Guideline Developers' Manual [24].

**Clinical evidence**

The research fellow critically appraised the full papers and undertook the data extraction. For non-observational studies, where possible this included meta-analysis of data and synthesis of data into a GRADE 'evidence profile'. The evidence profile shows for each outcome an overall assessment of both the quality of the evidence as a whole (low, moderate or high), as well as an estimate of the size of effect.

### Quality of evidence

The quality of clinical evidence is graded as follows:

**Table 2.2: Quality of evidence**

| Quality | Explanation |
|---|---|
| High | Further research is very unlikely to change our confidence in the estimate of effect. |
| Moderate | Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. |
| Low | Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate |
| Very low | Any estimate of effect is very uncertain. |

The quality of the evidence is dependent on the following factors

- study design
- limitations
- inconsistency
- indirectness
- imprecision

A footnote in the GRADE profile is provided detailing the reasons for downgrading the quality of the evidence.

### Study design

The quality of evidence for RCT studies is reduced according to the factors specified above. The quality of observational evidence or any other evidence can be increased if

- there is a large effect
- there is evidence that the influence of all plausible confounding evidence would reduce a demonstrated effect or suggest a spurious effect when results show no effect
- there is strong dose-response gradient

### Limitations in the design

The following limitations are likely to bias the effect of an intervention:

- unclear allocation concealment
- lack of blinding
- incomplete accounting of patients and outcome events for example not reporting the drop-out rate or if the drop-out rate was greater than 20%
- selective outcome reporting

If there were any limitations, these could be serious or very serious and the quality of the evidence was downgraded by one or two levels respectively, for example, from high to moderate or high to low.

### Inconsistency

Where there was a widely different estimate of treatment effect across studies, the evidence was downgraded by one or two levels. The $I^2$ statistic generated using Review Manager and

a visual inspection of the forest plots was used to check for consistency. Notable heterogeneity was indicated by an $I^2$ statistic greater than 50%.

**Imprecision**

Evidence was downgraded if:

- the total number of events was less than 300 (except for adverse events)
- the 95% confidence interval for the estimate of effect includes both negligible effect and appreciable benefit or appreciable harm. For dichotomous variables GRADE suggests that threshold for "appreciable benefit" or "appreciable harm" that should be considered for downgrading is a relative risk reduction (RRR) or relative risk increase (RRI) greater than 25%. For continuous variables, evidence was downgraded if the upper or lower confidence limit crosses an effect size of 0.5 in either direction. The exception was the outcome 'quality of life' using the Minnesota Living with Heart Failure questionnaire. The GDG agreed that the minimally important difference (MID) was 5 points in either direction. Thus, evidence is downgraded if the 95% confidence interval includes no effect and the upper or lower confidence limit crosses the MID, either for benefit or harm.

**Evidence synthesis for intervention studies**

If possible, a meta-analysis was performed on the data using Review Manager. Dichotomous outcomes were analysed as relative risks (RR) and with the 95%CI. Continuous data were analysed as weighted mean difference (WMD). Where possible, data from the intention-to-treat analyses were used. Fixed effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for the binary outcomes. The continuous outcomes were analysed using an inverse variance method for pooling weighted mean differences and, where the studies had different scales, standardised mean differences were used. If heterogeneity was present, a random effect model was used and the two outputs compared. If the two models gave comparable results, those yielded by the fixed effect model are reported. If the two models yielded different results heterogeneity was investigated.

Statistical heterogeneity was assessed by considering the chi-squared test for significance at $p<0.05$ or an I-squared inconsistency statistic of >50% to indicate significant heterogeneity. When there were a high number of studies, a p-value of 0.1 was taken as a threshold for heterogeneity. Where significant heterogeneity was present, we presented the results study by study.

Hazard ratios are reported in addition to relative risk for the mortality outcomes. Relative risks are referred to in the main text of the document unless there was a difference in the likely interpretation of the results (for example if one estimate of effect implied a significant benefit and the other estimate of effect no benefit or harm). The methods outlined in the paper by Tierney (REF) were used to estimate the 'O – E' and 'V' statistics. The data were analysed using the generic inverse variance method.

GRADE was not used for studies reporting on diagnostic accuracy. Here the sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio and diagnostic odds ratio were reported if available.

**Health economist evidence**

The economist critically appraised the full papers and undertook the data extraction. For economic studies, an assessment of applicability (directly applicable, partially applicable or not applicable) and methodological quality (minor limitations, potentially serious limitations, very serious limitations) was performed and tabulated with footnotes indicating the reasons for the assessment. Results, uncertainty and limitations of included economic analyses were also summarised and discussed. The costs presented have not been inflated. Studies judged to have an applicability rating of 'not applicable' were excluded. A judgement was

made on a question by question basis regarding whether to include studies with a quality rating of 'very serious limitations', depending on the availability and quality of the other evidence.

### 2.3.7 Undertaking new health economic analysis

The GDG agreed a priority area for original health economic modelling for the guideline. The analysis undertaken assessed the cost-effectiveness of serial measurement of circulating natriuretic peptide concentration for optimising medical therapy, compared to clinical assessment and to usual care. The full report is presented in Appendix H. A summary of results is also presented in the relevant chapter of the guideline.

The following general principles were adhered to:

- The GDG was consulted during the construction and interpretation of the model.
- The GDG informed the structure and the validity of model inputs.
- The model was based on clinical evidence identified from the systematic review of clinical evidence.
- Model inputs and assumptions were reported fully and transparently.
- Sensitivity analysis was used to explore uncertainties in model inputs and methods.
- Costs were estimated from an NHS and personal social services (PSS perspective).

### 2.3.8 Distilling and synthesising the evidence and developing recommendations

The evidence from each full paper was distilled into an evidence table and synthesised into an evidence profile and evidence statements before being presented to the GDG. The results of health economic modelling undertaken for the guideline were also presented to the GDG. This evidence was then reviewed by the GDG and used as a basis upon which to formulate recommendations.

The clinical evidence tables are in Appendix E and the health economics evidence tables are in Appendix G. These are available online from www.nice.org.uk/guidance/CG108/Guidance.

### 2.3.9 Agreeing the recommendations

The GDG employed formal consensus techniques to:

- ensure that the recommendations reflected the evidence-base
- approve recommendations based on lesser evidence or extrapolations from other situations
- reach consensus recommendations where the evidence was inadequate
- debate areas of disagreement and finalise recommendations.

The GDG also reached agreement on the following:

- recommendations as key priorities for implementation
- future research recommendations
- algorithms

In prioritising key priorities for implementation, the GDG took into account the following criteria:

- high clinical impact
- high impact on reducing variation in practice
- more efficient use of NHS resources

- allowing the patient to reach critical points in the care pathway more quickly.

### *2.3.10 Review of 2003 recommendations not within the update scope*

Recommendations made in the original 2003 guideline that were not within the scope of the partial update were reviewed to check for accuracy and consistency in light of the new recommendations made. Other minor editing changes made to the original recommendations are for purposes of clarity and directness. These recommendations are indicated as follows: [2003].

### *2.3.11 Tables of practical recommendations*

The tables of Practical Recommendations in the 2003 Guideline have not been included within this update. However, some of the information in the tables that the GDG considered to be particularly important, for both patients and clinicians, has been included in Appendix J. This will be used as one of the implementation tools on publication of the guideline.

### *2.3.12 Patient choice*

Whenever recommendations are made, it is recognised that informed patient choice is important in determining whether or not an individual patient chooses to undergo the investigation or accept treatment that is recommended.

### *2.3.13 Writing the guideline*

The first draft version of the guideline was drawn up by the technical team in accordance with the decisions of the GDG, incorporating contributions from individual GDG members in their expert areas and edited for consistency of style and terminology. The guideline was then submitted for a formal public and stakeholder consultation prior to publication. The registered stakeholders for this guideline are detailed on the NICE website www.nice.org.uk. Editorial responsibility for the full guideline rests with the GDG.

The following versions of the guideline are available:

**Table 2.3: Versions of the guideline**

| Version | Description |
|---|---|
| Full version: | Details the recommendations, the supporting evidence base and the expert considerations of the GDG. Published by the NCGC.<br>Available from www.nice.org.uk/guidance/CG108/Guidance |
| NICE version: | Documents the recommendations without any supporting evidence.<br>Available from www.nice.org.uk/guidance/CG108/NICEGuidance |
| "Quick reference guide": | An abridged version for healthcare professionals.<br>Available from www.nice.org.uk/guidance/CG108/QuickRefGuide<br>For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N2268) |
| "Understanding NICE guidance": | A lay version of the guideline recommendations<br>Available from www.nice.org.uk/guidance/CG108/PublicInfo<br>For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N2269). |

### *2.3.14 Structure of the Guideline document*

A **glossary** of abbreviations and terms is included in at the beginning of this document

The **key recommendations and algorithms** are in Section 3.

Sections 4-8 of the document contain the guidelines, each of which covers a set of related topics.

Topics for future research are listed in Section 9 and references are in Section 10.

For topics **not within the scope,** the recommendations are listed, and the reader is referred to the 2003 Guideline for the details of how these were derived.

The layout of topics **within scope** is as follows:

The **clinical introduction** to the topic is provided in one or two paragraphs that explain why the update was needed and set the recommendations in context.

The way in which the clinical and health economics evidence was appraised and analysed is described in the **methodological introductions**. They outline the a priori agreement of the GDG in relation to the inclusion and exclusion criteria together with the outcomes of interest.

The **GRADE evidence profiles** provide a synthesis of the evidence-base for intervention studies, the quality and describe what the evidence showed in relation to the outcomes of interest (including effect sizes). **Forest plots** (Appendix F) showing meta-analysis results are also provided for outcomes where appropriate. Then the **evidence statements** are given which summarise the evidence detailed in the **evidence tables** (Appendix E).

For diagnostic reviews, the clinical and health economic evidence from each full paper was distilled into an evidence table (Appendix E) and synthesised into evidence statements before being presented to the GDG.

The **health economics section** gives, where appropriate, an overview of the cost effectiveness evidence-base, or any economics modelling.

**From evidence to recommendations** sets out the Guideline Development Group's (GDG) decision-making rationale providing a clear and explicit audit trail from the evidence to the evolution of the recommendations.

The main **recommendations** follow**.**

The 'status' of each recommendation is indicated as follows:

- **[2003]**
    - Recommendation from the 2003 guideline where the **evidence has not been formally reviewed** for the 2010 update.
- **[2003, amended 2010]**
    - A small amendment has been made to the 2003 recommendation but the evidence has not been updated or reviewed.
- **[2010]**
    - Recommendation from the 2003 guideline where **evidence has been reviewed** but the recommendation is not changed. (This includes recommendations which are reworded in a new direct style.)
- **[new 2010]**
    - Recommendation from 2003 guideline which has been **changed following review of evidence**
    - New recommendation **following review of evidence**

This guideline includes two recommendations from the Myocardial Infarction: Secondary prevention guideline and are referenced accordingly.

# 3 Key priorities and algorithms

## 3.1 Key priorities for implementation

In agreeing key recommendations for implementation, the GDG took the following criteria into account:

- High clinical impact
- High impact on reducing variation in practice
- More efficient use of NHS resources
- Allowing the patient to reach critical points in the care pathway more quickly

**Diagnosis**

1. Refer patients with suspected heart failure and previous myocardial infarction (MI) urgently, to have transthoracic Doppler 2D echocardiography and specialist assessment within 2 weeks. **[new 2010]**
2. Measure serum natriuretic peptides (B-type natriuretic peptide [BNP] or N-terminal pro-B-type natriuretic peptide [NTproBNP]) in patients with suspected heart failure without previous MI. **[new 2010]**
3. Because very high levels of serum natriuretic peptides carry a poor prognosis, refer patients with suspected heart failure and a BNP level above 400 pg/ml (116 pmol/litre) or an NTproBNP level above 2000 pg/ml (236 pmol/litre) urgently, to have transthoracic Doppler 2D echocardiography and specialist assessment within 2 weeks. **[new 2010]**

**Treatment**

4. Offer both angiotensin-converting enzyme (ACE) inhibitors and beta-blockers licensed for heart failure to all patients with heart failure due to left ventricular systolic dysfunction. Use clinical judgement when deciding which drug to start first. **[new 2010]**
5. Offer beta-blockers licensed for heart failure to all patients with heart failure due to left ventricular systolic dysfunction, including :
    - older adults **and**
    - patients with:
        - peripheral vascular disease
        - erectile dysfunction
        - diabetes mellitus
        - interstitial pulmonary disease and
        - chronic obstructive pulmonary disease (COPD) without reversibility.**[new 2010]**
6. Seek specialist advice and consider adding one of the following if a patient remains symptomatic despite optimal therapy with an ACE inhibitor and a beta-blocker:
    - an aldosterone antagonist licensed for heart failure (especially if the patient has moderate to severe heart failure [NYHA[1] class III-IV] or has had an MI within the past month) or
    - an angiotensin II receptor antagonist (ARB) licensed for heart failure[2] (especially if the patient has mild to moderate heart failure [NYHA class II-III]) or

[1] The New York Heart Association classification of heart failure.

- hydralazine in combination with nitrate (especially if the patient is of African or Caribbean origin[3] and has moderate to severe heart failure [NYHA class III-IV]). **[new 2010]**

**Rehabilitation**

7. Offer a supervised group exercise-based rehabilitation programme designed for patients with heart failure.
    - Ensure the patient is stable and does not have a condition or device that would preclude an exercise-based rehabilitation programme[4].
    - Include a psychological and educational component in the programme.
    - The programme may be incorporated within an existing cardiac rehabilitation programme **[new 2010]**

**Monitoring**

8. All patients with chronic heart failure require monitoring. This monitoring should include:
    - a clinical assessment of functional capacity, fluid status, cardiac rhythm (minimum of examining the pulse), cognitive status and nutritional status
    - a review of medication, including need for changes and possible side effects
    - serum urea, electrolytes, creatinine and eGFR[5].**[2003, amended 2010]**
9. When a patient is admitted to hospital because of heart failure, seek advice on their management plan from a specialist in heart failure. **[new 2010]**

**Discharge Planning**

10. Patients with heart failure should generally be discharged from hospital only when their clinical condition is stable and the management plan is optimised. Timing of discharge should take into account patient and carer wishes, and the level of care and support that can be provided in the community. **[2003]**

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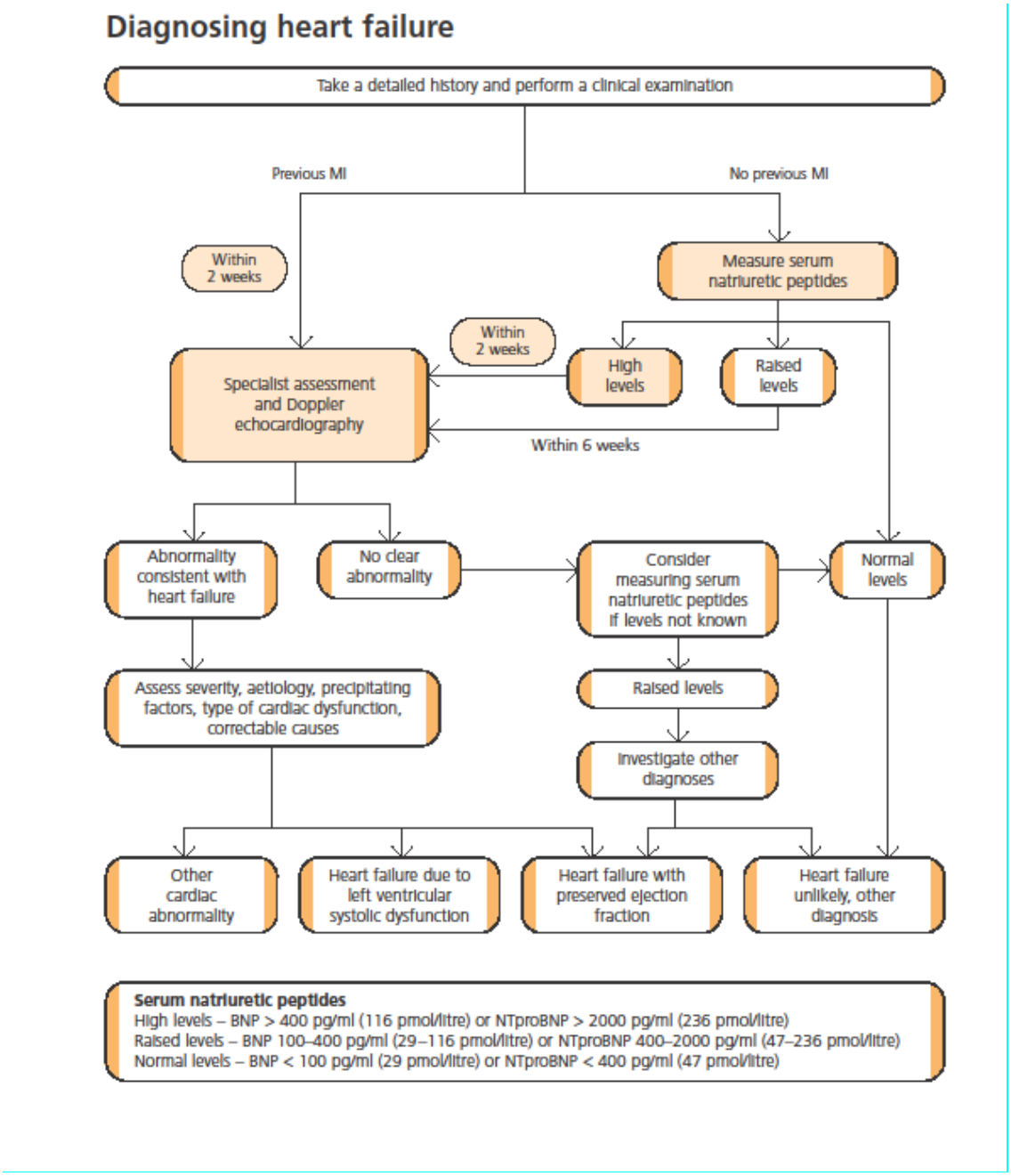
[2] Not all ARBs are licensed for use in heart failure in combination with ACE inhibitors.

[3] This does not include mixed race.

[4] The conditions and devices that may preclude an exercise-based rehabilitation programme include: uncontrolled ventricular response to atrial fibrillation, uncontrolled hypertension, and high-energy pacing devices set to be activated at rates likely to be achieved during exercise.

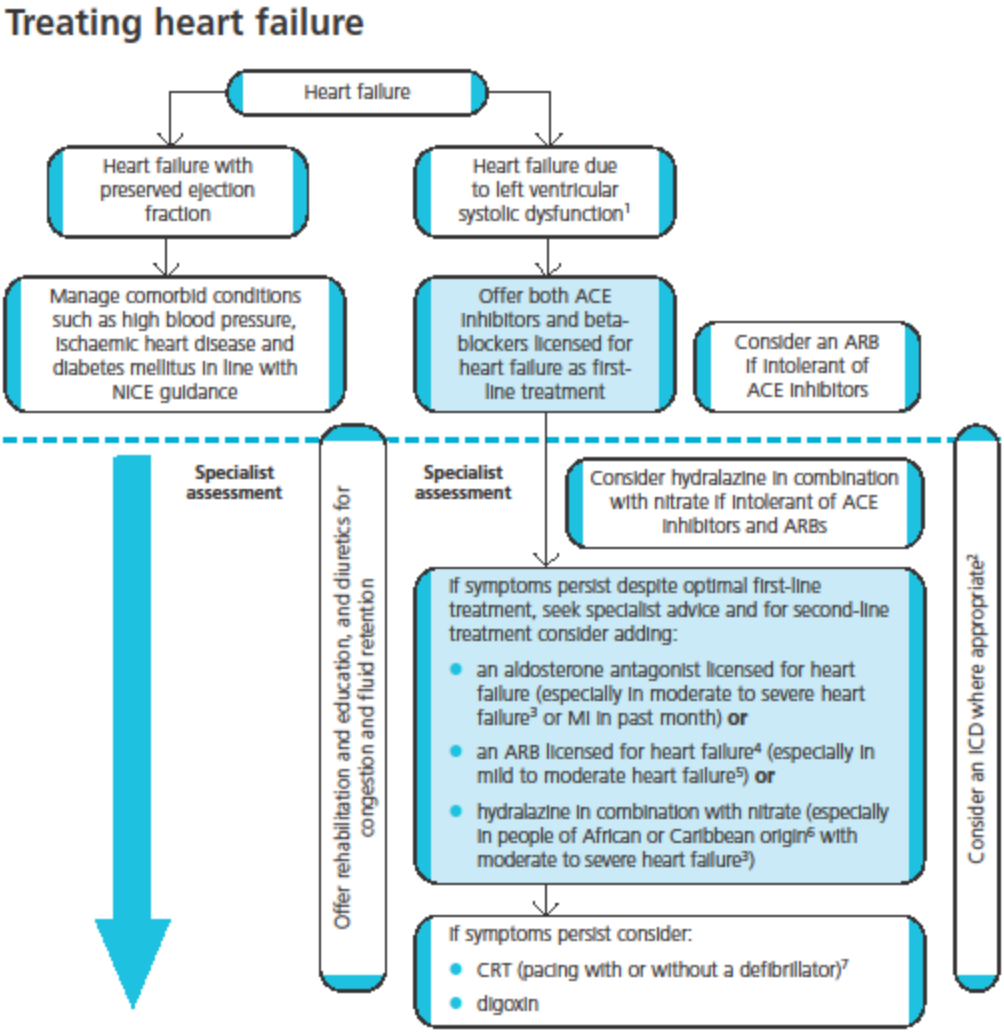
[5] This is a minimum. Patients with comorbidities or co-prescribed medications will require further monitoring. Monitoring serum potassium is particularly important if a patient is taking digoxin or an aldosterone antagonist.

## 3.2 Algorithm summarising recommendations for the diagnosis of heart failure




- Perform an ECG in all patients.
- Other recommended tests:
  - chest X-ray
  - blood tests: urea, creatinine, electrolytes, eGFR, full blood count, liver function tests, thyroid function tests, fasting glucose, and fasting lipids
  - urinalysis
  - peak flow or spirometry
- **Non-HF causes of high NP**: LVH, ischaemia, tachycardia, RV overload, hypoxaemia (including pulmonary embolism), renal dysfunction (eGFR<60 ml/min), sepsis, COPD, diabetes, age (>70 years), cirrhosis of the liver.
- **Factors causing low NP**: Obesity and treatment with diuretics, ACEI, BB, ARB and AA.

## 3.3 Algorithm for the treatment of symptomatic heart failure




[1] For more information on drug treatment see appendix J and 'Chronic kidney disease' (NICE clinical guideline 73).
[2] Consider an ICD in line with 'Implantable cardiovascular defibrillators for arrhythmias' (NICE technology appraisal guidance 95).
[3] NYHA class III–IV.
[4] Not all ARBs are licensed for use in heart failure in combination with ACE inhibitors.
[5] NYHA class II–III.
[6] This does not include mixed race. For more information see the full guideline at www.nice.org.uk/guidance/CG108
[7] Consider CRT in line with 'Cardiac resynchronisation therapy for the treatment of heart failure' (NICE technology appraisal guidance 120).

# 4 Diagnosing heart failure

## Introduction

Full evaluation of the patient with heart failure involves more than stating whether the syndrome is present or not; it requires consideration of the underlying abnormality of the heart, the severity of the syndrome, the aetiology, precipitating and exacerbating factors, identification of concomitant disease relevant to the management, and an estimation of prognosis.

Throughout this guideline the term 'echocardiography' refers to transthoracic Doppler echocardiography unless otherwise specified.

## 4.1 Symptoms, signs and investigation

Clinical question: What is the diagnostic accuracy of a collection of symptoms and signs vs. gold standard in the diagnosis of heart failure?

### *4.1.1 Clinical introduction*

The patient with heart failure presents with one or more symptoms that may be sensitive markers for heart failure, however, these are usually non-specific for heart failure. During physical examination, the clinician may elicit clinical signs that are either sensitive or specific. The reliance on the history and physical examination of a patient suspected of having heart failure could result in erroneous decisions being made. Studies have looked at the possibility of making the diagnosis on the basis of a constellation of symptoms and signs that may suggest the presence of heart failure. There has also been an expansion in the field of ancillary tests designed to detect abnormalities that may point to heart failure as the syndrome behind the patient's presentation. These tests rely either on imaging of the heart to assess its structure and function, or on the detection of the serum levels of certain peptides that are known to rise in the heart failure syndrome.

#### *Symptoms*

Patients with heart failure may have a number of symptoms, the most common being breathlessness, fatigue, exercise intolerance, and fluid retention [25,26].

One of the primary symptoms of heart failure is breathlessness, which can be exertional or at rest. Breathlessness at rest includes two specific but insensitive symptoms, namely orthopnoea and paroxysmal nocturnal dyspnoea. The degree of exertion required to elicit symptoms such as breathlessness may be used to grade the severity of symptoms into one of four functional classes (Table 4.1).[27] The functional class tends to deteriorate unevenly over time and the severity of symptoms does not necessarily equate with the severity of the underlying heart problem – mild symptoms may be found in patients with severe damage to the heart, and vice versa.[26,28] Changes in medication and diet can have very favourable or adverse effects on functional capacity in the absence of any measurable change in heart function, however the severity of symptoms may fluctuate even in the absence of changes in medication[29].

**Table 4.1:** New York Heart Association Classification of heart failure symptoms

| *Class* | *Symptoms* |
|---|---|
| I | No limitations. Ordinary physical activity does not cause fatigue, breathlessness or palpitation. (Asymptomatic left ventricular dysfunction is included in this category) |
| II | Slight limitation of physical activity. Such patients are comfortable at rest. Ordinary physical activity results in fatigue palpitation breathlessness or angina pectoris (symptomatically "mild" heart failure) |

| | |
|---|---|
| III | Marked limitation of physical activity. Although patients are comfortable at rest, less than ordinary physical activity will lead to symptoms (symptomatically "moderate" heart failure) |
| IV | Inability to carry out any physical activity without discomfort. Symptoms of congestive cardiac failure are present even at rest. With any physical activity, increased discomfort is experienced (symptomatically "severe" heart failure) |

Other non-specific symptoms of heart failure include nocturia, anorexia, abdominal bloating and discomfort, constipation, and cerebral symptoms such as confusion, dizziness and memory impairment[30,31]. None of these symptoms are specific for heart failure, and therefore can not be relied upon alone to make the diagnosis of heart failure [32,33] Other disorders may present with symptoms similar to those of heart failure (Table 4.2).

**Table 4.2: Other conditions that may present with symptoms similar to those of heart failure**

| |
|---|
| • Obesity. |
| • Chest disease – including lung, diaphragm or chest wall. |
| • Venous insufficiency in lower limbs. |
| • Drug-induced ankle swelling (eg dihydropyridine calcium channel blockers). |
| • Drug-induced fluid retention (eg NSAIDs). |
| • Hypoalbuminaemia. |
| • Intrinsic renal or hepatic disease. |
| • Pulmonary embolic disease. |
| • Depression and/or anxiety disorders. |
| • Severe anaemia or thyroid disease. |
| • Bilateral renal artery stenosis. |
| NB Elderly patients are particularly likely to have a number of concomitant medical problems. |

### *Signs*

An elevated jugular venous pressure has a high predictive value in the diagnosis of heart failure[30] but is often not present. Several studies have shown that other clinical signs such as tachycardia, third heart sound, and displaced apex beat, have less predictive value if found in isolation[26,29,31,33-35].

When multiple signs and symptoms are present, a diagnosis can be made with greater confidence, but further assessment is required to identify the underlying functional abnormalities.

### *Reason for review*

Since the release of the NICE guidance of 2003 new evidence on the diagnostic accuracy of signs and symptoms of heart failure has been published.

## *4.1.2 Clinical Methodological introduction*

Studies were included that reported on the diagnostic accuracy of a collection of, or individual, symptoms and signs (breathlessness, effort intolerance, raised jugular venous pressure "JVP", third heart sound, displaced apex beat, murmurs, fluid retention "oedema", fatigue) compared to a gold standard in the diagnosis of heart failure. Three systematic reviews (SR) were included[36-38].

No systematic reviews were found that reported on the diagnostic accuracy of a combination of symptoms or signs. There was some overlap of the studies included in the three SRs, however all three were included in this review as they were each addressing a slightly

different population or setting. The tables below summarise the populations, reference standards and settings covered by each.

Two of the SRs were of high quality [37,38]. One of the SRs [36] was moderate quality as the literature search may not have been sufficiently rigorous to identify all the relevant studies as only Medline was used.

**Limitations**

- The overlap of included papers in each SR causes the risk of double-counting.
- It is not known how representative the patients included in the studies are of those routinely seen (and diagnosed) in the different settings
- The final diagnosis of chronic heart failure may not have been made independently of the individual findings, and therefore may over-estimate the sensitivities and specificities.

**WANG 2005:**

- The SR may not be relevant to this guideline as the included populations were people presenting to the emergency department, which could be viewed as acute presentation/acute heart failure. However, not all the patients with the acute presentation have acute heart failure, as the symptoms used to make the diagnosis were those that usually suggest the presence of chronic heart failure. Also, the results are specific for patients with dyspnoea within the emergency setting and may not be generalised to outpatient and inpatient settings or to patients without dyspnoea.

**MANT 2009:**

- There was considerable variation across the studies. These differences may have been due to differing definitions of the symptoms or signs, or to differences in the patient group studied. In particular, it is likely that those presenting to accident and emergency will have had more severe heart failure.

Table 4.3: Summary of methodological characteristics of included studies

| | Overlap of included studies | Population/Setting | Symptoms/signs | Reference standard |
|---|---|---|---|---|
| MANT 2009<br><br>N=15 studies | 6 of the studies included in MADHOK 2008 + 4 in WANG 2005 (see below for details) | Suspected cases of heart failure in primary care, emergency department, hospital and outpatient settings and studies from population cohort or screening studies.<br><br>Studies varied whether they included patients with previously diagnosed heart failure or not; both groups of studies were included in the review.<br><br>in general practice (5 studies)<br><br>N= 2,527 patients<br><br>patients referred from primary to secondary care (5 studies) | Symptoms and signs:<br><br>History of MI, Dyspnoea, Orthopnoea, Paroxysmal nocturnal dyspnoea, Oedema, Tachycardia, Elevated JVP, Cardiomegaly, Added heart sounds,<br><br>Lung crepitation, Hepatomegaly | Adequate reference standards were prospective planned evaluation of:<br><br>a) a clinical diagnosis including all information, for example using ESC (European Society of Cardiology) criteria.<br><br>b) echocardiographic criteria for left ventricular systolic dysfunction (LVSD) (such as |

| | | | | |
|---|---|---|---|---|
| | | N=1,249 patients<br>in acute care (5 studies)<br>N= 1,890 patients | | assessment of left ventricular ejection fraction or global assessment of ventricular function)<br>c) echocardiographic criteria for heart failure with preserved left ventricular ejection fraction. |
| MADHOK 2008<br><br>N= 24 studies<br><br>N= 5 studies assessed the usefulness of various symptoms and signs | 6 of the studies overlapped with those included in MANT 2009 (Alehagen et al, 2003; Hobbs et al, 2002; Cowie et al, 1997; Fox et al, 2000; Lim et al, 2006; Zaphiriou et al, 2005). No overlap with WANG 2005 | Participants recruited from a community or primary care setting and had symptoms suggestive of LVSD.<br><br>N= 10,710 patients | Symptoms, signs (history of MI, diabetes, hypertension; fatigue; dyspnoea; orthopnoea; PND; peripheral oedema; abnormal breath sounds; raised JVP; displaced apex beat; 3rd heart sound) diagnostic tests (ECG, chest x-ray and/or natriuretic peptides) | Echocardiogram |
| WANG 2005<br><br>N= 22 studies<br>N= 18 studies included in the meta-analysis. | 4 of the studies overlapped with those included in MANT 2009 (Mueller et al, 2005; Logeart et al, 2002; Knudsen et al, 2004; Morrison et al, 2002). No overlap with MADHOK 2008. | Adult patients with dyspnoea presenting to the emergency department, regardless of whether the patients had known cardiac or pulmonary diseases.<br><br>Total men (as reported in study): 5,237 | Some element of medical history, physical examination (symptoms and signs) and readily available diagnostic tests (chest radiograph, ECG and serum NP) | A diagnosis agreed upon by a panel of physicians after evaluating for appropriate symptoms and signs of heart failure and an appropriate measure of cardiac dysfunction. |

### *4.1.3 Clinical evidence statements*

**a) Dyspnoea**

Two of the SRs reported on the diagnostic accuracy of dyspnoea [37,38].

Table 4.4: Diagnostic accuracy of dyspnoea

| | Sensitivity (%) | Specificity (%) | Positive likelihood ratio (95% CI) | Negative likelihood ratio (95% CI) |
|---|---|---|---|---|
| **All settings + patients** (MANT 2009) | 83 | 54 | 1.79 (1.30-2.47) | 0.31 (0.12-0.79) |
| **LVSD in primary care** (MADHOK 2008) | - | - | 1.15 (1.09 - 1.21) | 0.50 (0.20 - 1.26) |

**b) Dyspnoea on exertion**

One SR reported on the diagnostic accuracy of dyspnoea on exertion [36]

Table 4.5: Diagnostic accuracy of dyspnoea on exertion

| | Sensitivity (%) | Specificity (%) | Positive likelihood ratio (95% CI) | Negative likelihood ratio (95% CI) |
|---|---|---|---|---|
| **Emergency department** (WANG 2005) | 84 | 34 | 1.3 (1.2-1.4) | 0.48 (0.35-0.67) |

**c) Orthopnoea**

All three SRs reported on the diagnostic accuracy of orthopnoea [36-38].

Table 4.6: Diagnostic accuracy of orthopnoea

| | Sensitivity (%) | Specificity (%) | Positive likelihood ratio (95% CI) | Negative likelihood ratio (95% CI) |
|---|---|---|---|---|
| **All settings + patients** (MANT 2009) | 44 | 89 | 3.91 ( 1.51-10.11) | 0.63 ( 0.53-0.74) |
| **LVSD in primary care** (MADHOK 2008) | - | - | 1.59 (range 0.89 - 3.58) | 0.89 (range 0.77 - 1.04) |
| **Emergency department** (WANG 2005) | 50 | 77 | 2.2 (1.2-3.9) | 0.65 (0.45-0.92) |

One study reported on the diagnostic accuracy of orthopnoea in a subgroup of patients with a history of asthma or COPD [36]

Table 4.7: Diagnostic accuracy of orthopnea in patients with history of asthma or COPD

| | Sensitivity (%) | Specificity (%) | Positive likelihood ratio (95% CI) | Negative likelihood ratio (95% CI) |
|---|---|---|---|---|
| **Emergency department** (WANG 2005) | 70 | 44 | 1.3 (1.1-1.5) | 0.68 (0.48-0.95) |

### d) Paroxysmal nocturnal dyspnoea (PND)

Two of the SRs reported individual results on the diagnostic accuracy of PND [36,38]

Table 4.8: Diagnostic accuracy of PND

| | Sensitivity (%) | Specificity (%) | Positive likelihood ratio (95% CI) | Negative likelihood ratio (95% CI) |
|---|---|---|---|---|
| **LVSD in primary care** (MADHOK 2008) | - | - | 1.71 (range 1.12 - 2.23) | 0.87 (range 0.75 - 0.99) |
| **Emergency department** (WANG 2005) | 41 | 84 | 2.6 (1.5-4.5) | 0.70 (0.54-0.91) |

### e) Oedema

Two of the SRs reported on the diagnostic accuracy of oedema [36,37]

Table 4.9: Diagnostic accuracy of oedema

| | Sensitivity (%) | Specificity (%) | Positive likelihood ratio (95% CI) | Negative likelihood ratio (95% CI) |
|---|---|---|---|---|
| **All settings + patients** (MANT 2009) | 53 | 72 | 3.91 (1.51-10.11) | 0.63 (0.53-0.74) |
| **Emergency department** (WANG 2005) | 51 | 76 | 2.1 (0.92-5.0) | 0.64 (0.39-0.91) |

One SR reported on the diagnostic accuracy of lower extremity oedema [36] in all patients and a subgroup of patients with a history of asthma or COPD.

Table 4.10: Diagnostic accuracy of lower extremity oedema

| | Sensitivity (%) | Specificity (%) | Positive likelihood ratio (95% CI) | Negative likelihood ratio (95% CI) |
|---|---|---|---|---|
| **Emergency department** (WANG 2005) -all patients | 50 | 78 | 2.3 (1.5-3.7) | 0.64 (0.47-0.87) |
| Subgroup | 69 | 75 | 2.7 (2.2-3.5) | 0.41 (0.30-0.57) |

### f) Elevated JVP

All three SRs reported on the diagnostic accuracy of elevated JVP [36-38]

Table 4.11: Diagnostic accuracy of elevated JVP

| | Sensitivity (%) | Specificity (%) | Positive likelihood ratio (95% CI) | Negative likelihood ratio (95% CI) |
|---|---|---|---|---|
| **All settings + patients** (MANT 2009) | 52 | 70 | 1.73 (1.23-2.43) | 0.68 (95% CI 0.56-0.84) |
| **LVSD in primary care** (MADHOK 2008) | - | - | 4.36 (range 2.66 - 7.44) | 0.88 (0.83 - 0.91) |
| **Emergency department** (WANG 2005) | 39 | 92 | 5.1 (3.2-7.9) | 0.66 (0.57-0.77) |

One study reported on the diagnostic accuracy of elevated JVP in a subgroup of patients with a history of asthma or COPD [36]

Table 4.12: Diagnostic accuracy of elevated JVP in patients with history of asthma or COPD

| | Sensitivity (%) | Specificity (%) | Positive likelihood ratio (95% CI) | Negative likelihood ratio (95% CI) |
|---|---|---|---|---|
| **Emergency department** (WANG 2005) | 41 | 90 | 4.3 (2.8-6.5) | 0.65 (0.54-0.78) |

### g) Displaced apex beat

One SR reported on the diagnostic accuracy of a displaced apex beat [38]

Table 4.13: Diagnostic accuracy of displaced apex beat

| | Sensitivity (%) | Specificity (%) | Positive likelihood ratio (95% CI) | Negative likelihood ratio (95% CI) |
|---|---|---|---|---|
| **LVSD in primary care** (MADHOK 2008) | - | - | 15.96 (8.24 - 30.93) | 0.58 (range 0.35 - 0.93) |

### h) Added heart sounds

All three SRs reported on the diagnostic accuracy of added heart sounds [36-38]

Table 4.14: Diagnostic accuracy of added heart sounds

| | Sensitivity (%) | Specificity (%) | Positive likelihood ratio (95% CI) | Negative likelihood ratio (95% CI) |
|---|---|---|---|---|
| **All settings + patients** (MANT 2009) *(all added heart sounds)* | 11 | 99 | 12.1 (95% CI 5.74-25.4) | 0.90 (95% CI 0.82-0.99) |
| **LVSD in primary care** (MADHOK 2008) *(added 3rd heart sound)* | - | - | 7.34 (range 1.56 - 32.37) | 0.92 (range 0.77 - 0.96) |
| **Emergency department** (WANG 2005) *(added third heart sound)* | 13 | 99 | 11 (4.9-25.0) | 0.88 (0.83-0.94) |
| **Emergency department** (WANG 2005) *(added fourth heart sound)* | 5 | 97 | 1.6 (0.47-5.5) | 0.98 (0.93-1.0) |

One study reported on the diagnostic accuracy of a third heart sound in a subgroup of patients with a history of asthma or COPD [36]

Table 4.15: Diagnostic accuracy of a third heart sound in patients with history of asthma or COPD

| | Sensitivity (%) | Specificity (%) | Positive likelihood ratio (95% CI) | Negative likelihood ratio (95% CI) |
|---|---|---|---|---|
| **Emergency department** (WANG 2005) | 17 | 100 | 57.0 (7.6-425) | 0.83 (0.75-0.91) |

### i) Lung crepitations/ rales/ abnormal breath sounds

All three SRs reported on the diagnostic accuracy of lung crepitation/ rales/ abnormal breath sounds [36-38].

Table 4.16: Diagnostic accuracy of lung crepitation/rales/abnormal breath sounds

| | Sensitivity (%) | Specificity (%) | Positive likelihood ratio (95% CI) | Negative likelihood ratio (95% CI) |
|---|---|---|---|---|
| **All settings + patients** (MANT 2009) | 51 | 81 | 2.64 (1.86-3.74) | 0.61 (0.55-0.68) |
| **LVSD in primary care** (MADHOK 2008) | - | - | 1.53 (1.17 - 1.19) | 0.85 (range 0.64 - 0.94) |
| **Emergency department** (WANG 2005) | 60 | 78 | 2.8 (1.9-4.1) | 0.51 (0.37-0.70) |

One study reported on the diagnostic accuracy of abnormal breath sounds in a subgroup of patients with a history of asthma or COPD [36]

Table 4.17: Diagnostic accuracy of abnormal breath sounds in patients with history of asthma or COPD

| | Sensitivity (%) | Specificity (%) | Positive likelihood ratio (95% CI) | Negative likelihood ratio (95% CI) |
|---|---|---|---|---|
| **Emergency department** (WANG 2005) | 71 | 73 | 2.6 (2.1-3.3) | 0.39 (0.28-0.55) |

### j). Fatigue

Two of the SRs reported on the diagnostic accuracy of fatigue [36,38]

Table 4.18: Diagnostic accuracy of fatigue

| | Sensitivity (%) | Specificity (%) | Positive likelihood ratio (95% CI) | Negative likelihood ratio (95% CI) |
|---|---|---|---|---|
| **LVSD in primary care** (MADHOK 2008) | - | - | 1.03 (0.84 - 1.25) | 0.98 (range 0.88 - 1.17) |
| **Emergency department** (WANG 2005) *(+ weight gain)* | 31 | 70 | 1.0 (0.74-1.4) | 0.99 (0.85-1.1) |

One study reported on the diagnostic accuracy of fatigue in a subgroup of patients with a history of asthma or COPD [36]

Table 4.19: Diagnostic accuracy of fatigue in patients with history of asthma or COPD

| | Sensitivity (%) | Specificity (%) | Positive likelihood ratio (95% CI) | Negative likelihood ratio (95% CI) |
|---|---|---|---|---|
| **Emergency department** (WANG 2005) | 74 | 34 | 1.1 (0.96-1.3) | 0.79 (0.54-1.2) |

**k). Hepatomegaly/ hepatic congestion**

One SR reported on the diagnostic accuracy of hepatomegaly [37]

Table 4.20: Diagnostic accuracy of hepatomegaly

| | Sensitivity (%) | Specificity (%) | Positive likelihood ratio (95% CI) | Negative likelihood ratio (95% CI) |
|---|---|---|---|---|
| **All settings + patients** (MANT 2009) | 17 | 97 | - | - |

One SR reported on the diagnostic accuracy of hepatic congestion in a subgroup of patients with a history of asthma or COPD [36]

Table 4.21: Diagnostic accuracy of heaptic congestion in patients with history of asthma or COPD

| | Sensitivity (%) | Specificity (%) | Positive likelihood ratio (95% CI) | Negative likelihood ratio (95% CI) |
|---|---|---|---|---|
| **Emergency department** (WANG 2005) | 14 | 94 | 2.4 (1.2-4.7) | 0.91 (0.84-1.0) |

### *4.1.4 Health Economic Methodological introduction*

The 2003 Guideline[22] highlighted the question of whether all patients with suspected heart failure should be referred for echocardiography, which would have substantial service implications. An economic model was constructed to compare this option with performing echocardiography only in patients with an abnormal ECG or natriuretic peptide measurement. The model found that the cost per life-year gained of echocardiography was very sensitive to the proportion of patients being sent for echocardiography who have the diagnosis of heart failure ultimately confirmed. The use of BNP (or NTproBNP) and ECG raises this proportion, and thus results in more efficient use of echocardiography facilities.

From our review, one UK cost-effectiveness analysis was identified and was presented to the GDG. This economic analysis assessed different diagnostic pathways in patients with chronic heart failure which may involve specialist clinical assessment of signs and symptoms, plasma concentration of natriuretic peptide (NP), and echocardiography (echo).

Mant et al. (2009)[37] presented economic modelling as part of their health technology appraisal (HTA). This economic analysis compared three diagnostic strategies for the assessment, in primary care, of patients with suspected chronic heart failure:

(1) 'Do nothing' (no more tests after evaluating symptoms and signs using a scoring system that they had developed - MICE (Male 2 points, history of myocardial

infarction 6 points, crepitations 5 points, and ankle oedema 3 points), which gives scores between 0 and 16 [6])

(2) 'NP' (following the evaluation of symptoms and signs, perform NP measurement then echo depending upon the result of the NP test, using decision cut off points for NP); and

(3) 'Echo' (following assessment of symptoms and signs, proceed straight to echo).

This economic modelling was conducted from a UK NHS perspective. The time horizon used was 6 months for the base case analysis, and 3 years for the secondary analysis. The sensitivity analysis considered time horizons of 5 and 10 years. The analysis included the cost of the diagnostic procedures (NP measurement and echocardiography) and the cost incurred when a patient with chronic heart failure was misdiagnosed and the treatment was delayed (hospitalisation and treatment costs). The diagnostic procedures' costs were varied in the sensitivity analysis.

Willingness to pay (WTP) thresholds for an additional case diagnosed were used to judge which strategy was the most cost-effective. In the base case analysis the threshold was assumed to be equal to the cost of a delay of up to 6-months for treating a patient with chronic heart failure who was misdiagnosed in the first instance, taking into account the impact on resource use (hospitalisation and treatment costs). For a secondary analysis, cost per additional case found was again reported but this time the WTP threshold was re-calculated by estimating the quality adjusted life years (QALY)s gained from early diagnosis (impact of early diagnosis on survival and quality of life) estimated for a 3-year time horizon using a threshold of £20,000 per QALY. WTP thresholds using QALYs gained were also calculated for 5- and a 10-year time horizons for use in the sensitivity analysis.

The sensitivity and specificity of natriuretic peptide measurement at different cut off points were taken from the meta-analysis presented in the HTA. [37] Echocardiography (including specialist assessment) was taken to be the reference standard. The probability of a patient having chronic heart failure was determined by the MICE scoring system. Incremental cost-effectiveness ratios (ICERs) were calculated comparing 'do nothing' versus 'NP', 'NP' versus 'echo', and 'do nothing' versus 'echo'. Results were compared to the WTP thresholds. For the different analyses, the most cost-effective option was presented by subgroup of patients as stratified by the MICE score. Table 4.22 presents the quality and applicability assessment of this analysis.

**Table 4.22: Economic study assessment**

| Study | Study quality* | Study applicability** |
|---|---|---|
| Mant 2009[37] | Minor limitations (a) | Directly applicable |

*Very serious limitations / Potentially serious limitations / Minor limitations; ** Directly applicable / Partially applicable / Not applicable

(a) Not all parameters subjected to uncertainty were varied in the sensitivity analysis

### *4.1.5 Health economic evidence statements*

Table 4.23 presents the results of the Mant et al. (2009) analysis[37]. These results suggested that, if patient benefits in terms of improved life expectancy and quality of life were taken into account (the QALY analysis), the optimum strategy was to refer patients with a low MICE score to natriuretic peptide measurement before echo, and other patients to echo directly.

[6] Clinical Scoring System to determine risk of heart failure (Male; Infarction; Crepitations; oEdema).

When the analysis did not consider life expectancy and quality of life (QALYs), patient management would depend on the MICE score. No further investigation was necessary for low MICE scores; natriuretic peptide (NP) measurement prior to echo (if NP raised above threshold) was required for intermediate scores; and referral directly to echo for high MICE scores. The QALY analysis is more in accord with NICE policy and therefore more relevant to the guideline.

The main limitation of this analysis is that if there is limited access to echo then this would lead to a delay in investigation which would offset the potential advantages of earlier diagnosis. This was not assessed in the sensitivity analysis. In addition, it was assumed echo plus clinical assessment was taken as the reference standard, and this can be challenged for diagnosis of some cases of heart failure with preserved ejection fraction.

**Table 4.23: Results – Mant 2009 economic analysis**

| **WTP £2,370 – Considering QALY gain at 3 years – Echo £100; NP £15** | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **MICE score** | **0** | **2** | **3** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **13** | **14** | **16** |
| ***Incremental Cost Effectiveness analysis*** | | | | | | | | | | | | | |
| ICER (echo v NP) | £3,227 | £810 | Echo* | Echo* | Echo* | | | | | | | | |
| ICER (echo v nothing) | £1,111 | £667 | £500 | £323 | £270 | | | | | | | | |
| ICER (NP v nothing) | £961 | £661 | £520 | £355 | £302 | | | | | | | | |
| **Decision** | NP | Echo | Echo | Echo | Echo | Echo** | Echo | Echo | Echo | Echo | Echo | Echo | Echo |
| **Sensitivity analysis – WTP £2,370 – Considering QALY gain at 3 years – Echo £150; NP £10 (least favourable to echo)** | | | | | | | | | | | | | |
| **MICE score** | **0** | **2** | **3** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **13** | **14** | **16** |
| ***Incremental Cost Effectiveness analysis*** | | | | | | | | | | | | | |
| ICER (echo v NP) | £6,488 | £3,882 | £2,605 | £915 | £273 | | | | | | | | |
| ICER (echo v nothing) | £1,667 | £1,000 | £750 | £484 | £405 | | | | | | | | |
| ICER (NP v nothing) | £1,083 | £809 | £659 | £472 | £408 | | | | | | | | |
| **Decision** | NP | NP | NP | Echo | Echo | Echo** | Echo | Echo | Echo | Echo | Echo | Echo | Echo |
| **Sensitivity analysis – WTP £3,470 – Considering QALY gain at 5 years – Echo £150; NP £10 (least favourable to echo)** | | | | | | | | | | | | | |
| **MICE score** | **0** | **2** | **3** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **13** | **14** | **16** |
| ***Incremental Cost Effectiveness analysis*** | | | | | | | | | | | | | |
| ICER (echo v NP) | £6,934 | £3,491 | £2,017 | | | | | | | | | | |
| ICER (echo v nothing) | £1,667 | £1,000 | £750 | | | | | | | | | | |
| ICER (NP v nothing) | £1,281 | £900 | £712 | | | | | | | | | | |
| **Decision** | NP | NP | Echo | Echo** | Echo | Echo | Echo | Echo | Echo | Echo | Echo | Echo | Echo |
| **Sensitivity analysis – WTP £5,370 – Considering QALY gain at 10 years – Echo £150; NP £10 (least favourable to echo)** | | | | | | | | | | | | | |
| **MICE score** | **0** | **2** | **3** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **13** | **14** | **16** |
| ***Incremental Cost Effectiveness analysis*** | | | | | | | | | | | | | |
| ICER (echo v NP) | £6,409 | £2,231 | | | | | | | | | | | |
| ICER (echo v nothing) | £1,667 | £1,000 | | | | | | | | | | | |
| ICER (NP v nothing) | £1,469 | £972 | | | | | | | | | | | |
| **Decision** | NP | Echo | Echo** | Echo | Echo | Echo | Echo | Echo | Echo | Echo | Echo | Echo | Echo |
| | | | | | | | | | | | | | |
| **WTP £270 – Not considering QALYs – Echo £100; NP £15** | | | | | | | | | | | | | |
| **MICE score** | **0** | **2** | **3** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **13** | **14** | **16** |
| ***Incremental Cost Effectiveness analysis*** | | | | | | | | | | | | | |
| ICER (echo v NP) | £1,356 | £959 | £780 | £570 | £490 | £384 | £296 | £200 | £94 | Echo* | | | |
| ICER (echo v nothing) | £1,111 | £667 | £500 | £323 | £270 | £222 | £192 | £169 | £152 | £139 | | | |
| ICER (NP v nothing) | £669 | £378 | £300 | £224 | £206 | £187 | £176 | £166 | £157 | £149 | | | |
| **Decision** | No test | No test | No test | NP | NP | NP | NP | Echo | Echo | Echo | Echo** | Echo | Echo |

| **Sensitivity analysis – WTP £270 – Not considering QALYs – Echo £50; NP £20 (most favourable to echo)** | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **MICE score** | **0** | **2** | **3** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **13** | **14** | **16** |
| ***Incremental Cost Effectiveness analysis*** | | | | | | | | | | | | | |
| ICER (echo v NP) | £661 | £410 | £263 | Echo* | Echo* | | | | | | | | |
| ICER (echo v nothing) | £556 | £333 | £250 | £161 | £135 | | | | | | | | |
| ICER (NP v nothing) | £498 | £310 | £247 | £182 | £161 | | | | | | | | |
| **Decision** | No test | No test | Echo | Echo | Echo | Echo** | Echo | Echo | Echo | Echo | Echo | Echo | Echo |
| **Sensitivity analysis – WTP £270 – Not considering QALYs – Echo £150; NP £10 (least favourable to echo)** | | | | | | | | | | | | | |
| **MICE score** | **0** | **2** | **3** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **13** | **14** | **16** |
| ***Incremental Cost Effectiveness analysis*** | | | | | | | | | | | | | |
| ICER (echo v NP) | £1,837 | £1,214 | £962 | £702 | £627 | £533 | £475 | £420 | £361 | £305 | £168 | £103 | Echo* |
| ICER (echo v nothing) | £1,667 | £1,000 | £750 | £484 | £405 | £333 | £288 | £254 | £227 | £208 | £181 | £174 | £163 |
| ICER (NP v nothing) | £878 | £458 | £353 | £261 | £241 | £222 | £211 | £204 | £197 | £192 | £182 | £179 | £172 |
| **Decision** | No test | No test | No test | NP | NP | NP | NP | NP | NP | NP | Echo | Echo | Echo |

* Echo dominates NP

** When Echo was shown to be the optimal intervention to be undertaken after clinical assessment for a specific MICE score, Echo was also the preferred intervention for higher MICE scores. ICERs were not reported by the autors for these higher MICE scores, where Echo was the preferred option.

### 4.1.6 From evidence to recommendations

The GDG recognised that the definition of heart failure was crucial to the interpretation of results of diagnostic studies. Studies, focussing on left ventricular systolic dysfunction (LVSD) alone would have different results from those that used a more inclusive definition of heart failure that included heart failure with preserved left ventricular ejection fraction (HFPEF). The GDG favoured a more inclusive definition (see section 2.1). While individual symptoms and signs appeared to be of limited utility, the GDG considered the potential role of a constellation of symptoms and signs in a scoring system. The clinical and health economic evidence on the MICE score suggested that patients in whom heart failure is suspected, who have a history of myocardial infarction, or have basal crepitations, or are males with ankle oedema, should be referred directly for echocardiography without undergoing any 'rule out' test such as ECG or NP as had been recommended in the 2003 guideline. The GDG were concerned whether the scoring system was practical in a clinical context. There were reservations by some GDG members over the reliability of ankle oedema and lung crepitations as signs of heart failure when obtained by GPs outside of the research setting. The GDG agreed with the concept that patients who had a high probability of having heart failure should be referred straight for echocardiography. It was noted that the economic model underpinning the MICE score assumed that the echocardiography was carried out immediately and that implicitly, the cost effectiveness of the strategy depended upon the ability to perform echocardiography in a timely fashion. Heart failure has a poor prognosis, early treatment is important, thus the GDG felt that comparisons with cancer services were appropriate. The improved prognosis of heart failure patients with left ventricular systolic dysfunction in the last decade[12] is likely to be related to the greater use of pharmacological therapy. Mortality within the first month of diagnosis remains high, 6%. The GDG noted that diagnosis did not revolve purely around the results of echocardiography. It was important to identify the type and severity of the cardiac abnormality responsible for the heart failure syndrome, and that the cost effectiveness of the use of the MICE score was contingent upon immediate initiation of appropriate management after diagnosis. The GDG felt that it was important to specify not just that the patient should have an echocardiogram, but also should be reviewed by a member of the specialist multi-disciplinary team.

The GDG discussed what factors might initiate an urgent referral for echocardiography without any 'rule out' tests. The GDG agreed that history of myocardial infarction was the important component of the MICE score to be adopted. The GDG recognised that high probability of heart failure also exists when there is a previous history of heart failure or when there is a history of rapid deterioration of breathing. They felt that such patients would be managed as an acute exacerbation of heart failure (which is outside the scope of this guideline).

The GDG considered the issue of people who have risk factors for heart failure (advanced age, hypertension, diabetes mellitus, family medical history of cardiomyopathy, and family history of premature coronary heart disease). The presence of these risk factors would not significantly alter the probability of heart failure in the context of presenting symptoms, therefore it would be inappropriate to recommend immediate use of echocardiography in such circumstances.

Other imaging modalities are important where the patient is not a good echo subject, or when further information is required to assess the presence of any underlying pathology such as ischaemia, certain types of cardiomyopathy or myocardial infiltration. It is important in the assessment to define whether heart failure is caused by left ventricular systolic dysfunction, or whether it is associated with preserved left ventricular ejection fraction. Other cardiac abnormalities such as valvular heart disease will need to be detected and defined.

### *4.1.7 Recommendations*

The recommendations were drafted after all the evidence for circulating natriuretic peptides had been considered.

## 4.2 Measurement of circulating natriuretic peptide concentration

**BNP1: natriuretic peptides vs gold standard**

What is the accuracy of natriuretic peptides *vs.* gold standard in the diagnosis of heart failure?

**BNP2: natriuretic peptides vs echocardiography**

What is the diagnostic accuracy of echo *vs.* natriuretic peptides in the diagnosis of diastolic dysfunction?

### *4.2.1 Clinical introduction*

The guidance of 2003 into the diagnosis and treatment of heart failure had highlighted the high negative predictive value of natriuretic peptides (NP) in heart failure. Measurement of these peptides could be useful to rule out the diagnosis of heart failure. There are several conditions that may affect the serum NP levels beyond heart failure, for example LVH, ischaemia, tachycardia, RV overload, hypoxaemia (including pulmonary embolism), renal dysfunction, sepsis, advanced age and cirrhosis of the liver.

**Reason for review**

In the last few years, evidence has accumulated on the use of natriuretic peptides[39] in two diagnostic settings:

1. The diagnosis of heart failure, as a screening test for patients suspected of having heart failure
2. The diagnosis of heart failure in the absence of left ventricular systolic dysfunction. Two options exist:
    a. Using natriuretic peptides in all patients suspected of having heart failure. The patient is then assigned to either heart failure with left ventricular systolic dysfunction, or heart failure with preserved left ventricular ejection fraction according to the left ventricular ejection fraction measured on echocardiography.
    b. Using natriuretic peptides following echocardiography in patients with suspected heart failure, if the left ventricular ejection fraction is preserved.

The GDG agreed to look at the issue of natriuretic peptides as a diagnostic tool for heart failure, for heart failure with preserved left ventricular ejection fraction and in serial monitoring (addressed in a later chapter).

### *4.2.2 BNP1: natriuretic peptides vs gold standard*

**What is the accuracy of natriuretic peptides *vs.* gold standard in the diagnosis of heart failure?**

#### 4.2.2.1 Clinical Methodological introduction

One Health Technology Assessment (HTA) was identified. The HTA reported the findings of a meta-analysis of studies comparing brain natriuretic peptide with a clinical diagnosis ('gold standard') of heart failure (search July 2006) [37]. No additional studies were identified.

'Gold standard' was defined as a prospective planned evaluation of a clinical diagnosis including all information, for example using European Society of Cardiology criteria (ESC) [37]. Of the twenty studies comparing BNP with the reference standard (clinical diagnosis), fourteen performed the reference test independent of the index test. Of the sixteen studies comparing NT-pro BNP with the reference standard (clinical diagnosis), fourteen performed the reference test independent of the index test.

The HTA excluded studies with an inappropriate reference standard, e.g. those that used measures of diastolic dysfunction alone or pulmonary capillary wedge pressure; retrospective study design, e.g. reference standard using a hospital discharge diagnosis of heart failure; used a case-control design; or that provided results such that 2x2 data could not be extracted.[37]

The meta-analysis pooled the sensitivities, specificities and likelihood ratios for each primary study across the different BNP and NT-pro BNP cut off points.

***BNP vs reference standard (N=20 studies)***

*Prevalence*

The prevalence of heart failure (proportion of true positives) varied according to the setting. See table below for a breakdown of the prevalence of clinically diagnosed heart failure reported according to referral setting [37].

Table 4.24: Prevalence of heart failure by care setting

| Setting | Prevalence (true positives/population) (%) | Prevalence range minimum – maximum |
|---|---|---|
| Total population N=5030 (N=20) | 2056/5030 (40.87%) | 5.49 to 91.67% |
| General practice setting N=678 (N=2) | 67/678 (9.89%) | 5.49 to 12.84% |
| GP patients referred to open access HF or echocardiography clinics N=507 (N=3) | 152/507 (29.98%) | 22.90 to 50.60% |
| Emergency Dept. setting N=3587 (N=12) | 1875/3587 (52.27%) | 35.0 to 91.67% |
| Inpatient setting N=258 (N=3) | 114/258 (44.29%) | 28.57 to 49.18% |

*Reference standard*

The reference tests included ESC criteria (2 or more cardiologists) N=4 studies; and clinical consensus (typically two cardiologists) N=8 studies) [37].

*Study quality*

Studies were of moderate to high quality as assessed using the Quality Assessment of Diagnostic Studies (QUADAS) checklist: 11/20 studies were unclear or did not test consecutive patients or a random selection of consecutive patients; 6/20 studies did not describe or had unclear selection criteria; 5/20 studies did not have or were unclear with respect to whether there was a short time period between the index and reference test such

that the target condition would not have changed between the two tests; 8/20 studies did not explain or were unclear regarding whether the reference test results were interpreted without knowledge of the results of the index test; and 16/20 did not explain or were unclear with respect to the explanation of withdrawals.[37]

### *NT-proBNP vs reference standard (N=16 studies)*

*Prevalence*

See Table **4.25** below for a breakdown of the prevalence of clinically diagnosed heart failure reported according to referral setting [37].

Table 4.25: Prevalence of heart failure according to referral setting

| Setting | Prevalence true positives/population (%) | Prevalence range minimum - maximum |
|---|---|---|
| Total population N=4280 (N=16) | 1176/4280 (27.48%) | 5.86 to 82.02% |
| General practice setting N=1469 (N=4) | 67/1469 (4.56%) | 5.49 to 12.84% |
| GP patients referred to open access HF or echocardiography clinics N=1031 (N=4) | 152/1021 (14.74%) | 22.95 to 50.60% |
| Emergency Dept. setting N=1407 (N=6) | 543/1407 (38.59%) | 27.32 to 82.02% |
| Outpatient setting N=119 (N=1) | 71/119 (59.66%) | NA |
| Inpatient setting N=254 (N=1) | 138/254 (54.33%) | NA |

**NA** Not applicable

*Reference standard*

The reference tests included ESC criteria of 2 or more cardiologists (N=4 studies) and clinical consensus typically two cardiologists (N=8 studies).[37]

*Study quality*

Studies were of moderate to high quality as assessed using the QUADAS checklist: 6/16 studies were unclear or did not test consecutive patients or a random selection of consecutive patients; 3/16 studies did not describe or had unclear selection criteria; 6/16 studies did not have or were unclear with respect to whether there was a short time period between the index and reference test such that the target condition would not have changed between the two tests; 5/16 studies did not explain or were unclear regarding whether the reference test results were interpreted without knowledge of the results of the index test; and 7/16 did not explain or were unclear with respect to the explanation of withdrawals [37].

### 4.2.2.2 Clinical Evidence Statement:

See Table **4.26** and Table **4.27** below for the findings of the meta-analysis on the diagnostic accuracy of BNP and NT-proBNP compared with the reference standard[37].

Table 4.26: Diagnostic accuracy of BNP compared to clinical diagnosis

| Setting (no. of studies) | Sensitivity (95%CI) | Specificity (95%CI) | Positive likelihood ratio (95%CI) | Negative likelihood (95%CI) | Diagnostic Odd Ratio (95%CI) |
|---|---|---|---|---|---|
| **Overall (N=20)** | 0.93 (0.91 to 0.95) | 0.74 (0.63 to 0.83) | 3.57 (2.44 to 5.21) | 0.09 (0.06 to 0.13) | 39.5 (21.44 to 72.6) |
| **General Practice (N=4)** | 0.84 (0.72 to 0.92) | 0.73 (0.65 to 0.80) | 3.12 (2.22 to 4.39) | 0.22 (0.11 to 0.42) | 14.3 (5.45 to 37.8) |

Table 4.27: Diagnostic accuracy of NT-proBNP compared with a clinical diagnosis

| Setting (no. of studies) | Sensitivity (95%CI) | Specificity (95%CI) | Positive likelihood ratio (95%CI) | Negative likelihood (95%CI) | Diagnostic Odd Ratio (95%CI) |
|---|---|---|---|---|---|
| **Overall (N=16)** | 0.93 (0.88 to 0.96) | 0.65 (0.56 to 0.74) | 2.70 (2.12 to 3.43) | 0.11 (0.07 to 0.18) | 24.6 (14.4 to 42.2) |
| **General Practice (N=8)** | 0.90 (0.81 to 0.96) | 0.60 (0.50 to 0.70) | 2.28 (1.82 to 2.86) | 0.16 (0.09 to 0.30) | 14.3 (7.73 to 26.5) |

### 4.2.2.3 Cut-off points for BNP and NT-proBNP for different post-test probabilities

(This table is reproduced from Mant et al (2009)[37].

| | MICE score | 0 | 2 | 3 |
|---|---|---|---|---|
| Post-test probability | | | | |
| 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 |

#### 4.2.2.4 Health Economic Methodological introduction

One UK cost-effectiveness analysis was identified from the economic review and was presented to the GDG. Mant et al. (2009)[37] developed this economic analysis as part of their health technology appraisal (HTA). They assessed different diagnostic pathways in patients with chronic heart failure, which may involve specialist clinical assessment of symptoms and signs, plasma concentration of natriuretic peptide, and echocardiography. This analysis was detailed in Section 4.1.4.

#### 4.2.2.5 Health Economic Evidence:

As detailed in Section 4.1.5, the Mant et al. (2009) cost-effectiveness analysis[37] suggested that the optimum strategy was, after assessment of symptoms and signs, to refer patients with a low MICE score to natriuretic peptide measurement before echo, and other patients to echo directly.

#### 4.2.2.6 From Evidence to Recommendation:

The GDG noted that the systematic review included studies that investigated the value of natriuretic peptides in diagnosing heart failure. It was felt that including studies that looked at all heart failure patients reflects clinical practice, where many patients admitted with heart failure do not have significantly reduced left ventricular ejection fraction. Nevertheless, including studies limited to left ventricular systolic dysfunction would not have altered the outcome of the review.

The quality of the evidence was moderate to high in the studies that utilised either BNP or NT-pro-BNP versus the clinical diagnosis of heart failure.

The GDG noted that the 2003 guidance proposed using natriuretic peptides when available. It was felt that this may have given the impression that their use was optional, contributing to low uptake. The GDG were impressed by the high negative predictive value of natriuretic peptides in the diagnosis of heart failure, and felt that this confirmed their potential value as a 'rule out test' - i.e. a low serum natriuretic peptide level in an untreated patient makes heart failure an unlikely cause for the patient's presentation.

However, the moderate specificity reflects that there are other causes of a raised natriuretic peptide level than heart failure.

Although cut-off points may vary according to the assay used, and would depend upon the clinical features (as per Mant et al analysis), the GDG noted the strong feedback from stakeholders that indicated natriuretic peptide 'cut off' levels would be important. The GDG noted that the evidence based cut off levels proposed in the Mant et al HTA were consistent with the consensus based recommendations of the European Society of Cardiology, but felt that having different levels for different clinical features would be difficult to implement.

The GDG noted that the evidence reviewed was of the role of natriuretic peptides in the diagnosis of chronic and not acute heart failure.

An advantage of measuring natriuretic peptide is that it can be performed straight away. This may alleviate anxiety more rapidly if it is normal, but may raise anxiety if further assessment is required. The GDG noted outside the evidence presented that the level of the natriuretic peptide was of prognostic as well as diagnostic value as it may identify patients with high chance of mortality irrespective of the cause of its rise.

The GDG were also aware that a high natriuretic peptide level is not only of diagnostic significance, but also of prognostic significance. Baseline natriuretic peptide level is predictive of risk of both subsequent hospitalisation and mortality, and these excess risks are manifest early after diagnosis. [40]. Therefore, it follows that people with very high natriuretic peptide levels (at a level of NT-pro BNP >2530 pg/ml from the Kubanek data) should be

diagnosed and treated as a matter of urgency. The GDG felt that investigation and therapy of those suspected of having heart failure should be no longer than 2 weeks for those with prior myocardial infarction or high natriuretic peptide (because of their worse prognosis and high probability of heart failure); and within 6 weeks for those with intermediate natriuretic peptide levels. The time limits are important to specify since the benefits of diagnosis (in terms of both reduced costs to the NHS and increased benefits to patients) diminish over time.

The GDG agreed to adopt the following thresholds:

1. BNP>400 pg/ml (>116 pmol/l) or NT-proBNP>2000 pg/ml (>236 pmol/l): Need an echocardiogram and specialist clinical assessment no longer than 2 weeks from the time of presentation.
2. BNP 100-400 pg/ml (29-116 pmol/l) or NT-proBNP 400-2000 pg/ml (47-236 pmol/l): Need an echocardiogram and clinical assessment by the Specialist within 6 weeks from the time of presentation.
3. BNP <100 pg/ml (<29 pmol/l) or NT-proBNP <400 pg/ml (<47 pmol/l), in the absence of heart failure therapy: Heart Failure is an unlikely cause for the presentation.

Natriuretic peptides can be raised in patients with no evidence of heart failure, such as: left ventricular hypertrophy, myocardial ischaemia, pulmonary hypertension, hypoxia, pulmonary embolism, right ventricular strain, COPD, liver failure, sepsis, diabetes and renal failure - even in the early stages of chronic kidney disease (GFR <60 ml/min). In addition, age >70 years and female gender increase baseline levels of natriuretic peptides (McDonagh TA, et al).[41]

On the other hand, caution must be exercised when interpreting the natriuretic peptides levels in the presence of obesity (BMI>35 kg/$m^2$) and therapy with diuretics, angiotensin converting enzyme inhibitors, beta-blockers, angiotensin receptor blockers and aldosterone antagonists, since these factors are associated with lower natriuretic peptide levels.

The GDG reflected on the 2003 guidance, which recommended either a natriuretic peptide or an ECG being performed as a triage test prior to echocardiography. In this 2010 update, the evidence for ECG was not reviewed, though it was noted that the systematic review by Mant et al had found ECG to be inferior to natriuretic peptide testing as a diagnostic test in heart failure, and did not increase diagnostic precision if added to a natriuretic peptide test and clinical assessment. Furthermore, the performance characteristics of ECG as a test for heart failure can be poor in primary care settings. {Khunti, 2004 4751 /id}. The GDG were of the opinion that performing an ECG should be part of the general assessment of a patient in whom heart disease was suspected to determine the patient's rhythm, heart rate control, the presence of conduction abnormalities, the duration of the QRS complex (to determine the appropriateness of cardiac re-synchronisation therapy), and to monitor heart failure patients having their beta-blocking doses up-titrated. While it was no longer recommended as part of the diagnostic algorithm for heart failure (being replaced by natriuretic peptide), the GDG wished to emphasise that the electrocardiogram remains an essential test to be performed in all patients with heart failure.

#### 4.2.2.7 Recommendations

The recommendations were drafted after all the evidence for circulating natriuretic peptides had been considered.

### *4.2.3 BNP2: natriuretic peptides vs echocardiography*

**What is the diagnostic accuracy of echo *vs.* natriuretic peptides in the diagnosis of diastolic dysfunction?**

#### 4.2.3.1 Clinical Methodological Introduction:

Studies were included that reported on the diagnostic accuracy (sensitivity, specificity, positive and negative predictive values) of either BNP or NT-proBNP compared to echocardiogram in patients with suspected heart failure with preserved left ventricular ejection fraction.

Eight prospective studies were included in the review {Hettwer, 2007 241 /id;Islamoglu, 2008 489 /id;Abhayaratna, 2006 784 /id;Dong, 2006 874 /id;Tschope, 2005 1871 /id;Wei, 2005 1927 /id;Knebel, 2008 2794 /id;Lubien, 2002 2929 /id}. The table below summarises the populations covered by the studies, these varied from a population sample of adults 60 to 86 years[42] to patients with preserved LV function and normal LV dimensions as determined by echocardiography and ventriculography[43].

The details of these studies are summarised in the table below. They were reported under the categories:

- Natriuretic peptides vs. Echo measures (N=3)
- Different natriuretic peptide levels and their concordance with echo (N=5)

The first group reported on the diagnostic accuracy of natriuretic peptides compared to the diagnostic accuracy of a variety of commonly used echo measures [43-45]. One study compared results with healthy controls [44].

The second group of studies looked at the diagnostic accuracy of differing levels of natriuretic peptides and their concordance with either an echo diagnosis of diastolic dysfunction or with different echo measures commonly used to diagnose diastolic dysfunction [42,46-49]. Two studies compared results with a group of healthy controls [46,48].

All of the studies had at least one area of possible bias. It was unclear in all the trials whether the natriuretic peptide results had been interpreted without knowledge of the results of the echocardiogram. The time period between the echocardiogram and natriuretic peptide test was unclear in six studies [42-44,48-50]. It was also unclear in six studies whether the same clinical data was available when the natriuretic peptide test results were interpreted in the studies as would be available when the test is used in practice [42-44,47-49].

**Limitations**

Echocardiographic measures were used to confirm the diagnosis of diastolic dysfunction in most of these studies. However these measures are an imperfect gold standard for the diagnosis of heart failure with preserved left ventricular ejection fraction.

All the studies reported different BNP or NT-proBNP levels, different echo measures and used different criteria for diagnosing diastolic dysfunction making it difficult to combine their findings and produce a definitive conclusion.

## Summary of methodological characteristics of included studies

Table 4.28: Methodological characteristics of studies considering Natriuretic peptides vs. Echo measures

| | Aim of trial | Population | Type of test | Comparison | Diagnosis of diastolic dysfunction |
|---|---|---|---|---|---|
| **Islamoglu 2008**<br><br>N=30 | To look at the diagnostic performance of NT-proBNP in the assessment of post-operative left ventricular diastolic dysfunction in patients undergoing CABG, by comparing NT-proBNP with echo results (Ea + E/Ea ratio). | Patients who were undergoing coronary artery bypass graft (CABG) | N-Terminal Pro-Brain Natriuretic peptide<br><br>**NT-proBNP** | **Echocardiogram**<br><br>E/Ea ratio ≤15 diastolic function was normal; E/Ea >15 diastolic function was defined as abnormal. | When the echo measures:<br>- Ea <8 cm/s<br>- E/Ea >15<br>the diastolic function was defined as abnormal. |
| **Hettwer 2007**<br><br>**N=140** | To look at the diagnostic value of tissue Doppler imaging, flow propagation velocity and NT-proBNP in comparison with standard echo parameters in diastolic dysfunction. | Patients admitted to the cardiology department for:<br>1) dyspnoea of cardiac origin<br>2) clinical signs of heart failure with normal left ventricular systolic function<br>3) longstanding arterial hypertension | **NT-proBNP** | **Echocardiogram**<br><br>Myocardial relaxation velocity<br><br>Flow propagation velocity of transmitral inflow | In agreement with the guidelines of the 'European Study on Diastolic Heart Failure'- split into 3 patterns according to different echo measures (E/A ratio, DT, IVRT, S/D ratio):<br>1. impaired relaxation pattern.<br>2. pseudomormal pattern<br>3. restrictive pattern<br>(- figures provided) |

| | Aim of trial | Population | Type of test | Comparison | Diagnosis of diastolic dysfunction |
|---|---|---|---|---|---|
| **Tschope 2005**<br><br>N=118 | To look at the accuracy of NT-proBNP at detecting isolated diastolic dysfunction in comparison to left and right heart catherization, transmitral Doppler echo, pulmonary venous Doppler and tissue Doppler imaging in patients with suspected chronic heart failure despite preserved LV systolic function. | Patients with preserved LV function and normal LV dimensions as determined by echocardiography and ventriculography. | **NT-proBNP** | Echocardiography<br>Diastolic dysfunction diagnosed by abnormal values Tau, IVRT, DT, and/or by the E/A ratio | In agreement with the guidelines of the 'European Study on Diastolic Heart Failure'- the diagnosis of diastolic dysfunction was defined after the evidence of abnormal LV relaxation, filling, and/or diastolic distensibility in the presence of clinical signs of CHF, with demonstrable normal or only mildly impaired systolic function (EF>50%).<br>(- figures provided) |

*E: early phase wave representing the early phase filling of the ventricle as seen on Doppler flow pattern through the mitral and tricuspid valves on echocardiography*
*A: late phase (atrial) wave representing the late phase filling of the ventricle as seen on Doppler flow pattern through the mitral and tricuspid valves on echocardiography*
*Ea: early diastolic phase wave on tissue Doppler imaging of the mitral valve annulus on echocardiography*
*DT: Deceleration time of the E wave*
*S/D ratio: The ratio between the systolic and the diastolic waves on the trans-pulmonary venous flow pattern on Doppler echocardiography*
*Tau: The time constant of relaxation (one of the measures of the diastolic function of the ventricle).*

Table 4.29: Methodological characteristics of studies considering different natriuretic peptide levels and their concordance with echo

| | Aim of trial | Population | Type of test | Comparison | Diagnosis of diastolic dysfunction |
|---|---|---|---|---|---|
| Knebel 2008<br><br>N=137 | To assess the diagnostic value of NT-proBNP and the concordance with Tissue Doppler Echo (strain imaging, longitudinal displacement, E/E') in diastolic and systolic heart failure. (no diagnostic accuracy data provided for echo)<br><br>Controls vs. diastolic heart failure + systolic heart failure. | Patients with a clinical indication for echo from medical and surgical departments who were clinically stable (inpatients and outpatients)<br><br>31% diastolic dysfunction with preserved left ventricular function<br><br>31% healthy controls<br><br>38% systolic heart failure EF < 55% | NT-proBNP | Echocardiogram | Normal LVEF (≥55%), E/E'>10, E/A <1. The transmitral flow and TDI measures were adjusted to age-related cut off points. |
| Dong 2006<br><br>N=191 | To look at the correlation between different NT-proBNP levels with echo measurements of both systolic and diastolic function. E/Em measure used to diagnose diastolic dysfunction. (no data provided for echo). | Patients with history, symptoms, and/or physical findings compatible with cardiovascular disease (n=148) This group was subdivided in to:<br><br>1. those with LVEF ≥55%<br><br>2. those with LVEF <55%<br><br>Compared with healthy controls (n=43) | NT-proBNP | Echocardiogram<br><br>E/Em = mitral early filling wave to Doppler tissue early diastolic mitral annulus velocity ratio | Assessed by pulsed wave Doppler (PWD) transmitral inflow (LVEF, Em, E/Em ratio, E/A ratio, DT, IVRT, A wave and E wave). (no figures provided) |

| | Aim of trial | Population | Type of test | Comparison | Diagnosis of diastolic dysfunction |
|---|---|---|---|---|---|
| Abhayaratna 2006<br><br>N=1229 | To evaluate the ability of NT-proBNP to detect subjects with LV systolic dysfunction and diastolic dysfunction. Also to correlate NT-proBNP levels with clinical and echo findings in a sample of older patients (60-86 yrs) (no data provided for echo). | Population sample of adults 60 to 86 yrs | NT-proBNP | Echocardiography<br><br>Tissue Doppler measures used to determine diastolic dysfunction. | Graded as 3 categories (mild, moderate, severe) using Doppler evaluation of the mitral and pulmonary venous inflow and tissue Doppler of the lateral mitral annulus motion.<br><br>(no figures provided) |
| Lubien 2002<br><br>N=294 | To look at the accuracy of different levels of BNP in diagnosing diastolic abnormalities in patients with normal systolic function who were referred for echo. The diagnostic utility of BNP alone was compared with the echocardiographic probability of LV dysfunction. | Patients referred for Echo to evaluate LV dysfunction | Triage BNP assay | Echocardiography<br><br>Echo Doppler velocity (E, A velocities, IVRT, DT) | Classified in 3 categories:<br><br>1. impaired relaxation<br><br>2. pseudonormal<br><br>3. restrictive like<br><br>According to echo measures (E/A ratio, IVRT, DT, PVd/PVs)<br><br>(- figures provided) |
| Wei 2005<br><br>N=135 | To assess the value of bedside testing of BNP in the diagnosis of diastolic dysfunction in hypertensive patients. (no data for echo) | Consecutive Chinese patients with a history of hypertension for an average of 9.3 ± 7.8 (1-30 yrs). | BNP | Echocardiogram<br><br>Measures:<br><br>Doppler echo of transmitral flow, E and A peaks, diastolic time and the isovolumic relaxation time. | Based on 3 criteria:<br><br>1.) the presence of signs or symptoms of congestive heart failure,<br><br>2.) the echo measured LVEF >50%<br><br>3.) Echo evidence of abnormalities of left ventricular relaxation: |

| | Aim of trial | Population | Type of test | Comparison | Diagnosis of diastolic dysfunction |
|---|---|---|---|---|---|
| | | | | | E/A ratio <1.0 (<55 yrs old) or <0.8 (>55 yrs old); E peak deceleration time of more than 240 ms or isovolumic relaxation time <90ms. |

Echo measures:

Diastolic transmitral Doppler parameters:

- IVRT = Isovolumic relaxation time
- DT = early diastolic deceleration time
- E/A ratio = peak of early E and late A diastolic mitral flow velocities (early filling/atrial filling peak velocities)
- FPV = LV flow propagation velocity
- E/Em ratio: mitral E wave to Doppler tissue early diastolic lateral annulus velocity ratio

PVs and PVd = Pulmonary vein velocities during systole and diastole

PVd/PVs: the ratio between the amplitudes of diastolic wave of the pulmonary venous flow (PVd) to the systolic wave of the pulmonary venous flow on Doppler

LVESD and LVEDD = LV end-systolic and end-diastolic diameters

LVMI = Left ventricular mass index (evaluates hypertrophy)

PWT = end-diastolic LV posterior wall thickness

IVST = end-diastolic interventricular septal thickness

LVEF = LV ejection fraction (systolic dysfunction = <55% EF)

TDI= tissue Doppler imaging

### 4.2.3.2 Cinical Evidence Statement:

Natriuretic peptides vs. Echo measures (N=3):

| STUDY | Sensitivity % | Specificity % | Positive predictive value % | Negative predictive value % |
|---|---|---|---|---|
| **ISLAMOGLU 2008** | | | | |
| NT-pro BNP >854pg/mL | 87.5 | 55 | NR | NR |
| E/Ea ratio >13.5 | 87.5 | 86.4 | | |
| **HETTWER 2007** | | | | |
| NT-pro BNP > 94pg/mL | 65.6 | 77.8 | NR | NR |
| Myocardial relaxation velocity | 82.8 | 77.8 | | |
| Flow propagation velocity of transmittal inflow (below 55.9 cms) | 74.2 | 77.8 | | |
| **TSCHOPE 2005** | | | | |
| NT-pro BNP cut-off 120pg/mL | 69 | 91 | 63 | 93 |
| E/A ratio | 71 | 87 | 55 | 93 |
| E/A | 53 | 79 | 36 | 88 |
| Isovolumic Relaxation Time (IVRT) | 69 | 60 | 27 | 90 |
| Ealry diastolic deceleration time (DT) | 33 | 79 | 26 | 84 |

Different natriuretic peptide levels and their concordance with echo (N=5):

**A summary of the results is presented in the table below.**

| STUDY | Sensitivity | Specificity | Positive predictive value | Negative predictive value |
|---|---|---|---|---|
| **KNEBEL 2008**<br>NT-proBNP 489pg/mL<br>Normal vs reduced LVEF | 81.6 | 85.2 | 75.5 | 89.3 |
| **DONG 2006**<br>NT-proBNP 150pg/mL<br>E/Em ≥ 8<br>NT-proBNP 550pg/mL<br>E/Em > 15 | 74<br><br>100 | 71<br><br>100 | NR | NR |
| **ABHAYARATNA 2006**<br>Men 60 to 86 yrs<br>NT-proBNP 240pg/mL<br>Moderate diastolic dysfunction[1]<br>Women 60 to 86 yrs<br>NT-proBNP 270pg/mL<br>Moderate diastolic dysfunction | 83<br><br><br><br>89 | 85<br><br><br><br>86 | NR | NR |
| **LUBIEN 2002**<br>BNP 17.5pg/mL<br>Diastolic dysfunction[1]<br>BNP 62pg/mL<br>Diastolic dysfunction<br>BNP 92pg/mL<br>Diastolic dysfunction<br>BNP 130pg/mL<br>Diastolic dysfunction | 97 (92 to 99)<br>85 (77 to 90)<br>74 (65 to 81)<br>62 (53 to 71) | 45 (37 to 52)<br>83 (77 to 88)<br>98 (94 to 99)<br>98 (94 to 99) | 54 (47 to 81)<br>78 (70 to 84)<br>96 (89 to 98)<br>95 (87 to 98) | 95 (88 to 98)<br>89 (83 to 93)<br>85 (79 to 89)<br>79 (73 to 84) |
| **WEI 2005 42[2]**<br>BNP 40pg/mL<br>Diastolic dysfunction[3] | 79 | 92 | NR | NR |
| | | | | |

### 4.2.3.3 Health Economic Methodological introduction

No relevant cost-effectiveness evidence was identified involving the diagnosis of patients with chronic heart failure and preserved LVEF using echocardiography or plasma concentration of natriuretic peptides.

### 4.2.3.4 From evidence to recommendations

The GDG considered the evidence from the eight reviewed papers[42-49]. The most important reservation was that with the exception of one study[43], the basic design was to determine the extent to which natriuretic peptides predicted one or more echocardiographic abnormalities that were taken as surrogate markers for 'diastolic dysfunction'. There is no consensus as to what these echocardiographic parameters should be, and no evidence that these parameters are an appropriate reference standard. A further issue was that each study concentrated on one parameter or a set of parameters, making it impossible to draw a general conclusion that could cover all the echo parameters.

The GDG members were interested in the paper by Tschope *et al*[43] that looked at both echo and natriuretic peptides and compared the diagnostic accuracy of both methods to cardiac catheterisation. Although cardiac catheterisation using volume/pressure loops would have been the ideal method, it is hardly used outside research protocols. This paper suggested almost equal accuracy for both echocardiographic parameters and natriuretic peptides, and that both performed reasonably well.

The GDG observed that one of the studies (Dong *et al*)[46] had a small cohort of patients, and this may well have resulted in reporting high accuracy levels that were unreliable.

The GDG noted the conclusions of Lubien *et al*[49]*,* that natriuretic peptides can not differentiate heart failure with preserved left ventricular ejection fraction from heart failure due to left ventricular systolic dysfunction. The presence of a raised natriuretic peptide with normal left ventricular contraction on echocardiography, raises the suspicion of heart failure with preserved left ventricular ejection fraction. However, a normal level of natriuretic peptide in a patient suspected of, but not treated for, heart failure makes heart failure an unlikely diagnosis.

The GDG concluded that the specialist may consider the need to check the natriuretic peptide level in the patients with previous myocardial infarction who were referred directly and urgently for an echocardiogram and specialist assessment if their left ventricular ejection fraction was normal.

#### 4.2.3.5 Recommendations

See Section 4.3 below.

## 4.3 Recommendations for diagnosing heart failure

R1 Take a careful and detailed history, and perform a clinical examination and tests to confirm the presence of heart failure. **[2010]**

R2 Refer patients with suspected heart failure and previous myocardial infarction (MI) urgently, to have transthoracic Doppler 2D echocardiography and specialist assessment within 2 weeks. **[new 2010] KPI**

R3 Measure serum natriuretic peptides (B-type natriuretic peptide [BNP] or N-terminal pro-B-type natriuretic peptide [NTproBNP] in patients with suspected heart failure without previous MI. **[new 2010] KPI**

R4 Because very high levels of serum natriuretic peptides carry a poor prognosis, refer patients with suspected heart failure and a BNP level above 400 pg/ml (116 pmol/litre) or an NTproBNP level above 2000 pg/ml (236 pmol/litre) urgently, to have transthoracic Doppler 2D echocardiography and specialist assessment within 2 weeks.**[new 2010] KPI**

R5 Refer patients with suspected heart failure and a BNP level between 100 and 400 pg/ml (29-116 pmol/litre), or an NTproBNP level between 400 and 2000 pg/ml (47-236 pmol/litre) to have transthoracic Doppler 2D echocardiography and specialist assessment within 6 weeks. **[new 2010]**

R6 Be aware that:

- obesity or treatment with diuretics, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, angiotensin II receptor antagonists (ARBs) and aldosterone antagonists can reduce levels of serum natriuretic peptides
- high levels of serum natriuretic peptides can have causes other than heart failure (for example, left ventricular hypertrophy, ischaemia, tachycardia, right ventricular overload, hypoxaemia [including pulmonary embolism], renal

dysfunction [GFR < 60 ml/minute], sepsis, chronic obstructive pulmonary disease [COPD], diabetes, age > 70 years and cirrhosis of the liver). **[new 2010]**

R7 Perform transthoracic Doppler 2D echocardiography to exclude important valve disease, assess the systolic (and diastolic) function of the (left) ventricle, and detect intracardiac shunts. **[2003]**

R8 Transthoracic Doppler 2D echocardiography should be performed on high-resolution equipment, by experienced operators trained to the relevant professional standards. Need and demand for these studies should not compromise quality. **[2003**]

R9 Ensure that those reporting echocardiography are experienced in doing so. **[2003**]

R10 Consider alternative methods of imaging the heart (for example, radionuclide angiography, cardiac magnetic resonance imaging or transoesophageal Doppler 2D echocardiography) when a poor image is produced by transthoracic Doppler 2D echocardiography. **[2003**]

R11 Consider a serum natriuretic peptide test (if not already performed) when heart failure is still suspected after transthoracic Doppler 2D echocardiography has shown a preserved left ventricular ejection fraction. **[new 2010]**

R12 Be aware that:

- a serum BNP level less than 100 pg/ml (29 pmol/litre) or an NTproBNP level less than 400 pg/ml (47 pmol/litre) in an untreated patient makes a diagnosis of heart failure unlikely
- the level of serum natriuretic peptide does not differentiate between heart failure due to left ventricular systolic dysfunction and heart failure with preserved left ventricular ejection fraction. **[new 2010]**

R13 Perform an ECG and consider the following tests to evaluate possible aggravating factors and/or alternative diagnoses:

- chest X-ray
- blood tests:
    - electrolytes, urea and creatinine
    - eGFR (estimated glomerular filtration rate)
    - thyroid function tests
    - liver function tests
    - fasting lipids
    - fasting glucose
    - full blood count
- urinalysis
- peak flow or spirometry. **[2003, amended 2010]**

R14 Try to exclude other disorders that may present in a similar manner. **[2003**]

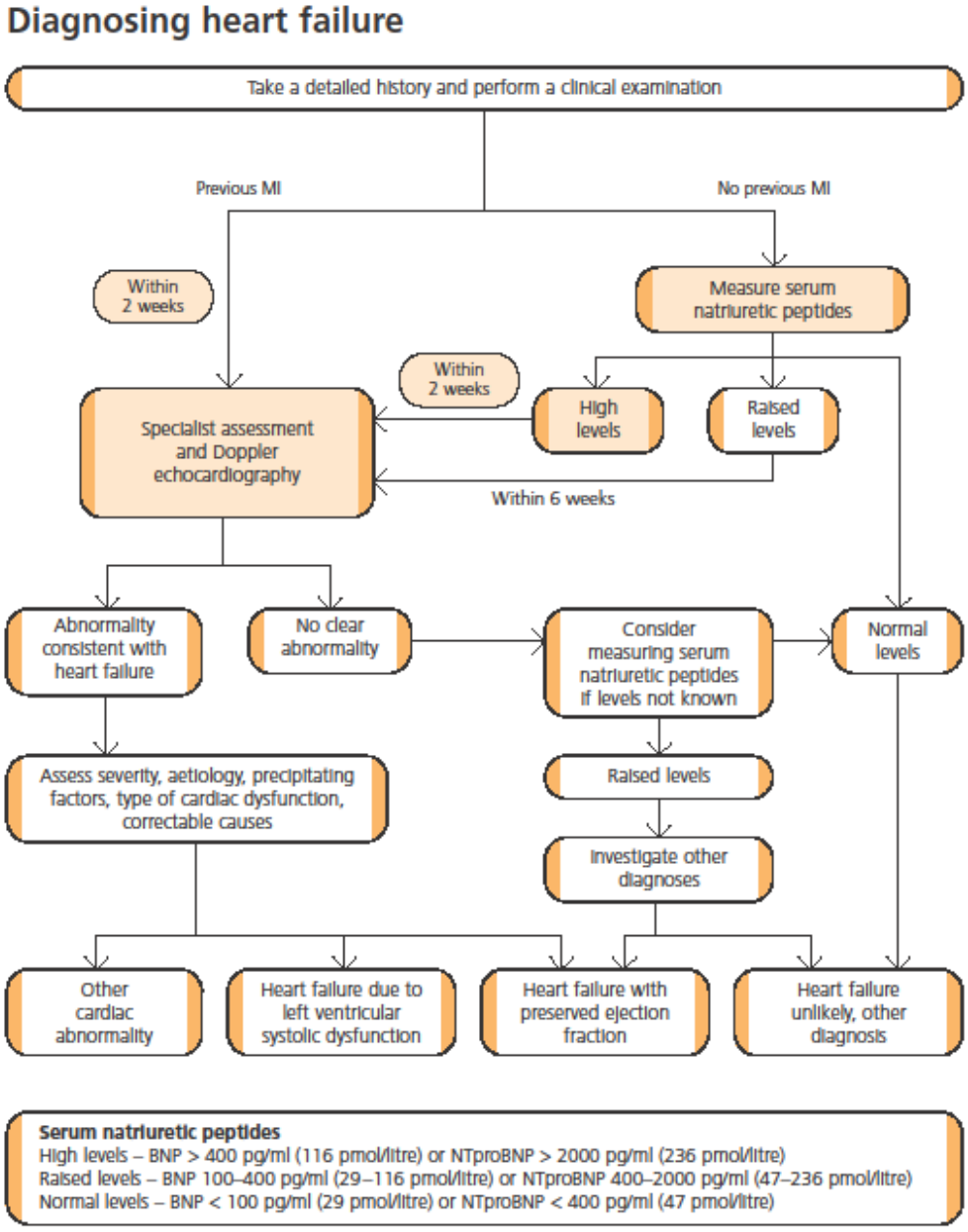
R15 When a diagnosis of heart failure has been made, assess severity, aetiology, precipitating factors, type of cardiac dysfunction and correctable causes. **[new 2010]**

**Review of existing diagnosis:**

R16 The basis for historical diagnosis of heart failure should be reviewed, and only patients whose diagnosis is confirmed should be managed in accordance with this guideline. **[2003]**

R17 If the diagnosis of heart failure is still suspected, but confirmation of the underlying cardiac abnormality has not occurred, then the patient should have appropriate further investigation. **[2003]**

## 4.4 Diagnostic algorithm




- Perform an ECG in all patients.
- Other recommended tests:
  - chest X-ray
  - blood tests: urea, creatinine, electrolytes, eGFR, liver function tests, full blood count, thyroid function tests, fasting glucose, and fasting lipids
  - urinalysis
  - peak flow or spirometry

**Non-HF causes of high NP:** LVH, ischaemia, tachycardia, RV overload, hypoxaemia (including pulmonary embolism), renal dysfunction (GFR<60 ml/min), sepsis, COPD, diabetes, age >70 years, cirrhosis of the liver.
**Factors causing low NP:** Obesity and treatment with diuretics, ACEI, BB, ARB, AA.

# 5 Treating heart failure

## Introduction

Until 1986 the management of most patients with heart failure had relied on the symptomatic relief of the features of congestion by the use of diuretics, with or without digoxin. These measures had no impact on patients' poor prognosis. Since then, several hypotheses into the management of heart failure have been developed, including the haemodynamic, the neuro-endocrine and the inflammatory hypotheses. Several classes of drugs have been introduced, with significant impact on patients' morbidity and mortality. Medical therapy is now available with two aims:

1. Improving the patients' morbidity: by reducing the patient's symptoms, improving their exercise tolerance, reducing their hospitalisation rate and improving their quality of life.
2. Improving the patient's prognosis, through the reduction of all cause mortality or their heart failure-related mortality.

Therapeutics available for heart failure have expanded since 1986 and include a wide array of medication that are not without side effects. This is one of the many reasons why the decisions on the management of heart failure have to take into account patients' preferences. These preferences do change with time and with the varying perspectives that patients may have on their condition and their lives. Involving the patient in management decisions requires that the provision of information to patients and their carers becomes an integral component of management of patients, and their rehabilitation.

Apart from a small number of recent advances in the understanding and therapy of heart failure with preserved left ventricular ejection fraction, most of the evidence supporting the therapeutic interventions in heart failure come from trials that recruited patients with heart failure due to left ventricular systolic dysfunction (LVSD).

The complexity of both the diagnostic process and the therapeutic options, as well as the continuing difficulties in the diagnosis and management of heart failure with preserved left ventricular ejection fraction, dictate the recurrent involvement of specialists. In addition, the role of the multidisciplinary team in the continuing management of heart failure patients is pivotal.

The partial update includes topics where new evidence has emerged since the publication of the heart failure guidelines of 2003.

The guidance for the treatment of heart failure is presented under the following headings:



## 5.1 Lifestyle

This topic (with the exception of rehabilitation which is covered in Chapter 6) was not within the scope of the partial update (2010). For more information on the following aspects of lifestyle please refer to Appendix M, the 2003 Guideline[22]:

- Exercise training (7.1.1)
- Smoking (7.1.3)

- Alcohol (7.1.4)
- Diet and nutrition (7.1.5)
- Natural supplementary therapies (7.1.6)
- Sexual activity (7.1.7)
- Vaccination (7.1.8)
- Air travel (7.1.9)
- Driving regulations (7.1.10)

### *5.1.1 Recommendations on lifestyle*

#### Exercise training

Please see Chapter 6 Rehabilitation

#### Smoking

For guidance on smoking cessation refer to the following NICE guidance:

- Smoking cessation services. NICE public health guidance No.10 (2008). available from www.nice.org.uk/PH10.
- Brief interventions and referral for smoking cessation in primary care and other settings. NICE public health intervention guidance No.1 (2006). Available from www.nice.org.uk/PH1.
- Varenicline for smoking cessation. NICE technology appraisal No.123 (2007). Available from www.nice.org.uk/TA123.

R18 Patients should be strongly advised not to smoke. Referral to smoking cessation services should be considered. **[2003]**.

#### Alcohol

R19 Patients with alcohol-related heart failure should abstain from drinking alcohol. **[2003]**

R20 Healthcare professionals should discuss alcohol consumption with the patient and tailor their advice appropriately to the clinical circumstances. **[2003]**

#### Sexual activity

R21 Healthcare professionals should be prepared to broach sensitive issues with patients, such as sexual activity, as these are unlikely to be raised by the patient. **[2003]**

#### Vaccination

R22 Patients with heart failure should be offered an annual vaccination against influenza. **[2003]**

R23 Patients with heart failure should be offered vaccination against pneumococcal disease (only required once). **[2003]**

#### Air travel

R24 Air travel will be possible for the majority of patients with heart failure, depending on their clinical condition at the time of travel. **[2003]**

#### Driving regulations

R25 Large Goods Vehicle and Passenger Carrying Vehicle licence: physicians should be up to date with the latest Driver and Vehicle Licensing Agency guidelines. Check the website for regular updates: www.dft.gov.uk/dvla. **[2003]**

## 5.2 Pharmacological treatment of heart failure

### *Introduction*

Pharmacological interventions in heart failure were driven by symptomatic therapy for many decades. The two pillars of therapy were diuretics and digoxin. Attempts to improve patient outcomes were doomed to fail until the pathophysiology underpinning heart failure started to be addressed through the use of agents that attempted to correct the haemodynamic disturbances and neuro-endocrine over-activity. This has led to major advances in the pharmacological management of heart failure. The morbidity and mortality rates of heart failure have progressively fallen through the accumulative effects of several classes of agents including angiotensin converting enzyme inhibitors, beta-blockers, aldosterone antagonists, combined arterial and venous dilators (combined hydralazine and nitrates) and angiotensin receptor blockers. These advances have been achieved in the treatment of heart failure associated with reduced left ventricular ejection fraction or HF with LVSD, which comprises almost 50% of the heart failure patient population.

Since the late 1990s, research effort has focussed on patients with heart failure who have either a normal left ventricular ejection fraction, or no significant reduction of the left ventricular ejection fraction. These patients are said to have heart failure with preserved left ventricular ejection fraction (HFPEF). There are several theories to explain this syndrome. Some believe this is caused by pure diastolic dysfunction. Others propose a type of systolic dysfunction that affects the long axis of the left ventricle, which can be missed when the concentric contraction of the left ventricle is assessed, as this would not be reduced. Different imaging modalities produce varied estimates of the left ventricular ejection fraction, and some believe that the normal ejection fraction rises with age. Therefore, it is possible that some patients are mislabelled as having HFPEF.

Further research is needed into the detection of HFPEF and a better understanding of the pathophysiological processes. This may lead to more successful therapeutic interventions. Up until now, research on how to treat patients with HFPEF has primarily been concerned with testing agents used in the treatment of HF with LVSD.

Where there are studies specifically addressing HFPEF, these are highlighted in separate sub-sections.

Valve disease, atrial fibrillation and other causes of heart failure (including congenital heart disease, cardiomyopathies and specifc cardiac muscle disease such as amyloid disease) were not reviewed in this 2010 partial update. For more information see Section 7.6.1 of the 2003 Guideline [22] and Atrial fibrillation. NICE clinical guidance 36 (2006) available from www.nice.org.uk/CG36

The decision on which drugs to include in the update of the guideline was made following consultation of the scope. A review of new evidence published after 2003 was carried out in order to determine whether any changes to current recommendations where likely to be required. Decisions on which drugs required a full review of the literature were made as a result of this exercise and whether other NICE guidance relevant for a heart failure population was already available.

The following agents were not considered in the update. For more information

refer to Appendix M, the 2003 Guideline[22]:

- Amiodarone (7.2.7)
- Anticoagulants (7.2.8)
- Inotropic agents (7.2.12)
- Calcium channel blockers (7.2.13)
- Diuretics (7.2.1)

- Digoxin (7.2.5)
- Statins (7.2.10)
- Others (Nesiritide, Levosimendan, d-sotalol, epoproserol, magnesium supplementation, vitamin E supplementation, interferon/thymomodulin, human recominant growth hormone, L-cartinine, pentoxifylline, and immunosuppressants (7.2.14)

# Drugs reviewed in partial update

## *5.2.1 Angiotensin converting enzyme inhibitors (ACEI)*

The evidence for the use of angiotensin converting enzyme inhibitors (ACEI) in HF with LVSD had been appraised in 2003. There is evidence to support the use of ACEI in all patients with HF with LVSD. ACEI improve symptoms, reduce hospitalisation rate, and improve survival rate. This is applicable in all age groups.

The GDG considered the impact of the new evidence looking at the sequence of therapy in relation to ACEI and beta-blockers, within the section on beta-blockers (Section 5.2.2).

The GDG also looked at the combination of ACEI with angiotensin receptor blockers (ARB) (Section 5.2.6).

## *Angiotensin Converting Enzyme Inhibitors in HFPEF*

**Clinical question:**

**ACE: What is the efficacy and safety of ACEI in people with heart failure and preserved left ventricular ejection fraction?**

### 5.2.1.1 Clinical introduction

ACEI are effective agents in the treatment of heart failure with LVSD, of hypertension and in reducing adverse cardiovascular events in patients with ischaemic heart disease and diabetes mellitus [51,52].

Patients with HFPEF have similar symptoms and almost the same outcomes as those with LVSD. Not infrequently they report a history of hypertension. Some of these patients will have diabetes mellitus or ischaemic heart disease.

**Reasons for Review**

Since the publication of the 2003 guidelines on chronic heart failure, evidence on the use of ACEI in the management of patients with HFPEF, especially the elderly, has been published.

### 5.2.1.2 Clinical Methodological introduction

**ACE I: Angiotensin Converting Enzyme (ACEI) inhibitor vs. Placebo**

*Populations:*

- LVEF ≥ 40% [53,54]
- Mean age range: 75-78 years [53,54]
- >50% female [53,54]

*Background medication:*

- Beta Blockers >60% [54]
- Beta Blockers <20% [53]

*Intervention:*

- Quinapril (up to 40mg) [53]

- Perindopril (4mg) [54]

*Comparison:*

- Placebo [53,54]

#### 5.2.1.3 Clinical evidence statements

Compared with placebo, ACE inhibitors significantly reduced:

- HF hospitalisation (follow-up one year) [moderate quality]

There was no significant difference between ACE inhibitors and placebo for:

- All cause mortality or unplanned hospitalisation (follow-up 12 months) [moderate quality]
- All cause mortality (follow-up 6 to 12 months and 12 to 54 months) [moderate quality]
- CV mortality (follow-up one year and 12 to 54 months) [moderate quality]
- HF hospitalisation (follow-up 12 to 54 months) [moderate quality]
- Adverse events (follow up 6 to 18 months) [moderate quality]
- Quality of life (follow-up 6 months) [moderate quality]
- NYHA class (follow-up 6 months) [moderate quality]

The evidence profile below summarises the quality of the evidence and outcome data from 2 randomised-control trials (RCT) [53,54] comparing **ACE inhibitors vs. placebo in HFPEF.**

**NOTE:** A major limitation of the Zi study was the very small sample size (N=74) compared to the Cleland study (N=850).

## Evidence Profile: ACE inhibitors vs placebo in HFPEF

**Question:** Should ACE inhibitors vs placebo be used for CHF?
**Bibliography: Zi** M, Carmichael N, Lye M. The effect of quinapril on functional status of elderly patients with diastolic heart failure. *Cardiovascular Drugs & Therapy.* 2003; 17(2):133-139. Cleland JG, Tendera M, Adamus J et al. The perindopril in elderly people with chronic heart failure (**PEP-CHF**) study. *European Heart Journal.* 2006; 27(19):2338-2345.

| Quality assessment | | | | | | | Summary of findings | | | | | Hazard ratio |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality | |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | ACE inhibitors | placebo | Relative (95% CI) | Absolute | | |
| **All cause mortality or unplanned hospitalisation (no. of patients) (follow-up 12 months)** | | | | | | | | | | | | |
| 1 PEP-CHF | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | none | 46/420 (11%) | 65/426 (15.3%) | RR 0.72 (0.5 to 1.02) | 43 fewer per 1000 (from 76 fewer to 3 more) | ⊕⊕⊕O MODERATE | |
| **All cause mortality or unplanned hospitalisation (no. of patients) (follow-up 12-54 months)** | | | | | | | | | | | | |
| 1 PEP-CHF | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | none | 100/420 (23.8%) | 107/426 (25.1%) | RR 0.95 (0.75 to 1.2) | 13 fewer per 1000 (from 63 fewer to 50 more) | ⊕⊕⊕O MODERATE | |
| **All cause mortality (no. of patients) (follow-up 6-12 months)** | | | | | | | | | | | | |
| 2 PEP-CHF ZI | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | none | 18/456 (3.9%) | 20/464 (1%)<br>19% | RR 0.91 (0.49 to 1.71) | 0 fewer per 1,000<br>17 fewer per 1,000 | ⊕⊕⊕O MODERATE | 0.92 (0.49 to 1.74) |
| **All cause mortality (no. of patients) - 12 to 54 months (follow-up 12 to 54 months)** | | | | | | | | | | | | |
| 1 PEP-CHF | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | none | 56/1420 (3.9%) | 53/1426 (3.7%)<br>0% | RR 1.06 (0.73 to 1.53) | 2 more per 1000 (from 10 fewer to 20 more)<br>0 more per 1,000 | ⊕⊕⊕O MODERATE | 0.94 (0.65 to 1.37) |
| **CV mortality (no. of patients) (follow-up 1 years)** | | | | | | | | | | | | |
| 1 PEP-CHF | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | none | 10/420 (2.4%) | 17/426 (4%) | RR 0.60 (0.28 to 1.29) | 16 fewer per 1000 (from 29 fewer to 12 more) | ⊕⊕⊕O MODERATE | 0.59 (0.27 to 1.30) |
| **CV mortality (no. of patients) - 12 to 54 months (follow-up 12 to 54 months)** | | | | | | | | | | | | |
| 1 PEP-CHF | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | none | 38/1420 (2.7%) | 40/1426 (2.8%) | RR 0.96 (0.62 to | 1 fewer per 1000 (from | ⊕⊕⊕O | 0.96 (0.62 to 1.50) |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 0% | 1.47) | 11 fewer to 13 more)<br>0 fewer per 1,000 | MODERATE | |
| **HF hospitalisation (no. of patients) (follow-up 1 years)** | | | | | | | | | | | | |
| 1 PEP-CHF ZI | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | none | 34/420 (8.1%) | 53/426 (12.4%) | RR 0.65 (0.43 to 0.98) | 43 fewer per 1000 (from 2 fewer to 71 fewer) | ⊕⊕⊕O MODERATE | |
| **HF hospitalisation (no. of patients) - 12 to 54 months (follow-up 12 to 54 months)** | | | | | | | | | | | | |
| 1 PEP-CHF ZI | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | none | 64/1420 (4.5%) | 73/1426 (5.1%)<br>0% | RR 0.89 (0.65 to 1.21) | 6 fewer per 1000 (from 18 fewer to 11 more)<br>0 fewer per 1,000 | ⊕⊕⊕O MODERATE | |
| **Quality of life (McMaster questionnaire) (follow-up 6 months; measured with: McMaster questionnaire; range of scores: 16-112; Better indicated by more)** | | | | | | | | | | | | |
| 1 ZI | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[2] | none | 36 | 38 | - | MD -0.20 (-2.01 to 1.61) | ⊕⊕⊕O MODERATE | |
| **Improvement in NYHA class from III to II (no. of patients) (follow-up 6 months)** | | | | | | | | | | | | |
| 1 ZI | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious | none | 1/36 (2.8%) | 2/38 (5.3%) | RR 0.53 (0.05 to 5.57) | 25 fewer per 1000 (from 50 fewer to 242 more) | ⊕⊕⊕O MODERATE | |
| **Adverse events (no. of patients) (follow-up 6-18 months)** | | | | | | | | | | | | |
| 2 PEP-CHF ZI | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[3] | none | 39/456 (8.6%) | 32/464 (4%)<br>28% | RR 1.28 (0.97 to 1.69) | 11 more per 1,000<br>78 more per 1,000 | ⊕⊕⊕O MODERATE | |

[1] < 300 events
[2] upper or lower confidence limit crosses an effect size of 0.5 in either direction.
[3] 95% confidence interval around the pooled or best estimate of effect includes both negligible effect and appreciable benefit or appreciable harm

#### 5.2.1.4 Health Economic Methodological introduction

The 2003 Guideline[22] concluded that the treatment of patients with heart failure and LVSD with ACE inhibitors is cost effective, largely due to the costs saved from the reduced risk of hospitalisation. Treatment was cost saving and had very favourable cost effectiveness ratios even when conservative assumptions were employed.

No relevant economic analysis was identified from our review assessing the cost-effectiveness of ACEI in patients with heart failure and preserved LVEF**.**

#### 5.2.1.5 Health economic evidence statements

Clinical evidence showed that ACEI therapy did not improve mortality but it significantly reduced hospital admissions in patients with heart failure and preserved LVEF. Given that ACEI treatment is relatively cheap; the use of this therapy in patients with HFPEF is likely to be cost-effective.

#### 5.2.1.6 From evidence to recommendations

***Relative value placed on the outcomes considered***

In the two appraised trials[54];[53] compared to placebo, ACEI had no effect on all cause mortality at 6-12 months or on the rate of adverse events at 6-18 months. In the small study by Zi et al, there was no impact on quality of life at 6 months or on the rate of improvement of patients with NYHA Class III to II at 6 months. In PEP-CHF trial[54], treatment with ACEI resulted in significant (35%) reduction in the rate of heart failure hospitalisation at 1 year, while it had no impact on cardiovascular mortality at 1 year.

There was no difference between those given placebo and those given ACEI in terms of the side effects, quality of life or the New York Heart Association functional class.

However, at completion of the PEP-CHF study by Cleland et al[54], there was an insignificant trend towards reduced hospitalisation at 5 years. The significant reduction in heart failure hospitalisation at 1 year in PEP-CHF was derived from a post-hoc analysis. The GDG felt both trials were underpowered with wide confidence intervals around the results. Therefore, the GDG believed that there was insufficient evidence of effectiveness of ACEI in HFPEF to recommend their general use in patients with HFPEF.

***Quality of evidence***

The evidence reported on all the parameters alluded to above from the two trials was of moderate quality.

***Trade-off between clinical benefits and harms***

While the GDG did not consider that a post hoc finding of a reduction in heart failure hospitalisation at one year was sufficient to recommend the widespread use of ACEI in HFPEF in the absence of any other significant benefit, it was noted that there was no evidence of significant harm either, with adverse event rates similar in active treatment and placebo arms of the two trials.

***Trade-off between net health benefits and resource use***

No relevant economic analysis was identified from our review assessing the cost-effectiveness of ACEI in patients with heart failure and preserved LVEF**.** From clinical trials, net resource use would be likely to be low given that hospital admissions might be reduced, and ACEI therapy is of relatively low cost. However, the GDG noted that the pre-specified hospitalisation endpoint was non-significant and the GDG therefore did not attach weight to the reduction of hospitalisation at one year.

***Use of ACEI in left ventricular systolic dysfunction***

The evidence base for use of ACEI in left ventricular systolic dysfunction was not formally reviewed. The GDG noted the 2003 recommendations. The GDG endorsed that ACEI doses should be up-titrated slowly up to the target doses used in randomised controlled trials (RCTs). The safety of treatment with ACEI is best achieved by adhering to the protocols used in the clinical trials and proposed in the 2003 guidelines as practical recommendations, as well as the recommendations of the NICE chronic kidney disease guideline. It is particularly important to measure the serum urea, electrolytes, creatinine and eGFR before the initiation of ACEI, following each dose increment, and then at regular intervals.

#### 5.2.1.7 Recommendations

The GDG decided the evidence was inadequate to support the use of ACEI in HFPEF. With regard to the use of ACEI in left ventricular systolic dysfunction, the 2003 practical recommendations were endorsed:

- Start ACE inhibitor therapy at a low dose and titrate upwards at short intervals (for example, every 2 weeks) until the optimal tolerated or target dose is achieved. **[2010]**
- Measure serum urea, creatinine, electrolytes and eGFR at initiation of an ACE inhibitor and after each dose increment.[7,8] **[2010]**

### *5.2.2 Beta Blockers*

**Clinical question:**

What is the efficacy and safety of beta blockers in comparison to placebo, optimal medical management or other beta blockers in people with chronic heart failure?

#### 5.2.2.1 Clinical introduction

The 2003 guidance appraised the evidence on the use of beta-blockers in heart failure due to left ventricular systolic dysfunction (HF with LVSD). The findings and most of the recommendations in the document remain valid. Patients who have HF with LVSD who do not have reversible chronic obstructive pulmonary disease should be considered for the introduction of beta-blockers at low doses. These should be up-titrated slowly. The introduction of beta-blockers in these patients reduces morbidity, hospitalisation, and mortality. The latter includes a reduction of sudden cardiac death.

**Reasons for Review**

Since the 2003 guidelines, randomised clinical trials have been published looking at comparing selective and non-selective beta-blockers in the treatment of heart failure, at the order of therapeutic strategies (ACEI/BB), and at the use of other beta-blockers in elderly patients with heart failure. There may also be some indirect evidence of the use of these agents in patients with heart failure with preserved left ventricular ejection fraction (HFPEF).

[7] For practical recommendations on treatment with ACE inhibitors see 'Chronic kidney disease' (NICE clinical guideline 73).

[8] For more information see Appendix J.

### 5.2.2.2 Clinical Methodological introduction

**a) BB: What is the safety and efficacy of BB vs placebo in older adults with chronic heart failure?**

**b) What is the safety and efficacy of selective vs non-selective BBs in chronic heart failure?**

**c) What is the safety and efficacy of BBs in patients with non LVSD chronic heart failure?**

**d) What is the safety and efficacy of BB then ACEI vs ACEI then BB for chronic heart failure?**

## a) Beta blockers versus placebo in older adults with chronic heart failure

Five papers were identified comparing beta-blockers with placebo in older adults with chronic heart failure [55; 56; 57; 58; 59]. Two of these papers were in a sub-population derived from RCTs carried out on all patients with chronic heart failure [55; 56]. Table **5.1** below summarises the patient population and intervention for each study. Patients with COPD were excluded in all studies except one study [58].

Table 5.1: Patient population and intervention: beta blockers in older adults with heart failure

| Study | Patient population | Intervention |
|---|---|---|
| DEEDWANIA<br>N=1982 | Patients ≥ 65 yrs with EF ≤ 30% and NYHA II to IV | Metroprolol CR/XL 25 mg<br>NYHA II<br>12.5 mg NYHA III and IV<br>Dose doubled at each 2-week period until target dose of 200 mg or highest tolerated |
| EDES<br>N=260 | Patients with chronic heart failure aged more than 65 yrs<br>Inclusion criteria: stable clinical course, LVEF ≤ 35%, stable medication with ACEI and/or ARBs, diuretics, and/or digitalis for 2 weeks prior to inclusion | Nebivolol<br>Titration period of 8 weeks. 1.25 mg double every 14 days until highest tolerated or maximum of 10 mg/day |
| ERDMANN<br>N=539<br>Sub-group analysis | Patients ≥ 71 yrs with chronic heart failure<br>Inclusion criteria: NYHA II, IV<br>EF ≤35%<br>Concomitant medication diuretics and ACEI | Bisoprolol<br>1.25 mg to a maximum of 10 mg/day |
| FLATHER<br>N=2128 | Adults ≥ 70 yrs with a clinical history of chronic heart failure and at least one of the following: documented hospital admission within the previous 12 mths with a discharge diagnosis of congestive heart failure or documented LVEF ≤ 35% within the previous 6mths. | Nebivolol<br>Initial dose of 1.25 mg once daily, if tolerated, increased to 2.5 and 5 mg respectively, every 1 to 2 weeks, to a target of 10 mg once daily over a maximum of 16 wks |

### b) Evidence profile: Beta blockers versus placebo for patients with LVEF > 35%

One paper pre-specified subanalysis analysis from SENIORS exploring the efficacy of beta-blockers in patients with LVEF > 35%.

Table 5.2: Population and intervention: efficacy of beta blockers in patients with LVEF >35%

| Study | Patient population | Intervention |
|---|---|---|
| Van Veldhuisen<br>N=2111 | Adults ≥ 70 yrs with a clinical history of chronic heart failure and at least one of the following: documented hospital admission within the previous 12 months with a discharge diagnosis of congestive heart failure or documented LVEF ≥ 35% within the previous 6months. | Nebivolol<br>Initial dose of 1.25 mg once daily, if tolerated, increased to 2.5 and 5 mg respectively, every 1 to 2 weeks, to a target of 10 mg once daily over a maximum of 16 weeks |

NOTE: The study reported the following statistically significant differences between patients with reduced LVEF and those with preserved LVEF at baseline:

- Proportion of women: LVEF ≤ 35% 29.8%; LVEF > 35% 49.9%
- NYHA functional class II: LVEF ≤ 35% 52.8%; LVEF > 35% 62.5%
- NYHA functional class III: LVEF ≤ 35% 42.5%; LVEF > 35% 32.2%
- Sitting systolic blood pressure (mm Hg): LVEF ≤ 35% 135.5; LVEF > 35% 145.4
- Sitting diastolic blood pressure (mm Hg): LVEF ≤ 35% 79.2; LVEF > 35% 82.9
- Proportion on diuretic: LVEF ≤ 35% 87.9%; LVEF > 35% 83.1%
- Proportion on Angiotensin converting enzyme inhibitor: LVEF ≤ 35% 80.5%; LVEF > 35% 85.9%
- Proportion on Angiotensin II antagonist: LVEF ≤ 35% 9.9%; LVEF > 35% 5.6%
- Proportion of Aldosterone antagonist: LVEF ≤ 35% 32.1%; LVEF > 35% 5.6%

### c) Selective vs non-selective beta blockers in chronic heart failure in reduced LVEF?

Three papers were identified comparing selective with non-selective ß blockers for chronic heart failure[60];[61];[62]. One of the papers[61] reported on additional data from the main study[60]. Both studies excluded patients with COPD. Table **5.3** below summarises the patient population and interventions by study.

Table 5.3: Patient population and interventions: selective vs non-selective beta blockers

| Study | Patient population | Selective BB | Non-selective BB |
|---|---|---|---|
| SANDERSON<br>N=51 | Patients with typical symptoms of heart failure and reduced LV ejection fraction (0.45 or lower) | Metoprolol<br>Four week titration period increasing the dose from 3.125 to 25 mg twice daily at weekly intervals | Carvedilol<br>Titration as for intervention. Dose titrated from 6.25 to 50 mg twice daily. |
| POOLE-WILSON<br>N=3029 | Adults with symptomatic chronic heart failure (NYHA II | Metroprolol<br>5 mg bd | Carvedilol<br>3.125 mg bd |

| | | | |
|---|---|---|---|
| | to IV), at least one cardiovascular admission during the past 2 yrs, on stable heart failure treatment. Left ventricular ejection fraction had to be 0.35 or lower measured within the previous 3 months | Target dose: 50 mg bd | Target dose: 25 mg bd |

### d) Beta blockers then ACEI compared with ACEI then beta blockers in reduced LVEF

One study was identified comparing beta-blockers then ACEI with ACEI then beta-blockers [63]. Patients with COPD were excluded. Table **5.4** below summarises the patient population and intervention for each study.

Table 5.4: Patient population and intervention: BB then ACEI vs ACEI then BB

| Study | Patient population | BB then ACEI | ACEI then BB |
|---|---|---|---|
| WILLHEIMER<br>N=1010 | Adults of 65 yrs or older with mild to moderate CHF (NYHA II or III) and LVEF ≤ 35%.<br>Inclusion criteria: clinically stable, without clinically relevant fluid retention or diuretic adjustment in the 7 days before randomisation | ß blocker first<br>Bisoprolol<br>1.25 mg QD<br><br>Progressively titrated at two week intervals (or slower if intolerant)<br>Target dose 10 mg QD<br>Maintenance period 16 weeks if drug used first<br>During the 6 month monotherapy phase, initiation of adjuvant therapy with angiotensin-receptor blocker or an aldosterone-receptor blocker was not permitted (continuing on aldosterone was allowed). This could be introduced in the combination therapy phase. Open treatment with beta-blocker or an ACEI inhibitor was prohibited<br>Combination therapy: Addition of enalapril and up titration as for monotherapy phase | ACEI first<br>Enalapril<br>2.5 mg BID<br><br>Progressively titrated at two week intervals (or slower if intolerant)<br>Target dose 10 mg BID<br>Maintenance period 22 weeks if drug used first<br>Procedure as for ß blocker<br>Combination therapy: beta-blocker introduced as for intervention |

#### 5.2.2.3 Clinical evidence statements

### a) Beta blockers versus placebo in older adults with chronic heart failure

Compared with placebo, beta-blockers had a significant reduction on

- Mortality – all cause up to 27 months [low quality]
- Sudden death – up to 24 months [low quality]

Compared with placebo, beta-blockers were associated with no significant differences for:

- All cause hospitalisation – up to 27 months [moderate quality]
- Quality of life – Minnesota Living with Heart Failure at 40 weeks [low quality]
- Adverse events – no. of patients at 40 weeks [low quality]
- Adverse events – no. of patients (leading to withdrawal of study medication) at 12 months [low quality]

The evidence profile below summarises the quality of evidence and outcome data from five papers[55],[56],[57],[58],[59] comparing beta-blockers with placebo in older adults with chronic heart failure.

## Evidence profile for comparison of beta-blockers with placebo in older adults

**Bibliography:** Deedwania PC, Gottlieb S, Ghali JK et al. Efficacy, safety and tolerability of beta-adrenergic blockade with metoprolol CR/XL in elderly patients with heart failure. *European Heart Journal.* 2004; 25(15):1300-1309. Ref ID 2710; 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. *European Journal of Heart Failure.* 2005; 7(4):631-639. Ref ID: 312; Erdmann E, Lechat P, Verkenne P et al. Results from post-hoc analyses of the CIBIS II trial: effect of bisoprolol in high-risk patient groups with chronic heart failure. *European Journal of Heart Failure.* 2001; 3(4):469-479. Ref ID: 705; Flather MD, Shibata MC, Coats AJS et al. FASTTRACK Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *European Heart Journal.* 2005; 26(3):215-225. Ref ID: 2849

| Quality assessment | | | | | | | Summary of findings | | | | | Hazard ratio |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality | |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | Beta blockers | control | Relative (95% CI) | Absolute | | |
| **Mortality - all cause (follow-up 8-27 months)** | | | | | | | | | | | | |
| 4 Deedwania Edes Erdmann Flather | randomised trial | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | None | 273/2252 (12.1%) | 348/2240 (6%)<br>25% | RR 0.78 (0.67 to 0.90) | 13 fewer per 1,000<br>55 fewer per 1,000 | ⊕⊕OO LOW | 0.77 (0.66 to 0.91) |
| **Sudden death (follow-up 21 to 24 months)** | | | | | | | | | | | | |
| 2 Deedwania Flather | randomised trial | serious[3] | no serious inconsistency | no serious indirectness | serious[4] | None | 86/2057 (4.2%) | 142/2053 (6.9%) | RR 0.60 (0.47 to 0.78) | 28 fewer per 1000 (from 15 fewer to 37 fewer) | ⊕⊕OO LOW | 0.59 (0.45 to 0.77) |
| **All cause hospitalisation (follow-up 21 to 27 months)** | | | | | | | | | | | | |
| 3 Deedwania Erdmann Flather | randomised trial | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | None | 729/2118 (34.4%) | 763/2114 (34%)<br>51% | RR 0.95 (0.88 to 1.03) | 17 fewer per 1,000<br>25 fewer per 1,000 | ⊕⊕⊕O MODERATE | |
| **Quality of Life (follow-up 40 weeks; measured with: Minnesota Living with Heart Failure; range of scores: 0-105; Better indicated by less)** | | | | | | | | | | | | |
| 1 Edes | randomised trial | serious[5] | no serious inconsistency | no serious indirectness | serious[6] | None | 134 | 126 | - | MD 1.88 (-1.58 to 5.34) | ⊕⊕OO LOW | |
| **No. of patients experiencing adverse event (follow-up 40 weeks)** | | | | | | | | | | | | |
| 1 Edes | randomised trial | serious[7] | no serious inconsistency | no serious indirectness | serious[4] | None | 81/134 (60.4%) | 78/126 (61.9%) | RR 0.98 (0.8 to 1.19) | 12 fewer per 1000 (from 124 fewer to 118 more) | ⊕⊕OO LOW | |
| **Adverse events - leading to withdrawal of medication (follow-up mean 12 months)** | | | | | | | | | | | | |
| 1 Deedwania | randomised trial | serious[8] | no serious inconsistency | no serious indirectness | serious[4] | None | 121/990 (12.2%) | 132/992 (13.3%) | RR 0.92 (0.73 to 1.16) | 11 fewer per 1000 (from 36 fewer to 21 more) | ⊕⊕OO LOW | |

[1] Erdmann and Deedwania sub-populations of all patients with CHF
[2] Best estimate of effect includes both negligible effect and appreciable benefit
[3] Deedwania sub-population
[4] < 300 events
[5] Poor allocation concealment; drop-outs > 20%
[6] 95% confidence interval includes no effect and the upper or lower confidence limit crosses the minimal important difference (MID), either for benefit of harm
[7] Allocation concealment poor; drop out rate > 20%
[8] Allocation concealment unclear; unclear drop-out rates - sub-population

**b) Beta blockers versus placebo for patients with preserved LVEF (LVEF > 35%)**

For patients with LVEF > 35%, there was no significant difference between beta-blockers and placebo for:

- All cause hospitalisation or CV hospitalisation (no of patients) at 21 mths [moderate quality]
- All cause mortality (no of patients) at 21 mths [moderate quality]
- All cause mortality –at 21 mths [moderate quality]
- All cause hospitalisation - (no of patients) at 21 mths [moderate quality]

The evidence profile below summarises the quality of evidence and outcome data from the one paper comparing beta-blockers with placebo for chronic heart failure and preserved LVEF

## Evidence profile for comparison of beta-blockers with placebo for chronic heart failure and preserved LVEF (LVEF > 35%)

**Question:** Should Beta blockers be used for Chronic heart failure - older adults?
**Bibliography:** van Veldhuisen DJ, Cohen SA, Bohm M et al. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: Data From SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors With Heart Failure). *Journal of the American College of Cardiology.* 2009; 53(23):2150-2158. Ref ID: 36

| Quality assessment | | | | | | | Summary of findings | | | | | Hazard ratio |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality | |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | Beta blockers | control | Relative (95% CI) | Absolute | | |
| **All cause mortality or CV hospitalisation (no of patients) - LVEF > 35% (follow-up 21 months)** | | | | | | | | | | | | |
| 1 Van Veldhuisen 2009 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | None | 110/380 (28.9%) | 125/372 (33.6%) | RR 0.86 (0.7 to 1.07) | 47 fewer per 1000 (from 101 fewer to 24 more) | ⊕⊕⊕O MODERATE | |
| **All cause mortality - LVEF > 35% (follow-up 21 months)** | | | | | | | | | | | | |
| 1 Veldhuisen 2009 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | None | 52/380 (13.7%) | 55/372 (14.8%) | RR 0.93 (0.65 to 1.31) | 10 fewer per 1000 (from 52 fewer to 46 more) | ⊕⊕⊕O MODERATE | 0.92 (0.62 to 1.33) |
| **All cause mortality or HF hospitalisation - LVEF > 35% (follow-up 21 months)** | | | | | | | | | | | | |
| 1 Veldhuisen 2009 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | None | 81/380 (21.3%) | 88/372 (23.7%) | RR 0.90 (0.69 to 1.18) | 24 fewer per 1000 (from 73 fewer to 43 more) | ⊕⊕⊕O MODERATE | |
| **All cause hospitalisation (no of patients) - LVEF > 35% (follow-up 21 months)** | | | | | | | | | | | | |
| 1 Veldhuisen 2009 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | None | 127/380 (33.4%) | 130/372 (34.9%) | RR 0.96 (0.78 to 1.17) | 14 fewer per 1000 (from 77 fewer to 59 more) | ⊕⊕⊕O MODERATE | |

[1] < 300 events

**c) Selective vs non-selective beta blockers in chronic heart failure?**

Compared to non-selective beta blockers, selective beta-blockers were associated with a significant increase in:

- Mortality – all cause mean follow-up 58 months [moderate quality]
- Sudden death - mean follow-up 58 months [moderate quality]

Compared to non-selective beta blockers, selective beta-blockers were associated with no significant differences for:

- Mortality and hospitalisation – all cause mean follow-up 58 months [high quality]
- Quality of life – Minnesota Living with Heart Failure follow-up 12 weeks [moderate quality]
- Adverse events – no. of patients experiencing mean follow-up 58 months [high quality]

The evidence profile below summarises the quality of evidence and outcome data from three papers comparing selective with non-selective beta blockers for chronic heart failure [60]; [61]; [62].

## Evidence profile for comparison of selective vs non-selective beta blockers

**Question:** Should Selective BB vs non-selective BB be used for chronic heart failure?
**Bibliography: Bibliography:** Poole-Wilson PA SK. 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(9377):7-13. Ref ID: 215; Sanderson JE, Chan SK, Yip G et al. Beta-blockade in heart failure: a comparison of carvedilol with metoprolol. *Journal of the American College of Cardiology.* 1999; 34(5):1522-1528. Ref ID: 942

| Quality assessment | | | | | | | Summary of findings | | | | | Hazard ratio |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality | |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | Selective BB | non-selective BB | Relative (95% CI) | Absolute | | |
| **Mortality and hospitalisation - all cause (follow-up mean 58 months)** | | | | | | | | | | | | |
| 1 Poole-Wilson | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision | None | 1160/1518 (76.4%) | 1116/1511 (73.9%) | RR 1.03 (0.99 to 1.08) | 22 more per 1000 (from 7 fewer to 59 more) | ⊕⊕⊕⊕ HIGH | |
| **Mortality - all cause (follow-up mean 58 months)** | | | | | | | | | | | | |
| 1 Poole-Wilson | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | None | 600/1518 (39.5%) | 512/1511 (33.9%)<br>0% | RR 1.17 (1.06 to 1.28) | 58 more per 1000 (from 20 more to 95 more)<br>0 more per 1,000 | ⊕⊕⊕O MODERATE | 1.22 (1.08 to 1.37) |
| **Sudden death (follow-up mean 58 months)** | | | | | | | | | | | | |
| 1 Poole-Wilson | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | None | 262/1518 (17.3%) | 218/1511 (14.4%) | RR 1.20 (1.01 to 1.41) | 29 more per 1000 (from 1 more to 59 more) | ⊕⊕⊕O MODERATE | 1.35 (1.03 to 1.78) |
| **Quality of Life (follow-up 12 weeks; measured with: Minnesota Living with Heart Failure; range of scores: 0-105; Better indicated by less)** | | | | | | | | | | | | |
| 1 Sanderson | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[2] | None | 26 | 25 | - | MD -3.30 (-4.25 to -2.35) | ⊕⊕⊕O MODERATE | |
| **Adverse events - no. of patients (follow-up mean 58 months)** | | | | | | | | | | | | |
| 1 Poole-Wilson | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision | None | 1457/1518 (96%) | 1420/1511 (94%) | RR 1.02 (1 to 1.04) | 19 more per 1000 (from 0 more to 38 more) | ⊕⊕⊕⊕ HIGH | |

[1] 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect includes both negligible effect and appreciable harm.
[2] upper or lower confidence limit crosses an effect size of 0.5 in either direction.

### d) Evidence profile: Beta blockers then ACEI compared with ACEI then beta blockers

Compared to ACEI then beta blockers, beta blockers then ACEI were associated with no significant differences for:

- Mortality and hospitalisation – all cause mean follow-up 1.22 years [high quality]
- Mortality – all cause mean follow-up 1.22 years [moderate quality]
- Hospitalisation – all cause mean follow-up 1.22 years [high quality]
- Sudden death - mean follow-up 1.22 years [moderate quality]
- Adverse events – no. of patients experiencing mean follow-up 58 months [high quality]

The evidence profile below summarises the quality of evidence and outcome data from one study comparing beta blockers then ACEI with ACEI then beta blockers [63].

## Evidence profile for comparison of BB then ACEI vs ACEI then BB

**Bibliography:** Willenheimer R, van Veldhuisen DJ, Silke B et al. Effect on survival and hospitalisation of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence: results of the randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III.[see comment]. *Circulation.* 2005; 112(16):2426-2435. Ref ID: 4453

| Quality assessment | | | | | | | Summary of findings | | | | | Hazard ratio |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality | |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | BB plus ACEI | ACEI plus BB | Relative (95% CI) | Absolute | | |
| **Mortality and hospitalisation - all cause (follow-up mean 1.22 years)** | | | | | | | | | | | | |
| 1 Willenheimer | randomised trial | no serious limitations[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 178/505 (35.2%) | 186/505 (36.8%) | RR 0.96 (0.81 to 1.13) | 15 fewer per 1000 (from 70 fewer to 48 more) | ⊕⊕⊕⊕ HIGH | |
| **Mortality - all cause (follow-up mean 1.22 years)** | | | | | | | | | | | | |
| 1 Willenheimer | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[2] | none | 65/505 (12.9%) | 73/505 (14.5%) | RR 0.89 (0.65 to 1.21) | 16 fewer per 1000 (from 51 fewer to 30 more) | ⊕⊕⊕O MODERATE | 0.88 (0.63 to 1.22) |
| **Hospitalisation - all cause (follow-up mean 1.22 years)** | | | | | | | | | | | | |
| 1 Willenheimer | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision | none | 151/505 (29.9%) | 157/505 (31.1%) | RR 0.96 (0.8 to 1.16) | 12 fewer per 1000 (from 62 fewer to 50 more) | ⊕⊕⊕⊕ HIGH | |
| **Sudden death (follow-up mean 1.22 years)** | | | | | | | | | | | | |
| 1 Willenheimer | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[2] | none | 29/505 (5.7%) | 34/505 (6.7%) | RR 0.85 (0.53 to 1.38) | 10 fewer per 1000 (from 31 fewer to 25 more) | ⊕⊕⊕O MODERATE | 0.85 (0.52 to 1.39) |
| **Adverse event - serious (follow-up mean 1.22 years)** | | | | | | | | | | | | |
| 1 Willenheimer | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[2] | none | 113/505 (22.4%) | 111/505 (22%) | RR 1.02 (0.76 to 1.38) | 4 more per 1000 (from 53 fewer to 84 more) | ⊕⊕⊕⊕ HIGH | |

[1] Single blind
[2] < 300 events

### 5.2.2.4 Health Economic Methodological introduction

From the 2003 Guideline[22], economic evidence on beta-blockers consistently showed beta-blockers to be cost effective, largely through costs saved from the reduced risk of hospitalisation. In the UK, only carvedilol and bisoprolol were licensed for the treatment of heart failure at the time of issue of the 2003 Guideline. No study had made a direct comparison between carvedilol and bisoprolol, and there was no evidence on their relative cost-effectiveness.

From our review, one UK cost-effectiveness analysis assessing a beta-blocker in patients with chronic heart failure was identified and presented to the GDG.

Yao et al. (2008)[64] presented a cost-utility analysis based on the SENIORS trial, reporting cost per QALY gained. They constructed an individual patient-simulation model within a Markov framework, from a UK NHS perspective, and with a lifetime horizon. The compared interventions were nebivolol + standard care versus placebo + standard care (82.1% of patients were taking ACEI, 6.6% ARB, 27.6% aldosterone antagonist, 39.3% glycosides, 42.2% aspirin, and 82.1% diuretics). The SENIORS trial was conducted on a population of elderly patients with heart failure (≥ 70 years; mean age of 76.1). Nebivolol was up titrated during a 16-week period (target of 10mg once daily). The maximum dosage maintained during SENIORS was 1.25 mg/day in 7.2% of patients, 2.5 mg/day in 7.6%, 5 mg/day in 13.3%, and 10 mg/day in 71.9%. The probabilities used in the model were mainly taken from SENIORS (hospitalisation for cardio-vascular event, cardiac death, sudden death). Probability of death due to other causes was derived from mortality rates in the UK general population (age- and sex-specific, excluding cardiac-related deaths). It was assumed that every patient was 70 years old at the beginning of the study. Health-utility scores for each NYHA class were derived from the CARE-HF trial [65]. When a patient was hospitalised, a disutility score of -0.1 was applied. The cost components used in the analysis were: drug cost, GP visit cost, outpatient specialist visit cost, and cardiovascular hospitalisation cost. It was assumed that patients in the nebivolol group attended a GP visit each month for 3 months, and then once every 3 months. Once every 3 months was assumed for the standard-care group. It was also assumed that every cardiovascular hospitalisation was followed by two outpatient attendances. Future costs and benefits were discounted at 3.5% per annum. The sensitivity analysis varied the age of patients at the beginning of the analysis, the discount rate, and the number of outpatient visits. Table 5.5 presents the quality and applicability assessment of this economic analysis.

**Table 5.5: Economic study assessment**

| Study | Study quality* | Study applicability** |
|---|---|---|
| Yao 2008[64] | Minor limitations (a) | Directly applicable |

*Very serious limitations / Potentially serious limitations / Minor limitations; ** Directly applicable / Partially applicable / Not applicable

(a) Assumptions were used to estimate GP and outpatient attendances

### 5.2.2.5 Health economic evidence statements

Results of the Yao et al. (2008) analysis [64] are presented in Table 5.6. These results showed that adding nebivolol to standard care is cost-effective in the UK for elderly patients with heart failure. The main limitation of this analysis was that potentially important resource use measures were not collected in SENIORS and assumptions were necessary for numbers of GP and outpatient attendances. The GDG felt that the assumption used in the analysis of one GP visit each month for the first three months in the nebivolol cohort does not reflect current clinical practice as more visits are necessary after initiating nebivolol.

**Table 5.6: Results – Yao 2008 economic analysis**

| Incremental cost (£) | Incremental effects | ICER | Uncertainty |
|---|---|---|---|
| £1724 | 0.65 QALYs | Base-case analysis: £2656 per QALY gained | Sensitivity analysis:<br>(1) Variation of the age at the beginning of the modelling from 60 to 80 years (70 in base case): From £2265 to £3580 per QALY;<br>(2) Variation of number of outpatient visits after cardiovascular hospitalisation (3 instead of 2): £2654 per QALY; |

* When developing the analysis, unit costs in pound sterling were converted in Euro using 1 GBP = 1.478 Euro. We used the same converted rate to present results in pound sterling.

### 5.2.2.6 From evidence to recommendations

***Relative value placed on the outcomes considered***

The GDG noted that the new evidence concerned the use of beta-blockers in older people with heart failure, the relative effectiveness of the non-selective beta-blocker Carvedilol compared with the selective beta-blocker Metoprolol tartrate, and the sequencing of therapy: ACEI followed by beta-blockers compared with beta-blockers followed by ACEI.

***Quality of evidence***

The GDG noted the evidence for the use of Nebivolol in older people with heart failure in the SENIORS study [58]. The GDG reviewed the post-hoc analyses of two randomised controlled studies of the older adult population using Bisoprolol or Metoprolol CR/XL [55,56]. The consistency of the results of the post-hoc analyses in the elderly sub-groups (reduction in all cause mortality and sudden death) with the randomised controlled trial that had specifically looked at this population was noted.

***Trade-off between clinical benefits and harms***

The GDG noted that there were no studies that specifically looked at the use of beta-blockers in the treatment of HFPEF. One third of the population recruited into the SENIORS study of Nebivolol in heart failure in older adults [58] were patients with a left ventricular ejection fraction >40%. While the size of effect in the sub-group with an ejection fraction >35% was of similar magnitude to that seen in patients with LVSD, the effect in the sub-group with higher ejection fraction was non-significant. [59] The GDG considered that there was insufficient evidence to recommend using beta-beta-blockers in the treatment of HFPEF and that further research was required.

The GDG reviewed the COMET trial [60] comparing the impact of the non-selective beta-blocker Carvedilol to the selective beta-blocker Metoprolol tartarate in the treatment of heart failure. Although the study suggested that Carvedilol was superior at reducing all cause mortality and sudden death, the GDG were not convinced that this difference between Carvedilol and the short acting Metoprolol tartrate was necessarily applicable to other beta-blockers. The GDG noted that the MERIT-HF trial used the long-acting Metoprolol Succinate, and CIBIS II trial used Bisoprolol. Both Metoprolol Succinate and Bisoprolol are selective beta-blockers with outcomes in heart failure not dis-similar to those achieved in the trials that used Carvedilol. The GDG concluded that the implication is that the best results can be achieved by using the beta-blocking agents of proven efficacy in heart failure, namely: Carvedilol, Metoprolol Succinate, Bisoprolol, and Nebivolol.

The GDG considered the CIBIS III trial[63], and noted that heart failure patients derived similar outcome of therapy with ACEI followed by beta-blockers, to those treated with beta-blockers

followed by ACEI. The GDG accepted that both agents should be given in the absence of contra-indications irrespective of the sequence they are given. The GDG agreed that either agent (or both) could be commenced first (see Section 5.2.1 on ACEI). The clinical decision to use one of these two agents before the other, or to commence both of them simultaneously depends on the clinical status of the patient. Several factors could affect the choice, including the patient's blood pressure, heart rate, the presence of symptomatic ischaemia, arrhythmias and other co-morbidity.

The GDG expressed concern that certain subgroups of patients with heart failure continue to be under-treated with beta-blockers. These include patients with chronic obstructive pulmonary disease (COPD), peripheral vascular disease, diabetes mellitus, erectile dysfunction and older adults. Patients with asthma and reversible airway obstruction were excluded from the trials of beta blockers in heart failure. The remaining patients with COPD should be able to tolerate beta blockers, and are likely to benefit significantly from their use. These patients are undertreated when they develop heart failure, and their outcomes are worse than the average heart failure patient. There is no evidence that selective beta-blockers will worsen these patients' pulmonary function. (Salpeter 2005)[66]. Beta-blockers are often avoided in patients with peripheral vascular disease for fear of exacerbating intermittent claudication, but this concern is unfounded (Radack 1991)[67]. Although patients with recently unstable diabetes mellitus were excluded from some trials of beta-blockers in heart failure, significant numbers of diabetic patients have been included in beta-blocker trials such as COMET with no evidence that diabetes adversely influenced the effectiveness of the beta-blocker [68]; [69](COMET, MERIT-HF). Erectile dysfunction can be caused by some beta-blockers, but there are many causes including other medications and vascular disease. Discussion of these factors with the patient and explanation of the symptomatic and prognostic impact of beta-blockers in heart failure will better inform the decisions made by the patient and the health professional regarding these agents.

There is now sufficient evidence to justify the use of beta-blockers licensed for heart failure in patients in these groups, with the exception of patients who have COPD with reversible obstructive pulmonary disease. This group was excluded from the trials using selective beta-blockers such as bisoprolol (CIBIS II) [56]and Metoprolol CR/XL (MERIT-HF)[55]. The GDG noted that beta-blockers can be used in irreversible COPD. Moreover, in a meta-analysis of the trials on cardio-selective beta-blockers used in mild to moderate reversible COPD, no clinically significant adverse respiratory effects were demonstrated. (Salpeter 2005)[66].

The GDG suggested that if practitioners have particular concerns about side effects in patients with heart failure who also have irreversible COPD or peripheral vascular disease, then a selective beta-blocker licensed for heart failure could be considered.

The GDG considered the issue of managing patients who develop heart failure while on a beta-blocker not licensed for heart failure for another indication such as angina, hypertension, or arrhythmia. Contrary to the 2003 guidance, the GDG felt that it would be appropriate to switch to an agent licensed for use in heart failure, given the demonstrated significant impact these agents have on morbidity and mortality.

The GDG endorsed the 2003 practical recommendations. It is important, during the uptitration of beta-blockers, to monitor the patient's pulse rate, blood pressure and the clinical status, to avoid side effects such as symptomatic bradycardia and symptomatic hypotension. The uptitration should be undertaken gradually and slowly to achieve the target doses used in the clinical trials, if tolerated. The patient needs to be informed that transient pulmonary congestion could occur at times during uptitration of beta-blockers.

***Trade-off between net health benefits and resource use***

From the 2003 Guideline[22], economic evidence on beta-blockers consistently showed beta-blockers to be cost effective. Our review added a study[64] that addressed the use of beta blockers in older adults with heart failure. This study[64] demonstrated that these agents are also cost-effective for this specific population.

#### 5.2.2.7 Recommendations

- Offer both angiotensin-converting enzyme (ACE) inhibitors and beta-blockers licensed for heart failure to all patients with heart failure due to left ventricular systolic dysfunction. Use clinical judgement when deciding which drug to start first. **[new 2010]**
- Offer beta-blockers licensed for heart failure to all patients with heart failure due to left ventricular systolic dysfunction, including:
  - older adults **and**
  - patients with:
    - peripheral vascular disease
    - erectile dysfunction
    - diabetes mellitus
    - interstitial pulmonary disease and
    - chronic obstructive pulmonary disease (COPD) without reversibility. **[new 2010]**
- Introduce beta-blockers in a 'start low, go slow' manner, and assess heart rate, blood pressure, and clinical status after each titration. **[2010]**
- Switch stable patients who are already taking a beta-blocker for a comorbidity (for example, angina or hypertension), and who develop heart failure due to left ventricular systolic dysfunction, to a beta-blocker licensed for heart failure. **[new 2010]**

### *5.2.3 Aldosterone antagonists*

#### Clinical Question:

What is the efficacy and safety of using an aldosterone antagonist in addition to optimal medical management compared to placebo plus optimal medical management in adults with chronic heart failure?

#### 5.2.3.1 Clinical introduction

There is evidence of enhanced activity of the renin-angiotensin-aldosterone system in patients with heart failure. The modulation of this system started by the introduction of angiotensin-converting-enzyme inhibitors (ACEI), and followed by the introduction of the angiotensin receptor blockers in the treatment of heart failure. Spironolactone, an aldosterone antagonist, was contra-indicated in combination with ACEI, until the publication of the RALES study in 1999. This was reviewed in the 2003 guidance. The latter document confirmed that moderately to severely symptomatic patients with heart failure (NYHA Class III-IV) despite optimal medical therapy would attain lower hospitalisation rates and higher survival rates with the addition of spironolactone. Further evidence on the use of aldosterone antagonists in heart failure was expected in 2003.

## Reason for review

Since the publication of the 2003 guideline, new evidence for the use of Aldosterone Antagonists in heart failure has been published. NICE guidance on the management of patients with myocardial infarction includes advice on the use of aldosterone antagonists in patients with heart failure following acute myocardial infarction [70].

In patients on ACEI and beta-blockers who remain symptomatic, aldosterone antagonists as well as other options may be indicated.

### 5.2.3.2 Clinical Methodological introduction

**Aldosterone antagonist + optimal medical management vs. placebo + optimal medical management**

Three papers from the EPHESUS trial programme were identified comparing aldosterone antagonists plus optimal medical management with placebo plus optimal medical management in patients with heart failure post-MI [71,72,73];

PITT 2003 compared eplerenone with placebo in patients 3-14 days after acute myocardial infarction (MI) with left ventricular dysfunction. PITT 2005 was a post-hoc analysis reporting further outcomes at 30 days and PITT 2006 reported results for the subgroup of patients included in the EPHESUS trial with severe left ventricular impairment (LVEF ≤30%).

Two studies were identified comparing aldosterone antagonists plus optimal medical management with placebo plus optimal medical management in patients with heart failure due to severe left ventricular systolic dysfunction (LVEF <35%) [74,75].

PITT 1999 was a part of the RALES study comparing spironolactone with placebo in patients with heart failure and severe LVSD (LVEF <35%). Patients were included with a history of NYHA class II through IV, a left ventricular ejection fraction ≤ 35%, and a history of NYHA class III or IV within the prior six months of enrolment. ANON 1996 [75] was performed by the RALES investigators, this trial was intended as a dose finding trial for spironolactone in patients with HF due to severe LVSD (LVEF <35%).

The results from the EPHESUS severe heart failure subgroup were not meta-analysed with these results due to severe heterogeneity for the outcome heart failure hospitalisation, which may have been caused by the different populations (heart failure vs. heart failure post-MI), the different type of aldosterone antagonist used (spironolactone vs. eplerenone) or the difference in outcome (nonfatal HF hospitalisation vs. HF hospitalisation).

Three studies were identified comparing aldosterone antagonists plus optimal medical management with placebo plus optimal medical management in patients with chronic heart failure [76-78] .

Barr (1995) [78] compared spironolactone with placebo in a population with chronic heart failure (CHF) secondary to coronary heart disease. Macdonald (2004) [77]compared spironolactone with placebo in a population with mild heart failure, defined as patients who at diagnosis their CHF had been at least NYHA class II, but optimising their treatment had improved the patients' condition substantially into a stable and less symptomatic one. Agostoni (2005) [76] compared spironolactone with placebo in a population with CHF and reduced lung diffusion.

### 5.2.3.3 Clinical evidence statements

**a) Aldosterone antagonists plus optimal medical management vs. placebo plus optimal medical management in patients with heart failure post-MI.**

Compared with placebo, aldosterone antagonists resulted in a significant reduction of:

- Mortality all cause at 30 days [moderate quality]
- Mortality all cause at 16 months [high quality]
- Mortality all cause at 16 months – subgroup: severe LVSD / LVEF <35% [moderate quality]
- Sudden death at 16 months [moderate quality]
- Sudden death at 16 months – subgroup: severe LVSD / LVEF <35% [moderate quality]

Compared with placebo, aldosterone antagonists significantly increased:

- Hyperkalaemia at 16 months [high quality]

Compared with placebo, aldosterone antagonists had a non-significant effect on:

- Sudden death at 30 days [high quality]
- HF hospitalisation at 30 days [moderate quality]
- Nonfatal HF hospitalisation at 16 months– subgroup: severe LVSD / LVEF <35% [moderate quality]
- All hospitalisation at 16 months [high quality]

The evidence profile below summarises the quality of the evidence and outcome data from 3 studies [71-73] comparing **aldosterone antagonists plus optimal medical management with placebo plus optimal medical management in patients with heart failure post-MI.**

## Evidence profile: Aldosterone antagonists plus optimal medical management vs. placebo plus optimal medical management in patients with heart failure post-MI.

Question: Should aldosterone antagonist vs placebo be used for chronic heart failure post-MI?
Bibliography: Pitt B, Remme W, Zannad F et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med.* 2003; 348(14):1309-1321. Pitt B, Gheorghiade M, Zannad F et al. Evaluation of eplerenone in the subgroup of EPHESUS patients with baseline left ventricular ejection fraction [less-than or equal to] 30%. *European Journal of Heart Failure.* 2006; 8(3):295-301. Pitt B, White H, Nicolau J et al. Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. *Journal of the American College of Cardiology.* 2005; 46(3):425-431.

| Quality assessment | | | | | | | Summary of findings | | | | | Hazard ratio |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality | |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | aldosterone antagonist | placebo | Relative (95% CI) | Absolute | | |
| **All cause mortality (follow-up 30 days)** | | | | | | | | | | | | |
| 1 EPHESUS (2005) | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | None | 107/3319 (3.2%) | 153/3313 (4.6%) | RR 0.70 (0.55 to 0.89) | 14 fewer per 1000 (from 5 fewer to 21 fewer) | ⊕⊕⊕O MODERATE | 0.70 (0.54 to 0.89) |
| **All cause mortality (follow-up 16 months)** | | | | | | | | | | | | |
| 1 EPHESUS (2003) | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision | None | 478/3319 (14.4%) | 554/3313 (16.7%) | RR 0.86 (0.77 to 0.96) | 25 fewer per 1000 (from 7 fewer to 42 fewer) | ⊕⊕⊕⊕ HIGH | 0.92 (0.87 to 0.98) |
| **sudden death (follow-up 30 days)** | | | | | | | | | | | | |
| 1 EPHESUS (2005) | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision[1] | None | 30/3319 (0.9%) | 47/3313 (1.4%) | RR 0.64 (0.4 to 1) | 5 fewer per 1000 (from 8 fewer to 0 more) | ⊕⊕⊕⊕ HIGH | 0.43 (0.19 to 1.00) |
| **sudden death (follow-up 16 months)** | | | | | | | | | | | | |
| 1 EPHESUS (2003) | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[2] | None | 162/3319 (4.9%) | 201/3313 (6.1%) | RR 0.80 (0.66 to 0.98) | 13 fewer per 1000 (from 2 fewer to 22 fewer) | ⊕⊕⊕O MODERATE | 0.82 (0.69 0.98) |
| **HF hospitalisation (follow-up 30 days)** | | | | | | | | | | | | |
| 1 EPHESUS (2005) | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[3] | None | 114/3319 (3.4%) | 138/3313 (4.2%) | RR 0.82 (0.65 to 1.05) | 8 fewer per 1000 (from 15 fewer to 2 more) | ⊕⊕⊕O MODERATE | |
| **all hospitalisation (follow-up 16 months)** | | | | | | | | | | | | |
| 1 EPHESUS (2003) | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision | none | 1493/3319 (45%) | 1526/3313 (46.1%) | RR 0.98 (0.93 to | 23 fewer per 1000 | ⊕⊕⊕⊕ | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | 1.03) | (from 51 fewer to 9 more) | HIGH | |
| **hyperkalaemia (follow-up 16 months)** | | | | | | | | | | | | |
| 1 EPHESUS (2003) | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[3] | none | 113/3307 (3.4%) | 66/3301 (2%) | RR 1.71 (1.27 to 2.31) | 14 more per 1000 (from 5 more to 26 more) | ⊕⊕⊕⊕ HIGH | |
| **Subgroup: severe LVSD/LVEF≤30%** | | | | | | | | | | | | |
| **Mortality all cause (follow-up 16 months)** | | | | | | | | | | | | |
| 1 EPHESUS (2006) | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[2] | none | 205/1048 (19.6%) | 254/1058 (24%) | RR 0.81 (0.69 to 0.96) | 46 fewer per 1000 (from 10 fewer to 74 fewer) | ⊕⊕⊕O MODERATE | |
| **sudden death (follow-up 16 months)** | | | | | | | | | | | | |
| 1 EPHESUS (2006) | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | none | 71/1048 (6.8%) | 103/1058 (9.7%) | RR 0.70 (0.52 to 0.93) | 29 fewer per 1000 (from 7 fewer to 47 fewer) | ⊕⊕⊕O MODERATE | |
| **Hospitalisation non fatal HF (follow-up 16 months)** | | | | | | | | | | | | |
| 1 EPHESUS (2006) | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[2] | none | 152/1048 (14.5%) | 181/1058 (17.1%) | RR 0.85 (0.7 to 1.03) | 26 fewer per 1000 (from 51 fewer to 5 more) | ⊕⊕⊕O MODERATE | |

[1] total number of events is less than 300, 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect includes both negligible effect and appreciable benefit.
[2] 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect includes both negligible effect and appreciable benefit.
[3] total number of events is less than 300

**a) Aldosterone antagonists plus optimal medical management vs. placebo plus optimal medical management in patients with heart failure due to severe LVSD (LVEF <35%)[9].**

Compared with placebo, aldosterone antagonists had a significant reduction on:

- Mortality all cause at 24 months [moderate quality]
- HF hospitalisation at 24 months [moderate quality]

Compared with placebo, aldosterone antagonists had a significant increase on:

- Gynecomastia in men at 24 months [high quality]

Compared with placebo, aldosterone antagonists a non-significant increase on:

- Hyperkalaemia at 3 to 24 months [low quality]

The evidence profile below summarises the quality of the evidence and outcome data from 2 studies [74,75] comparing **aldosterone antagonists plus optimal medical management with placebo plus optimal medical management in patients with heart failure due to severe LVSD (LVEF <35%).**

[9] **Patients were included with a history of NYHA class II through IV, a left ventricular ejection fraction ≤ 35%, and a history of NYHA class III or IV within the prior six months of enrolment**

## Evidence profile: Aldosterone antagonists plus optimal medical management vs. placebo plus optimal medical management in patients with heart failure due to severe LVSD (LVEF <35%)[10].

**Question:** Should aldosterone antagonist vs placebo be used for heart failure due to severe LVSD (LVEF<35%)?
**Bibliography:** Anon. Effectiveness of spironolactone added to an angiotensin-converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure (the Randomized Aldactone Evaluation Study [RALES]). *American Journal of Cardiology.* 1996; 78(8):902-907. Pitt B, Zannad F, Remme WJ et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *New England Journal of Medicine.* 1999; 341(10):709-717.

| Quality assessment | | | | | | | Summary of findings | | | | | Hazard ratio |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality | |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | aldosterone antagonist | placebo | Relative (95% CI) | Absolute | | |
| **All cause mortality (follow-up 24 months)** | | | | | | | | | | | | |
| 1 PITT (RALES) 1999 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | none | 284/822 (34.5%) | 386/841 (45.9%) | RR 0.75 (0.67 to 0.85) | 138 fewer per 1000 (from 83 fewer to 184 fewer) | ⊕⊕⊕O MODERATE | 0.74 (0.63 to 0.86) |
| **HF hospitalisation a (follow-up 24 months)** | | | | | | | | | | | | |
| 1 PITT (RALES) 1999 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious | none | 215/822 (26.2%) | 300/841 (35.7%) | RR 0.73 (0.63 to 0.85) | 107 fewer per 1000 (from 64 fewer to - 146 fewer) | ⊕⊕⊕O MODERATE | |
| **hyperkalaemia (follow-up 3-24 months)** | | | | | | | | | | | | |
| 2 2 PITT (RALES) 1999 + PITT 1996 | randomised trial | serious[2] | no serious inconsistency | no serious indirectness | serious[3] | none | 21/869 (2.4%) | 11/881 (1.2%) | RR 1.88 (0.91 to 3.9) | 11 more per 1000 (from 1 fewer to 35 more) | ⊕⊕OO LOW | |
| **gynecomastia in men (follow-up 24 months)** | | | | | | | | | | | | |
| 1 PITT (RALES) 1999 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision | none | 55/603 (9.1%) | 8/614 (1.3%) | RR 7.00 (3.36 to 14.57) | 78 more per 1000 (from 31 more to 176 more) | ⊕⊕⊕⊕ HIGH | |

[1] 95% confidence interval around the pooled or best estimate of effect includes both negligible effect and appreciable benefit
[2] unlcear allocation concealment, unclear ITT
[3] total number of events is less than 300, 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect includes both negligible effect and appreciable benefit

[10] **Patients were included with a history of NYHA class II through IV, a left ventricular ejection fraction ≤ 35%, and a history of NYHA class III or IV within the prior six months of enrolment**

**b) Aldosterone antagonists plus optimal medical management with placebo plus optimal medical management in patients with chronic heart failure.**

Compared with placebo, aldosterone antagonists non-significantly increased:

- Hyperkalaemia >5.5 mmol/l at two months [low quality]
- Raised creatinine >300 umol/l at 8 weeks [low quality]

Compared with placebo, aldosterone antagonists non-significantly worsened:

- Quality of life- Minnesota Living with Heart Failure Questionnaire (MLWHFQ) score at 6 months [low quality]

Compared with placebo, aldosterone antagonists had a non-significant reduction on:

- Creatinine mean change at 6 months [low quality]

The evidence profile below summarises the quality of the evidence and outcome data from 3 studies [76-78] comparing **aldosterone antagonists plus optimal medical management with placebo plus optimal medical management in patients with chronic heart failure.**

## Evidence profile: Aldosterone antagonists plus optimal medical management vs. placebo plus optimal medical management in patients with chronic heart failure.

**Question:** Should aldosterone antagonist vs placebo be used for all chronic heart failure?
**Bibliography:** Agostoni P, Magini A, Andreini D et al. Spironolactone improves lung diffusion in chronic heart failure. *European Heart Journal.* 2005; 26(2):159-164. Macdonald JE, Kennedy N, Struthers AD. Effects of spironolactone on endothelial function, vascular angiotensin converting enzyme activity, and other prognostic markers in patients with mild heart failure already taking optimal treatment. *Heart.* 2004; 90(7):765-770. Barr CS, Lang CC. Effects of adding spironolactone to an angiotensin-converting enzyme inhibitor in chronic congestive heart failure secondary to coronary artery disease. *The American Journal of Cardiology.* 1995; 76(17):1259-1265.

| Quality assessment | | | | | | | Summary of findings | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality | Importance |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | aldosterone antagonist | placebo | Relative (95% CI) | Absolute | | |
| **quality of life (MLWHFQ) at 6 months (follow-up 6 months; measured with: Minnesota Living with Heart Failure Questionnaire; range of scores: 0-105; Better indicated by less)** | | | | | | | | | | | | |
| 2<br>AGOSTONI (2005)<br>MACDONALD (2004) | randomised trial | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 58 | 58 | - | MD 1.85 (-4.32 to 8.02) | ⊕⊕OO LOW | |
| **hyperkalaemia >5.5mmol/l (follow-up 2 months)** | | | | | | | | | | | | |
| 1<br>BARR (1995) | randomised trial | serious[3] | no serious inconsistency | no serious indirectness | serious[2] | none | 4/28 (14.3%) | 0/14 (0%) | RR 4.66 (0.27 to 80.84) | 0 more per 1000 (from 0 fewer to 0 more) | ⊕⊕OO LOW | |
| **raised creatinine >300umol/L (follow-up 8 weeks)** | | | | | | | | | | | | |
| 1<br>BARR (1995) | randomised trial | serious[3] | no serious inconsistency | no serious indirectness | serious[2] | none | 4/28 (14.3%) | 0/14 (0%) | RR 4.66 (0.27 to 80.84) | 0 more per 1000 (from 0 fewer to 0 more) | ⊕⊕OO LOW | |
| **creatinine mean change (follow-up 6 months; measured with: mg/dl; range of scores: -; Better indicated by less)** | | | | | | | | | | | | |
| 1<br>AGOSTONI (2005) | randomised trial | serious[4] | no serious inconsistency | no serious indirectness | serious[5] | none | 15 | 15 | - | MD -0.03 (-0.22 to 0.16) | ⊕⊕OO LOW | |

[1] 2/2 unclear allocation concealment, 1/2 open label, 1/2 >20%drop-out, 1/2 unclear ITT
[2] 95% confidence interval includes no effect and the upper or lower confidence limit crosses the minimal important difference (MID), either for benefit of harm (5 points or more)
[3] unclear allocation concealment, unclear ITT
[4] unclear allocation concealment, open-label
[5] the upper or lower confidence limit crosses an effect size of 0.5 in either direction.

#### 5.2.3.4 Health Economic Methodological introduction

From the 2003 Guideline[22], no relevant economic evidence relating to aldosterone antagonists in heart failure was identified. From our review, two cost-effectiveness analyses assessing the addition of an aldosterone antagonist to optimal medical treatment in patients with chronic heart failure were identified and presented to the GDG. The first one was a UK study assessing eplerenone in patients with heart failure and left ventricular systolic dysfunction post acute myocardial infarction, and the other was an Irish study assessing spironolactone in patients with severe chronic heart failure and left ventricular systolic dysfunction. We believe the healthcare system in Ireland is reasonably comparable to the UK's NHS.

***UK study assessing eplerenone***

Duerden et al. (2008)[79] presented a cost-effectiveness analysis conducted from a UK NHS perspective with a 3-year time horizon (reporting cost per life-year gained). This analysis was based on the EPHESUS trial and assessed the addition of eplerenone to optimal medical treatment in patients with heart failure and left ventricular systolic dysfunction post acute myocardial infarction. For the placebo cohort, resource use estimates were calculated using data from the *Office of National Statistics*, data from the England and Scotland NHS, and probabilities published by the NICE clinical guideline on secondary prevention of myocardial infarction[70]. In addition for the placebo cohort, survival estimates were derived from an 18-month epidemiological study assessing patients with all-cause heart failure and carried out in West London (Cowie 2000)[9]). Survival estimates from this study were extrapolated to 3 years (predicting a 48% survival). For the eplerenone cohort, additional resource use and additional survival were taken from EPHESUS (16-month follow-up) and extrapolated to 3 years. Costs considered in this assessment were the hospitalisation cost and the cost of eplerenone (additional drug cost for the treatment cohort). A 100% adherence and compliance to eplerenone was assumed. Future costs and benefits were discounted at 3.5% per annum. The sensitivity analysis varied mortality rates (increasing by 10%, 15%, and 20%). Table 5 7 presents the quality and applicability assessment of this economic analysis.

***Irish study assessing spironolactone***

Tilson et al. (2003)[80] conducted a cost-effectiveness analysis reporting cost per life-year gained and was based on the RALES trial. The analysis was developed from an Irish perspective and for a 10-year time horizon. The assessed population were patients with severe chronic heart failure (NYHA class III & IV) and left ventricular systolic dysfunction with a mean age of 65 years. Adding spironolactone to optimal medical management was compared to optimal medical treatment only (might include diuretics, ACEI, digoxin, BB, or a combination of these). Probabilities of death and hospitalisation for the placebo cohort were taken from a cohort of patients followed over 12 months in an Irish teaching hospital. The differences in probabilities of death and hospitalisation for the treatment cohort were taken from RALES. It was assumed that no difference in death and hospitalisation rates occurred between the cohorts after the 2-year mean duration of follow-up for RALES. Costs incorporated in the analysis were spironolactone treatment cost, hospitalisation cost for severe heart failure, and outpatient visit cost. A two-way sensitivity analysis varied probabilities of death and hospitalisation, and one-way sensitivity analyses varied the hospitalisation cost and added outpatient visits to the spironolactone cohort. Future costs and outcomes were discounted at 5% and 1.5% respectively. Table 5 7 presents the quality and applicability assessment of this economic analysis.

**Table 5 7: Economic study assessment**

| Study | Study quality* | Study applicability** |
|---|---|---|
| Duerden et al. (2008)[79] | Potentially serious limitations (a) | Directly applicable |
| Tilson et al. (2003)[80] | Potentially serious limitations (b) | Partially applicable (c) |

*Very serious limitations / Potentially serious limitations / Minor limitations; ** Directly applicable / Partially applicable / Not applicable

(a) Outcomes were not measured as QALYs; Short time horizon; Limited sensitivity analysis; Incremental cost per patient and incremental effect per patient were not reported; Economic assessment based on a population model

(b) Outcomes were not measured as QALYs; Incremental cost and incremental effect were not reported

(c) Analysis developed from an Irish perspective, a healthcare system reasonably comparable to the UK NHS; Population assessed limits the generalisation of results

### 5.2.3.5 Health economic evidence statements

***UK study assessing eplerenone***

Results of the Duerden et al. (2008) cost-effectiveness analysis[79] are presented in Table 5.8. These results showed that adding eplerenone to optimal medical treatment in patients with heart failure and left ventricular systolic dysfunction post acute myocardial infarction is cost-effective in the UK. Limitations of this study were that the analysis used a short time horizon (3 years) to assess a long-term treatment for a chronic disease, the analysis did not estimate QALYs, and the sensitivity analysis did not vary resource use estimates.

**Table 5.8: Results - Duerden 2008[79] economic analysis**

| Incremental cost (£) | Incremental effects | ICER | Uncertainty |
|---|---|---|---|
| Incremental cost per patient not reported | Incremental effect per patient not reported | Base-case analysis: £6,730 per life-year gained (LYG)* | - 10% Reduction in mortality: £2,771 per LYG<br>- 15% Reduction in mortality: £2,180 per LYG<br>- 20% Reduction in mortality: £1,812 per LYG |

* Using the utility score proposed by Mant 2009[37] of 0.65 for patients with heart failure, we estimated the threshold in cost per LYG equivalent to the £20,000 per QALY gained, proposed by NICE, to be £13,000 per LYG.

***Irish study assessing spironolactone***

Results of the cost-effectiveness analysis by Tilson et al. (2003)[80] are presented in Table 5.9. Considering a cost-effectiveness threshold of £13,000 per life-year gained, we concluded that adding spironolactone to optimal medical treatment is highly cost-effective in Ireland. Limitations of the study were that it did not incorporate quality of life, and the mean age of the population of patients in the RALES study was lower than in the Irish population of patient with chronic heart failure (65 vs 76 years).

Table 5.9: Results - Tilson 2003[80] economic analysis*

| Incremental cost (£) | Incremental effects | ICER | Uncertainty |
|---|---|---|---|
| Incremental cost per patient not reported | Incremental effect per patient not reported | Base-case analysis (pDeath = 0.18; pHosp = 0.25; 1 additional outpatient visit for spironolactone cohort; hosp cost = £1887): £291/ Life-Year Gained (LYG)** | - Two-way sensitivity analysis – variation of probabilities of death (0.16, 0.21) and hospitalisation (0.21, 0.29): from £193/LYG to £390/LYG<br>- One-way sensitivity analysis – additional outpatient visits required to initiate medication for spironolactone group (1, 2, 4): from £291/LYG to £710/LYG<br>- One-way sensitivity analysis – cost of hospitalisation varied (£663; £5826): from £455/LYG to spinorolactone cohort dominates[¥] the placebo cohort |

* Costs were converted to pound sterling using Purchasing Power Parities [81]

** Using the utility score proposed by Mant 2009[37] of 0.65 for patients with heart failure, we estimated the threshold in cost per LYG equivalent to the £20,000 per QALY gained, proposed by NICE, to be £13,000 per LYG.

[¥] It was more effective and less costly.

### 5.2.3.6 From evidence to recommendations

***Relative value placed on the outcomes considered***

The GDG reviewed the evidence of using aldosterone antagonists in the treatment of chronic heart failure. Two agents were assessed: Spironolactone and Eplerenone. The GDG noted that there was no direct comparison made between the two agents in the treatment of heart failure.

In the RALES study aldosterone antagonist spironolactone was added to loop diuretics and an ACEI in patients with moderate to severe chronic heart failure (NYHA Class III-IV) who remained symptomatic. The GDG noted the significant 30% reduction of both all cause mortality and heart failure hospitalisation at 24 months of therapy with spironolactone. This treatment also resulted in a significant rise in the incidence of gynaecomastia in males, with no significant rise in the risk of hyperkalaemia. However, subsequent observational evidence suggests that the rise in use of spironolactone following the publication of the RALES study was associated with a significant rise in the number of hospitalisations and mortality related to hyperkalaemia and renal failure in patients with chronic heart failure over the age of 66 years treated with ACEI and spironolactone. (Juurlink 2004)[82]. The GDG took this to highlight the importance of strict monitoring in such patients and of strict adherence to the inclusion and exclusion criteria used in the clinical trial.

In the EPHESUS study, use of the aldosterone antagonist eplerenone was tested in the treatment of symptomatic heart failure (LVEF<40%) after myocardial infarction, or in asymptomatic heart failure caused by left ventricular systolic dysfunction (LVEF<40%) after myocardial infarction in diabetic patients. Eplerenone was used in addition to conventional medical therapy (loop diuretics, ACEI/ARB, beta-blockers). The GDG debated whether the cohort of patients with heart failure after myocardial infarction could be considered as relevant to recommendations on the treatment of chronic heart failure. While the heart failure in this cohort had resulted from acute myocardial infarction, patients continued to display evidence of left ventricular systolic dysfunction (LVEF<40%, with symptoms unless diabetic)

some 3-14 days after myocardial infarction and management continued beyond the acute phase of the infarction. Therefore, the GDG decided that the evidence from this group of trials was relevant. Eplerenone therapy resulted in 14%, and 20% reductions of all cause mortality and sudden death, respectively, at 16 months. The GDG noted the evidence from subgroup analysis of the same trial suggesting better outcomes when the agent is started in the first 7 days following the acute event (Adamopoulos 2009)[83]. Not surprisingly, the impact of therapy was larger in the subgroup of patients with the more severe left ventricular systolic dysfunction (LVEF<30%). There was also a significant reduction of non-fatal heart failure hospitalisations at 16 months, for this group in a post-hoc analysis.

***Quality of evidence***

The GDG noted the greater weight to be given to results of pre-specified analyses of randomised controlled trials as opposed to post-hoc analyses of randomised controlled trials. The GDG felt it was not appropriate to combine the post-hoc analysis of the outcomes in the sub-group of patients with LVEF<30% treated with eplerenone [72], with the study of patients with LVEF<35% treated with spironolactone[74] in a meta-analysis since the two cohorts received different medical therapies and had different backgrounds.

The GDG looked at the small trials that assessed the impact of adding these agents in heart failure patients on quality of life, hyperkalaemia and renal failure. These results are superseded by the larger studies.

***Trade-off between clinical benefits and harms***

The general side effects of this class of drug are hyperkalaemia and renal impairment.

Since the initiation of aldosterone antagonists is a decision to be made by a specialist, and the decision whether to stop or reduce dose of aldosterone antagonists in the light of rises in serum creatinine and potassium or decline of eGFR is also to be made by a specialist, it is not appropriate to give detailed recommendations on how frequently to monitor renal function or when to stop these agents. The GDG recognised the value of the practical recommendations in the previous guideline, and were happy to support these, recognising that they would have a useful role in implementation of the guidance. In addition, the GDG accepts the NICE guidance on the diagnosis and management of Chronic Kidney Disease, recommending the addition of estimating GFR to the routine assessment and monitoring of renal function. Thus urea, electrolytes, creatinine and eGFR should be checked at 1 week, and at 1, 2, 3, and 6 months and 6 monthly thereafter. They also recommended that the aldosterone antagonist dose should be halved if the potassium rises to 5-5-5.9 mmol/l and stopped if the potassium rises above 6 mmol/l or the creatinine above 220 µmol/l. The latter is based on the evidence from the clinical trials of aldosterone antagonists in heart failure.

There are other side-effects that are pertinent to the non-selective aldosterone antagonist spironolactone, namely gynaecomstia and mastodynia

***Trade-off between net health benefits and resource use***

The GDG considered the health economic analysis[79] assessing eplerenone based on the EPHESUS trial[73]. On a three-year time horizon, the incremental cost-effectiveness ratio (ICER) was less than £7000 per life-year gained, making the use of eplerenone in heart failure after myocardial infarction already treated with beta-blockers and ACEI, a cost-effective therapy.

In the cost-effectiveness study by Tilson et al, conducted from an Irish perspective and based on the RALES study[80], the use of spironolactone was also cost effective (ICER of £291 per life-year gained).

There is no comparative study between the two aldosterone antagonists. The GDG felt that the two agents are probably comparable. From a health economic point of view, the substantially lower cost of spironolactone compared to eplerenone was noted. The current

evidence reviewed suggests that spironolactone should be used in severe chronic heart failure (NYHA Class III-IV), and eplerenone should be used in the patients with heart failure following myocardial infarction. The latter is in keeping with the guidance of NICE on the management of myocardial infarction complicated by heart failure.

The GDG are aware of two other trials: the EMPHASIS trial assessing the use of Eplerenone in mild heart failure (NYHA Class II), and the TOPCAT trial looking at the use of smaller doses of spironolactone in patients with heart failure and preserved left ventricular ejection fraction. The EMPHASIS trial was expected to complete recruitment in October 2011, however early termination in May 2010 is said by the sponsors to be due to superiority of eplerenone compared to placebo. The GDG did not have access to the data to analyse.

Another potential use of eplerenone might be where side effects specific to spironolactone (painful gynaecomastia) preclude the continuation of therapy.

The GDG agreed with the 2003 recommendation that a specialist should initiate spironolactone. The same applies to eplerenone.

The GDG suggested as a research recommendation a study investigating the best third agent in the treatment of heart failure, comparing AA vs. ARB in the treatment of heart failure patients who remain symptomatic after optimal therapy with ACEI and BB.

#### 5.2.3.7 Recommendations

The GDG drafted recommendations on the use of aldosterone antagonists as second-line treatment after considering evidence for angiotensin II receptor antagonists and hydralazine in combination with nitrates. See Recommendations R28 and R29.

- In patients with heart failure due to left ventricular systolic dysfunction who are taking aldosterone antagonists, closely monitor potassium and creatinine levels, and eGFR. Seek specialist advice if the patient develops hyperkalaemia or renal function deteriorates[11]. [**new 2010**]
- For patients who have had an acute MI and who have symptoms and/or signs of heart failure and left ventricular systolic dysfunction, treatment with an aldosterone antagonist licensed for post-MI treatment should be initiated within 3-14 days of the MI, preferably after ACE inhibitor therapy. (This recommendation is from 'MI: secondary prevention' NICE clinical guideline 48.) **[2007]**
- Patients who have recently had an acute MI and have clinical heart failure and left ventricular systolic dysfunction, but who are already being treated with an aldosterone antagonist for a concomitant condition (for example, chronic heart failure), should continue with the aldosterone antagonist or an alternative, licensed for early post-MI treatment. (This recommendation is from 'MI: secondary prevention', NICE clinical guideline 48.) **[2007]**

[11] For more information see Appendix J.

## *5.2.4 Isosorbide Dinitrate/Hydralazine combination*

**Clinical Question:**

What is the efficacy and safety of isosorbide dinitrate/hydralazine combination in comparison to a) Placebo, b) ACEI c) placebo + optimal medical treatment in the medical management of adults with heart failure*?*

### 5.2.4.1 Clinical introduction

The veno-dilator isosorbide dinitrate and the arterial dilator hydralazine were used in combination in 1986 in the VHeFT I trial to address the increased pre-load and the increased afterload in heart failure due to severe left ventricular systolic dysfunction. This was the first trial showing that pharmacological therapy could reduce mortality in heart failure. This was followed by the first trial of angiotensin converting enzyme inhibitors (ACEI) in heart failure in 1987. A comparison between the two interventions in 1991 (VHeFT-II trial) showed superiority of ACEI in terms of mortality reduction compared to the hydralazine and nitrate combination. The use of the combined vasodilators Hydralazine and Isosorbide Dinitrate was limited to the cohort of patients with heart failure and severe chronic kidney disease who are not on renal replacement therapy (without direct evidence advising this use). Due to the limited experience in using these agents at the time, it was appropriate for the 2003 guideline to limit their use to cases chosen by the specialist. The guideline raised concerns at the time about using them in combination with other therapeutics.

### Reason for review

Since the publication of the guideline in 2003 new evidence in relation to ethnicity has emerged.

### 5.2.4.2 Clinical Methodological introduction

**a) Isosorbide dinitrate/ hydralazine vs. placebo in addition to optimal medical management in the black population**

Four studies (2 RCTs) were identified comparing isosorbide and hydralazine combination versus placebo in addition to optimal medical management in the black population with heart failure[84-87]. In one RCT the patients self-identified as black (defined as of African descent)[85] and in one RCT the patients were defined as 'black' but no further details of ethnic origin were provided. Two of the studies reported on different outcomes from the main RCT study[86;84]. The studies by Carson [87] and Taylor [84] are analysed separately to reflect the differences in the background medications the patients were receiving. Table 5.10 below presents a summary of the patient population, background medications and interventions for each study.

**Table 5.10: Population and interventions for studies**

| Study | Patient population | Background medications | Intervention | Control |
|---|---|---|---|---|
| CARSON<br>VHEFT I: N=642<br><br>VHEFT II: N=804 | Black (no further details of ethnic origin provided) male patients with a history of heart failure or documentation of left ventricular enlargement or dysfunction by chest radiography, | **'Nearly all patients were receiving diuretics and/or digoxin** | **VHEFT I:**<br>- prazosin 5mgX4/day<br>OR<br>- combination of (hydralazine 75mg + isosorbide dinitrate 40mg)X4/ day.<br>**VHEFT II:**<br>- combination of (hydralazine 75mg | **VHEFT I:**<br>- placebo<br>**VHEFT II:**<br>**-** enalapril 10mgX2/day |

| | | | | |
|---|---|---|---|---|
| | echocardiography, or radionuclide ventriculography. One of the following was required (i) a radiographic cardiothoracic ratio (CTR) >0.55, an echocardiographic left ventricular end-diastolic diameter >2.7 cm/m² of body surface area, or radionuclide left ventricular ejection fraction (EF) <0.45. Patients also had to have reduced maximal exercise tolerance.<br><br>NYHA class<br><br>VHEFT I<br><br>II-III<br><br>VHEFT II I 6%, II 51%, III 43%, IV 0.4% | | + isosorbide dinitrate 40mg)X4/ day | |
| TAYLOR N=1050 | Patients 18 yrs or older, self-identified as black (defined as of African descent), who had NYHA class III or IV heart failure for at least three months<br><br>Inclusion criteria: On standard therapy for heart failure, as deemed appropriate by their physicians; such therapy included angiotensin-converting-enzyme inhibitors (ACEIs), beta blockers for at least three months before randomisation, digoxin, spronolactone and diurectics<br><br>Evidence of left ventricular ejection fraction (LVEF) within the six months preceding | Diuretic 90%<br>ACEI 70%<br>ARB 17%<br>Beta-blocker 74%<br>Carvedilol 56%<br>Digoxin 60%<br>Spironolactone 39% | Fixed-dose combination of isosorbide dinitrate plus hydralazine<br><br>N=518<br><br>37.5 mg hydralazine hydrochloride + 20 mg isosorbide dinitrate three times daily<br><br>Dose increased to two tables three time daily, total dose 225 mg hydralazine and 120 mg isosorbide<br><br>Increase in dose was dependent on the absence of drug-induced side effects | Placebo<br><br>N=532 |

| | | | | |
|---|---|---|---|---|
| | randomisation in the form of resting LVEF of no more than 35% or a resting LVEF of less than 45% with a left ventricular internal end-diastolic diameter of more than 2.9 cm per square meter of body-surface area, or more than 6.5 cm on the basis of echocardiography (Echo) | | | |

### b) Isosorbide dinitrate plus hydralazine vs. ACE I in the black population

One RCT was identified comparing isosorbide dinitrate + hydralazine vs ACEI in the black population [87].

### c) Isosorbide dinitrate plus hydralazine vs. placebo in different age groups

One post hoc sub-group analysis of an RCT was identified comparing isosorbide dinitrate + hydralazine versus placebo in addition to optimal medical management in different age groups[88]. Table 5.11 below summarises the patient population and intervention for this study.

**Table 5.11: Population and interventions for RCT (Cohn et al.)**

| Study | Patient population | Intervention |
|---|---|---|
| COHN<br>N=459 | Men between the ages of 18 to 75 yrs with chronic heart failure<br>Inclusion criteria: evidence of cardiac dysfunction (cardiothoracic ratio ≥ 55 on chest radiography, echocardiographic left ventricular internal diameter in diastole > 2.7 cm/m² body-surface area, or radionuclide ejection fraction < 0.45) in association with reduced exercise intolerance as assessed by progreesive maximal exercise test on a bicycle ergometer | Hydralazine 75 mg plus isosorbide dinitrate 40 mg |

### d) Isosorbide dinitrate plus hydralazine vs. ACE I in different age groups

One post hoc sub-group analysis of an RCT was identified comparing isosorbide dinitrate + hydralazine versus ACE I in different age groups[89]. Table 5.12 below summarises the patient population and intervention for this study.

**Table 5.12: Population and intervention RCT (Johnson et al.)**

| Study | Patient population | Intervention | Comparison |
|---|---|---|---|
| JOHNSON<br>N=804 | Black (no further details of ethnic origin provided) male patients between 18-75 yrs old with chronic CHF. Patients had to have demonstrable cardiac dysfunction confirmed by radionuclide ejection | Hydralazine 300mg + isosorbide dinitrate 160mg & one placebo<br><br>**Run-in period**:<br>All patient had at least 4 weeks to establish optimal | Enalapril 20mg & 2 placebos |

| | | | |
|---|---|---|---|
| | fraction <45%, a cardiothoracic ratio ≥ 0.55, or a left ventricular internal diameter at end diastole (LVIDD) >2.7 cm/m² determined by two-dimensionally directed M-mode echo. Patients also had to demonstrate reduced exercise tolerance in a maximal – exercise bicycle ergometer test (peak oxygen consumption <25 mL·kg-1·min-1 at termination of the test for dyspnoea or fatigue.) | therapeutic dosages of digoxin and a diuretic agent, and any conflicting or nonstudy drugs were discontinued. | |

### 5.2.4.3 Clinical evidence statements

#### a) Isosorbide + hydralazine vs. placebo + optimal medical management in the black population

**TAYLOR [84]**

Compared with placebo (+optimal medical therapy), the combined isosorbide dinitrate plus hydralazine (+optimal medical therapy) has a significant reduction in:

- All cause mortality 0 to 18 months [moderate quality]
- Hospitalisation for heart failure mean 12.8 months [moderate quality]
- Cardiovascular death mean 10 months [moderate quality]

Compared with placebo (+optimal medical therapy), the combined isosorbide dinitrate plus hydralazine (+optimal medical therapy) has a significant improvement in:

- Composite score follow-up range 0 to 18 months [high quality]
- Quality of life [moderate quality]

Compared with placebo (+optimal medical therapy), the combined isosorbide dinitrate plus hydralazine (+optimal medical therapy) was associated with a:

- significant increase in headache [high quality] and dizziness [high quality]

Compared with placebo (+optimal medical therapy), the combined isosorbide dinitrate plus hydralazine (+optimal medical therapy) had no significant effect on:

- The number of unplanned emergency room admissions or unscheduled office visits [moderate quality]

The evidence profile below summarises the quality of the evidence and outcome data from 4 studies (2 RCTs) [84-87] comparing isosorbide dinitrate + hydralazine versus placebo in addition to optimal medical management in the black population (patients self-identified as black: defined as of African descent). Two of the studies reported on different outcomes

## EVIDENCE PROFILE: isosorbide dinitrate + hydralazine (+ optimal medical management) versus placebo (+ optimal medical management) in the black population

**Question:** -Should isosorbide dintrate and hydralazine (vs. placebo) be used in addition to optimal medical therapy in black opatients?
**Bibliography:** Taylor AL, Ziesche S, Yancy C et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. New England Journal of Medicine. 2004; 351(20):2049-2057. Ref ID: 61; Taylor AL, Ziesche S, Yancy CW et al. Early and sustained benefit on event-free survival and heart failure hospitalisation from fixed-dose combination of isosorbide dinitrate/hydralazine: consistency across subgroups in the African-American Heart Failure Trial. Circulation. 2007; 115(13):1747-1753; Angus DC, Linde ZW, Tam SW et al. Cost-effectiveness of fixed-dose combination of isosorbide dinitrate and hydralazine therapy for blacks with heart failure. Circulation. 2005; 112(24):3745-3753;

| Quality assessment | | | | | | | Summary of findings | | | | | Hazard ratio |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality | |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | Isosorbide +/- hydralazine | control | Relative (95% CI) | Absolute | | |
| **composite score (follow-up 0-18 months; range of scores: -6-2; Better indicated by more)** | | | | | | | | | | | | |
| 1 TAYLOR 2004 | randomised trial | no serious limitations[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 518 | 532 | - | MD 0.4 (0.16 to 0.64) | ⊕⊕⊕⊕ HIGH | |
| **all cause mortality (follow-up 0-18 months)** | | | | | | | | | | | | |
| 1 TAYLOR 2004 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | none | 32/518 (6.2%) | 54/532 (10.2%) | RR 0.61 (0.40 to 0.93) | 53 fewer per 1000 (from 18 fewer to 79 fewer) | ⊕⊕⊕O MODERATE | 0.65 (0.37 to 1.15) |
| **Cardiovascular death (follow-up mean 10 months)** | | | | | | | | | | | | |
| 1 TAYLOR 2007 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | none | 26/518 (5%) | 45/532 (8.5%) | RR 0.59 (0.37 to 0.95) | 35 fewer per 1000 (from 4 fewer to 54 fewer) | ⊕⊕⊕O MODERATE | 0.60 (0.38 to 0.95) |
| **Hospitalisation for CHF (follow-up mean 12.8 months)** | | | | | | | | | | | | |
| 1 ANGUS | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[2] | none | 173/518 (33.4%) | 251/532 (47.2%) | RR 0.71 (0.61 to 0.82) | 23 fewer per 1000 (from 14 fewer to -31 fewer) | ⊕⊕⊕O MODERATE | |
| **Total no. of ER and unscheduled office visits (follow-up mean 12.8 months)** | | | | | | | | | | | | |
| 1 ANGUS | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | none | 32/518 (6.2%) | 43/532 (8.1%) | RR 0.76 (0.49 to 1.19) | 19 fewer per 1000 (from 41 fewer to 15 more) | ⊕⊕⊕O MODERATE | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **quality of life (Minnesota Living with Heart Failure) (follow-up mean 6 months; range of scores: 0-105; Better indicated by less)** | | | | | | | | | | | | |
| 1 TAYLOR 2004 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[3] | none | 518 | 532 | - | MD -2.9 (-5.43 to -0.37) | ⊕⊕⊕O MODERATE | |
| **adverse events- headache (follow-up 0-18 months)** | | | | | | | | | | | | |
| 1 TAYLOR 2004 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision | none | 243/518 (46.9%) | 102/532 (19.2%) | RR 2.45 (2.01 to 2.98) | 278 more per 1000 (from 194 more to 380 more) | ⊕⊕⊕⊕ HIGH | |
| **adverse events-dizziness (follow-up 0-18 months)** | | | | | | | | | | | | |
| 1 TAYLOR 2004 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision | none | 152/518 (29.3%) | 65/532 (12.2%) | RR 2.40 (1.84 to 3.13) | 171 more per 1000 (from 102 more to 260 more) | ⊕⊕⊕⊕ HIGH | |

[1] < 300 events; pooled or best estimate of effect includes both negligible effect and appreciable benefit
[2] 95% confidence interval includes no effect and the upper or lower confidence limit crosses the minimal important difference (MID), either for benefit of harm
[3] 95% confidence interval includes no effect and the upper or lower confidence limit crosses the minimal important difference (MID), either for benefit of harm

## CARSON [87]

Compared with placebo, the combined isosorbide dinitrate plus hydralazine had no significant effect on:

- All cause mortality up to 66 months (5.5 yrs) [moderate quality]
- Hospitalisation for heart failure 66 months [moderate quality]

The evidence profile below summarises the quality of the evidence and outcome data from the one RCT[87] comparing isosorbide dinitrate + hydralazine versus placebo in the black population (patients self-identified as black: defined as of African descent).

**Question:** Should Isosorbide + hydralazine be used vs placebo?
**Bibliography:** Carson P, Ziesche S, Johnson G et al. Racial differences in response to therapy for heart failure: Analysis of the Vasodilator-Heart Failure Trials. Journal of Cardiac Failure. 1999; 5(3):178-187. Ref ID: 650

| Quality assessment | | | | | | | Summary of findings | | | | | Hazard Ratio |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality | |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | Isosorbide +/- hydralazine | control | Relative (95% CI) | Absolute | | |
| **all cause mortality (follow-up 0-5.5 years)** | | | | | | | | | | | | |
| 1 CARSON | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | none | 15/49 (30.6%) | 35/79 (44.3%) | RR 0.69 (0.42 to 1.13) | 53 fewer per 1000 (from 18 fewer to 79 more) | ⊕⊕⊕O MODERATE | 0.65 (0.37 to 1.15) |
| **hospitalisation for CHF (follow-up 66 months)** | | | | | | | | | | | | |
| 1 CARSON | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | none | 11/49 (22.4%) | 16/79 (20.3%) | RR 1.11 (0.56 to 2.19) | 22 more per 1000 (from 89 fewer to 242 more) | ⊕⊕⊕O MODERATE | |

[1] < 300 events; pooled or best estimate of effect includes both negligible effect and appreciable benefit

b) **Isosorbide dinitrate plus hydralazine vs. ACE I in the black population**

Compared with ACEI, isosorbide dinitrate plus hydralazine had no significant effect on:

- All cause mortality follow-up 0 to 66 months [moderate quality]
- Hospitalisations for chronic heart failure follow-up 0 to 66 months [moderate quality]

The evidence profile below summarises the quality of the evidence and outcome data from 1 RCT [87] comparing isosorbide + hydralazine versus ACE I in the black population.

## EVIDENCE PROFILE: isosorbide dinitrate + hydralazine versus ACE I in the black population

**Question:** Should isosorbide dinitrate + hydralazine vs ACE I be used for chronic heart failure in black population?
**Bibliography:** Carson P, Ziesche S, Johnson G et al. Racial differences in response to therapy for heart failure: Analysis of the Vasodilator-Heart Failure Trials. Journal of Cardiac Failure. 1999; 5(3):178-187. Ref ID: 650

| Quality assessment | | | | | | | Summary of findings | | | | | Hazard Ratio |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality | |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | isosorbide + hydralazine[2] | ACE I | Relative (95% CI) | Absolute | | |
| **all cause mortality (follow-up 0-66 months)** | | | | | | | | | | | | |
| 1 CARSON 1999 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | none | 39/109 (35.8%) | 39/106 (36.8%) | RR 0.97 (0.68 to 1.39) | 11 fewer per 1000 (from 118 fewer to 144 more) | ⊕⊕⊕O MODERATE | 0.97 (0.62 to 1.51) |
| **hospitalisation for CHF (follow-up 0-66 months)** | | | | | | | | | | | | |
| 1 CARSON 1999 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | none | 23/109 (21.1%) | 24/106 (22.6%) | RR 0.93 (0.56 to 1.55) | 16 fewer per 1000 (from 99 fewer to 124 more) | ⊕⊕⊕O MODERATE | |

[1] total number of events is less than 300 and 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect includes both negligible effect and appreciable benefit

## c) Isosorbide dinitrate plus hydralazine vs. placebo in different age groups

Compared with placebo, the post-hoc sub group analysis did not detect a significant difference for isosorbide plus hydralazine compared with placebo in the > 60 yrs or < 60 yrs for:

- all cause mortality [low quality]

The evidence profile below summarises the quality of the evidence and outcome data from 1 RCT (post-hoc sub group analysis) [88] comparing isosorbide dinitrate + hydralazine versus placebo in different age groups. The table below summarises the patient population and intervention for this study.

### Evidence profile: isosorbide dinitrate + hydralazine versus placebo in different age groups

**Question:** Should isosorbide dinitrate + hydralazine vs placebo be used for chronic heart failure in different age groups?
**Bibliography:** Cohn JN, Archibald DG, Francis GS. Veterans Administration Cooperative Study on Vasodilator Therapy of Heart Failure: Influence of prerandomization variables on the reduction of mortality by treatment with hydralazine and isosorbide dinitrate. Circulation. 1987; 75(5 II SUPPL.):IV. Ref ID: 660

| Quality assessment | | | | | | | Summary of findings | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | | |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | isosorbide + hydralazine | placebo | Relative (95% CI) | Absolute | Quality | Hazard ratio |
| **all cause mortality rate in <60yrs (per annum)** | | | | | | | | | | | | |
| 1 COHN 1987 | randomised trial | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 12/93 (12.9%) | 24/136 (17.6%) | RR 0.73 (0.39 to 1.39) | 48 fewer per 1000 (from 107 fewer to 69 more) | ⊕⊕OO LOW | 0.72 (0.37 to 1.41) |
| **all cause annual mortality > 60 yrs (per annum)** | | | | | | | | | | | | |
| 1 COHN 1987 | randomised trial | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 16/93 (17.2%) | 26/137 (19%)<br>0% | RR 0.91 (0.52 to 1.59) | 17 fewer per 1000 (from 91 fewer to 112 more)<br>0 fewer per 1,000 | ⊕⊕OO LOW | 0.90 (0.48 to 1.66) |

[1] Post-hoc sub group analysis
[2] total number of events is less than 300; 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect includes both negligible effect and appreciable benefit

### d) Isosorbide plus hydralazine vs. ACE I in different age groups

The evidence profile below summarises the quality of the evidence and outcome data from 1 RCT (post-hoc subgroup analysis) [89] comparing isosorbide dinitrate + hydralazine versus ACE I in different age groups. The table below summarises the patient population and intervention for this study.

Compared with ACEI, the post-hoc sub group analysis did not detect a significant difference for isosorbide dinitrate plus hydralazine compared with ACEI in the over 60 yrs or < 60 yrs for:

- all cause mortality at 2 yrs [low quality]

**Evidence profile: comparing isosorbide dinitrate + hydralazine versus ACE I in different age groups**

| **Author(s):**<br>**Date:** 2009-03-11<br>**Question:** Should isosorbide dinitrate + hydralazine vs ACE I be used for chronic heart failure in different ages?<br>**Settings:**<br>**Bibliography:** Reference Johnson G, Carson P, Francis GS et al. Influence of prerandomization (baseline) variables on mortality and on the reduction of mortality by enalapril. Veterans Affairs Cooperative Study on Vasodilator Therapy of Heart Failure (V-HeFT II). V-HeFT VA Cooperative Studies Group. Circulation. 1993; 87(6:Suppl):Suppl-9. Ref ID: 184 **Quality assessment** | | | | | | | **Summary of findings** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | **No of patients** | | **Effect** | | **Quality** | **Hazard ratio** |
| **No of studies** | **Design** | **Limitations** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **isosorbide + hydralazine** | **ACE I** | **Relative (95% CI)** | **Absolute** | | |
| **all cause mortality at 2 years <60 yrs (follow-up 2 years)** | | | | | | | | | | | | |
| 1<br>JOHNSON 1993 | randomised trial | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 65/176 (36.9%) | 56/172 (32.6%) | RR 1.13 (0.85 to 1.51) | 42 more per 1000 (from 49 fewer to 166 more) | ⊕⊕OO LOW | 1.14 (0.84 to 1.55) |
| **all cause mortality at 2 years >60 yrs (follow-up 2 years)** | | | | | | | | | | | | |
| 1<br>JOHNSON 1993 | randomised trial | serious[1] | no serious inconsistency | no serious indirectness | Serious | none | 88/225 (39.1%) | 76/231 (32.9%) | RR 1.19 (0.93 to 1.52) | 63 more per 1000 (from 23 fewer to 171 more) | ⊕⊕OO LOW | 1.24 (0.91 to 1.68) |

[1] post-hoc subgroup analysis
[2] total number of events is less than 300; 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect includes both negligible effect and appreciable benefit

### 5.2.4.4 Health Economic methodological introduction

From the 2003 Guideline[22], one US study considered the cost effectiveness of isosorbide dinitrate and hydralazine combination in comparison to standard therapy with digoxin and diuretics, using data from the V-HeFT I trial. This was found to be a cost-effective therapy in the US context, but the generalisability of this result to the UK is questionable.

From our review, one cost-effectiveness analysis assessing the isosorbide dinitrate +hydralazine (ISDN+HYD) combination in patients with chronic heart failure was identified and presented to the GDG.

Angus et al. (2005)[86] developed a cost-effectiveness analysis based on the African-American Heart Failure Trial (A-HeFT), reporting cost per life-year gained. A US Medicare perspective was taken, and an 18-month time horizon (A-HeFT follow-up) and a lifetime horizon were considered. The assessed population was black people with moderate to severe heart failure (94.9% with class III NYHA heart failure). Compared interventions were (1) standard therapy (beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, aldosterone antagonist, digoxin and diuretics); and (2) standard therapy + (ISDN+HYD) combination therapy (20mg / 37.5mg), starting with one tablet three times daily and titrating to two tablets three times daily as tolerated. Survival estimates for the 18-month analysis were taken from the A-HeFT study. Resource use estimates were also taken from the A-HeFT study. To extrapolate survival for a lifetime horizon, the authors used survival estimates reported by Bardy et al.[90] (NYHA class III patients) and assumed no additional survival benefits of ISDN+HYD therapy beyond the duration of the trial. In addition, it was assumed that there would be no additional benefits of ISDN+HYD therapy in terms of resource use after 18 months (the ISDN+HYD therapy cost was the only additional cost for the treatment arm after 18 months). A secondary analysis on a lifetime horizon was conducted considering one additional year of effect of ISDN+HYD therapy beyond the duration of the trial. Cost components considered were hospitalisation (including physician cost), emergency room visits, unscheduled physician visits, scheduled physician visits, ISDN+HYD therapy, concomitant medication and other cares. Table 5.13 presents the quality and applicability assessment of this economic analysis.

**Table 5.13: Economic study assessment**

| Study | Study quality* | Study applicability** |
|---|---|---|
| Angus et al. (2005)[86] | Minor limitations (a) | Partially applicable (b) |

*Very serious limitations / Potentially serious limitations / Minor limitations; ** Directly applicable / Partially applicable / Not applicable

(a) Outcomes were not measured as QALYs; Incremental effect not reported

(b) Analysis developed from the US perspective; Population assessed limits the generalisation of results

### 5.2.4.5 Health economic evidence statements

Results of the Angus et al. (2005) analysis[86] are presented in Table 5.14. Bootstrapping was used to estimate confidence around the within trial cost-effectiveness results (18 months). Results show that ISDN/HYD therapy is cost-effective in black people with advanced heart failure in the US. According to the A-HeFT trial, the ISDN+HYD combination therapy improves survival, and leads to fewer hospitalisations, shorter hospitalisations, and consequently lower healthcare costs. Combining cost and health outcomes, ISDN+HYD is a dominant therapy (more effective and less costly) at least over a short time horizon. We can also conclude that this therapy is associated with a favourable cost-effectiveness profile in a long-time horizon. However, the generalisation of these results in a UK context is

questionable as this study was conducted from a US perspective, a health-care system not directly comparable to the UK NHS.

**Table 5.14: Results - Angus 2005[86] economic analysis***

| | 18 months time horizon (A-HeFT follow-up) | | Lifetime horizon | |
|---|---|---|---|---|
| | **Main analysis** | **Bootstrap simulation sampling** | **No additional benefits of ISDN/HYD therapy beyond the duration of trial (18 months)** | **One additional year of effect of ISDN/HYD therapy beyond the duration of trial (18 months)** |
| **Heart failure-related cost** | Dominant** (incremental cost: £337)¥ | 49% dominant; 66% better than ~£6300 per Life-Year Gain (LYG)¥¥ | £26,419 per LYG | £14,474 per LYG |
| **All healthcare-related cost** | Dominant** (incremental cost: £1093)¥ | 71% dominant; 82% better than ~£6300 per LYG | £28,063 per LYG | £20,794 per LYG |

* Costs were converted in pound sterling using Purchasing Power Parities[81]

** Improved survival and saved cost

¥ Incremental effect not reported

¥¥ Using the utility score proposed by Mant 2009[37] of 0.65 for patients with heart failure, we estimated the threshold in cost per LYG equivalent to the £20,000 per QALY gained proposed by NICE to be £13,000 per LYG.

### 5.2.4.6 From evidence to recommendations

***Relative value placed on the outcomes considered***

The GDG reviewed the statement from the 2003 guidelines concerning the use of the combination of Hydralazine and Isosorbide Dinitrate in heart failure, and felt that the 2003 conclusions were valid, even though they were based on a trial when the baseline therapy in 1986 was diuretics and digoxin only. The GDG noted that the main studies related to this subject, since the publication of the 2003 guidelines, were on the use of the combination in the black population, who were found to be less responsive than non-blacks to treatment with Angiotensin Converting Enzyme Inhibitors (ACEI).[85],[84],[86],[87] Subsequent evidence of benefit for the combination of hydralazine and nitrates was found from subgroup analyses of prospective studies using the combination either against placebo or in comparison to ACEI. Evidence for the impact of the combination in black patients with moderate to severe heart failure (mainly NYHA III) came from the AHEFT study where the combination of hydralazine and nitrates was given in addition to optimal therapy that included ACEI/ARB, BB and Aldosterone antagonists. The GDG noted that adding the combination to optimal therapy (ACEI, BB and AA) in such patients reduced morbidity and mortality.

The response was related to the treatment with the combination rather than with one of the two drugs. It was felt that patients should be simultaneously commenced on both drugs, and that the doses should be increased gradually according to tolerance, aiming to achieve the target doses used in the clinical trials.

The GDG considered the use of the term ‘black’ as used in these studies. Black patients of African and Carribean descent have been found to derive less benefit than non-blacks from ACEI in both heart failure and hypertension trials, and it is this group in the UK to which this evidence is applicable.

### *Quality of evidence*

The RCT evidence on the treatment of black people with heart failure with hydralazine and nitrate *vs.* placebo and vs ACEI was of moderate to high quality. The evidence for the age groups analysis was of low quality due to the inclusion of post-hoc subgroup analysis from RCT data [88,89].

### *Trade-off between clinical benefits and harms*

In a post-hoc analysis in blacks, the treatment of black people with heart failure with hydralazine and nitrate *vs.* placebo resulted in reduced morbidity and mortality, better quality of life but with more headache and dizziness. The comparison with ACEI was associated with wide confidence intervals. The GDG noted that the patients included in the AHEFT trial [85] were already treated with ACEI, beta-blockers (BB), and aldosterone antagonists suggesting that earlier concerns about the safety of the combination in the presence of treatment with ACEI and BB could be allayed.

The GDG noted that the effect of the combination is not limited to an age group. The GDG also noted that side-effects could limit some patients' tolerance of the treatment with the combination.

The GDG discussed the potential use of the combination in heart failure patients with renal dysfunction, in whom ACEI and ARB could not be used. The GDG noted the publication of the Chronic Kidney Disease Guideline No. 73 (2008) that gives recommendations on the management of patients with impaired renal function who may be on ACEI, ARB and/or aldosterone antagonists [91].

There is no evidence on the use of this combination in non-black patients who remain symptomatic after treatment with ACEI and beta-blockers. In the absence of such evidence, one could consider adding these agents on the pathophysiological basis of the helpful vasodilatation offered by these agents in such patients. In addition to the lack of evidence in this regard, and to the potential for intolerance related to side-effects, the introduction of these agents requires the patient's blood pressure to be adequate or raised. It may be that non-black hypertensive patients with heart failure who remain symptomatic after treatment with ACEI and beta-blockers and who could not have ARB or aldosterone antagonists could benefit from the introduction of this combination. The GDG noted that international guidelines (ESC/ACC/AHA) made such a recommendation but felt that, in the absence of firm evidence to support this, a research recommendation was more appropriate.

The addition of this combination should be initiated by a specialist.

### *Trade-off between net health benefits and resource use*

The GDG noted that the health economic review suggested that the addition of this combination in black patients, who remain symptomatic of heart failure while on ACEI and beta-blockers, is cost saving over 18 months. It is likely to be cost-effective over the lifetime as long as the effects observed in trials continue for some months beyond the 18 month trial follow-up. The GDG noted that the cost-effectiveness analysis[86] was developed from a US perspective, so may be of limited applicability to the UK NHS. The GDG felt that the short time horizon was not a significant limitation given that life expectancy is short in patients who remain at NYHA class III (94% of the cohort) despite treatment with ACEI and beta-blockers.

#### 5.2.4.7 Recommendations

- Seek specialist advice and consider hydralazine in combination with nitrate for patients with heart failure due to left ventricular systolic dysfunction who are intolerant of ACE inhibitors and ARBs. **[2010]**

The GDG also drafted a recommendation on the use of hydralazine in combination with nitrate as second-line treatment, after considering evidence for aldosterone antagonists and ARBs. See Recommendations R28 and R29.

### *5.2.5 Angiotensin-II receptor antagonists vs placebo*

**Clinical question:**

What is the efficacy and safety of angiotensin-II receptor antagonists (ARB) in comparison to placebo in the medical management of adults with heart failure?

#### 5.2.5.1 Clinical introduction

The modulation of the renin-angiotensin-aldosterone axis as an integral pathway for the therapy of heart failure is well established. This is achieved through the addition of ACEI and aldosterone antagonists. In addition, angiotensin receptor blockers (Antagonists of type I receptor of Angiotensin II) are proven as anti-hypertensive agents, working to modulate the renin-angiotensin-aldosterone axis. Unlike ACEI they do not cause dry cough, one of the most common causes of stopping ACEI therapy. When patients are intolerant of ACEI, the introduction of angiotensin receptor blockers (ARB) is frequently proposed as an alternative. This was the position in 2003 when the existing guidelines were published. However no firm recommendation was possible at that stage.

**Reasons for Review**

New randomised clinical trials have reported on the use of ARBs in the treatment of heart failure due to left ventricular systolic dysfunction as an add-on to ACEI, in the treatment of heart failure due to left ventricular systolic dysfunction where ACEI are not tolerated, in heart failure with preserved left ventricular ejection fraction and in heart failure due to left ventricular systolic dysfunction caused by myocardial infarction. Some of the trials looking at similar populations produced different results. Thus, there is a need for a review and appraisal of the evidence.

Traditionally, when ACEI are not tolerated due to side effects (such as cough), an ARB is used. However, the question arises as to whether ARBs exert the same effect as ACEI. In addition, another question is whether all ARBs exert the same effect. Clarification is needed on the potential risks from combining ACEI, ARB and beta-blockers. Another issue is whether patients who remain symptomatic despite therapy with ACEI and beta blockers should be additionally treated with ARBs, aldosterone antagonists or the combination of hydralazine and nitrates.

#### 5.2.5.2 Clinical Methodological introduction

**Angiotensin-II receptor antagonists (ARBS) vs. placebo**

**(a). In patients with heart failure and LVSD:**

Five studies were identified comparing ARBs vs. placebo in heart failure with left ventricular systolic dysfunction (LVSD) [92-96].

In all the studies the use of background angiotensin-converting enzyme inhibitors (ACE-I) was not permitted during the trial period.

*Populations:*

- NYHA class II-IV and LVEF ≤40% (CHARM-alternative, Val-HeFT-post-hoc analysis)
- NYHA class II-III and LVEF ≤45% (STRETCH, ARCH-J)
- NYHA class II-IV, mean pulmonary capillary wedge pressure ≥15 mmHg (Mazayev)

*Intervention:*

- Candesartan- CHARM-alternative (up to 32 mg/day), STRETCH (up to 16mg/day), ARCH-J (up to 8mg/day)
- Valsartan -Val-HeFT-post-hoc analysis (up to 160mg x2/day) Mazayev (40, 80 or 160mg x2 day)

*Note:*

- Hypotension was reported as either an adverse event or a cause for discontinuation. In the post hoc subgroup, hypotension was reported as a persistent standing systolic BP < 80 mm Hg or symptoms of hypotension and a cause of treatment discontinuation.

**(b) In patients with HFPEF:**

In I-PRESERVE [97] treatment with an angiotensin-converting enzyme inhibitor (ACEI) was only permitted when such therapy was considered essential, 25% of included patients were subsequently on a background of ACE inhibitor at baseline. In CHARM-preserved [98] initially ACE inhibitors were not allowed as concomitant therapy, however with the publication of new trials, their use was permitted in appropriate patients; 20% of included patients were subsequently on a background of ACE inhibitor at baseline.

*Populations:*

- NYHA class II-IV, LVEF >40% (CHARM-preserved)
- NYHA class II-IV, LVEF ≥45% (I-PRESERVE)

*Intervention:*

- Candesartan- CHARM-preserved (up to 32mg/day)
- Irbesartan- I-PRESERVE (up to 300mg/day)

*Note:*

Hypotension was reported as either a serious adverse events or a cause for discontinuation

### 5.2.5.3 Clinical evidence statements

**a) ARBs vs. placebo in heart failure with left ventricular systolic dysfunction (LVSD).**

Compared with placebo, angiotensin-II receptor antagonists had a significant reduction on:

- HF hospitalisation [moderate quality]
- Composite score (CV mortality and HF hospitalisation) [moderate quality]

Compared with placebo, angiotensin-II receptor antagonists significantly increased:

- Hyperkalaemia [moderate quality]
- Raised creatinine [moderate quality]
- Hypotension [moderate quality]

Compared with placebo, angiotensin-II receptor antagonists significantly improved:

- Quality of life scores (MLWHFQ) [moderate quality]

Compared with placebo, angiotensin-II receptor had a non-significant affect on:

- All cause mortality [high quality]
- All cause mortality post-hoc subgroup [low quality]
- Hypotension post-hoc subgroup [low quality]
- Mean increase in creatinine post-hoc subgroup [moderate quality]

Change in NYHA class was reported in one study [95]:

- Improved: placebo: 28/201 (14%); 4mg: 39/203 (19%); 8mg 41/202 (20%); 16mg: 34/201 (17%); Total on Candesartan: 114/606 (24%)
- No change: placebo: 170/201(85%); 4mg: 162/203 (80%); 8mg: 161/202 (80%); 16mg: 165/201 (82%); Total on Candesartan: 488/ 606 (81%)
- Deterioration: placebo: 3/210 (1%); 4mg: 2/203 (1%); 8mg: 0/202 (0%); 16mg: 2/201 (1%); Total on Candesartan: 4/606 (0.7%)

The evidence profile below summarises the quality of the evidence and outcome data from 5 studies [92-96] comparing **ARBs vs. placebo in heart failure with left ventricular systolic dysfunction (LVSD)**

## Evidence profile: ARBs vs. placebo in heart failure with left ventricular systolic dysfunction (LVSD).

**Question:** Should angiotensin II receptor blockers (ARBs) vs. placebo be used for chronic heart failure?
**Bibliography:** Matsumori A. Efficacy and safety of oral candesartan cilexetil in patients with congestive heart failure. *European Journal of Heart Failure.* 2003; 5(5):669-677 **ARCH-J**. Maggioni AP, Anand I, Gottlieb SO et al. Effects of valsartan on morbidity and mortality in patients with heart failure not receiving angiotensin-converting enzyme inhibitors. *Journal of the American College of Cardiology.* 2002; 40(8):1414-1421 **Val-HeFT-post-hoc.** Granger CB, McMurray JJ, Yusuf S 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(9386):772-776. Riegger GAJ, Bouzo H, Petr P et al. Improvement in exercise tolerance and symptoms of congestive heart failure during treatment with candesartan cilexetil. *Circulation.* 1999; 100(22):2224-2230 **STRETCH**. Mazayev VP, Fomina IG, Kazakov EN et al. Valsartan in heart failure patients previously untreated with an ACE inhibitor. *International Journal of Cardiology.* 1998; 65(3):239-246.

| Quality assessment | | | | | | | Summary of findings | | | | | Hazard ratio |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality | |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | angiotensin II receptor blockers (ARBs) | placebo | Relative (95% CI) | Absolute | | |
| **All cause mortality (follow-up 1-24 months)** | | | | | | | | | | | | |
| 4 Mazayez, STRETCH, CHARM-alternative, ARCH-J | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision | none | 278/1869 (14.9%) | 301/1396 (0.47%)<br>30% | RR 0.90 (0.79 to 1.04) | 0 fewer per 1,000<br>30 fewer per 1,000 | ⊕⊕⊕⊕ HIGH | 0.84 (0.71 to 0.99) |
| **All cause mortality- post hoc subgroup (follow-up 24 months)** | | | | | | | | | | | | |
| 1 Val-HeFT- post-hoc analysis | randomised trial | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 32/185 (17.3%) | 46/181 (25.4%) | RR 0.68 (0.46 to 1.02) | 84 fewer per 1000 (from 147 fewer to 15 more) | ⊕⊕OO LOW | 0.65 (0.41 to 1.02) |
| **HF hospitalisation (follow-up 7.5-24 months)** | | | | | | | | | | | | |
| 2 CHARM-alternative, ARCH-J | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[3] | none | 215/1161 (18.5%) | 303/1159 (12%)<br>28% | RR 0.71 (0.61 to 0.83) | 34 fewer per 1,000<br>81 fewer per 1,000 | ⊕⊕⊕O MODERATE | |
| **Composite score: CV death and HF hospitalisation (follow-up median 33.7 months)** | | | | | | | | | | | | |
| 1 CHARM-alternative | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[3] | none | 334/1013 (33%) | 406/1015 (40%) | RR 0.82 (0.73 to 0.93) | 72 fewer per 1000 (from 28 fewer to 108 fewer) | ⊕⊕⊕O MODERATE | |
| **Hyperkalaemia (follow-up median 33.7 months)** | | | | | | | | | | | | |
| 1 CHARM-alternative | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[2] | none | 19/1013 (1.9%) | 3/1015 (0.3%) | RR 6.35 (1.88 to 21.38) | 16 more per 1000 (from 3 more to 61 more) | ⊕⊕⊕O MODERATE | |
| **Raised creatinine (follow-up 3-24 months)** | | | | | | | | | | | | |
| 2 CHARM- | randomised | no serious | no serious | no serious | serious[4] | none | 79/1646 (4.8%) | 31/1226 | RR 2.14 | 22 more per | ⊕⊕⊕O | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| alternative, STRETCH | trial | limitations | inconsistency | indirectness | | | | (2%)<br>3% | (1.42 to 3.22) | 1,000<br>34 more per 1,000 | MODERATE | |
| **Mean increase in creatinine- post hoc subgroup (follow-up 24 months; measured with: mg/dl; range of scores: -; Better indicated by less)** | | | | | | | | | | | | |
| 1 Val-HeFT- post-hoc analysis | randomised trial | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 185 | 181 | - | MD 0.08 (0.08 to 0.08) | ⊕⊕⊕O MODERATE | |
| **Hypotension (follow-up 1-24 months)** | | | | | | | | | | | | |
| 3 CHARM-alternative, STRETCH, Mazayev | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[4] | none | 48/1239 (3.9%) | 11/1188 (1.3%)<br>1.3% | RR 4.06 (2.15 to 7.64) | 0 more per 1,000<br>39 more per 1,000 | ⊕⊕⊕O MODERATE | |
| **Hypotension- post hoc subgroup (follow-up 24 months)** | | | | | | | | | | | | |
| 1 Val-HeFT- post-hoc | randomised trial | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 1/185 (0.5%) | 1/181 (0.6%) | RR 0.98 (0.06 to 15.52) | 0 fewer per 1000 (from 6 fewer to 87 more) | ⊕⊕OO LOW | |
| **Quality of life score (MLWHFQ)- post hoc subgroup (follow-up 1 years; measured with: Minnesota Living with Heart Failure Questionnaire; range of scores: 0-105; Better indicated by less)** | | | | | | | | | | | | |
| 1 Val-HeFT- post-hoc analysis | randomised trial | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 185 | 181 | - | MD -5.16 (-5.77 to -4.55) | ⊕⊕⊕O MODERATE | |

[1] post hoc analysis of the patients not receiving ACE I taken from the original Val-HeFT trial
[2] total number of events is less than 300, 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect includes both negligible effect and appreciable benefit or appreciable harm.
[3] 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect includes both negligible effect and appreciable benefit or appreciable harm.
[4] total number of events is less than 300

### b) ARBs vs. placebo in heart failure with preserved ejection fraction (HFPEF).

Compared with placebo, angiotensin-II receptor antagonists significantly increased:

- Hyperkalaemia [moderate quality]
- Raised creatinine [moderate quality]

Compared with placebo, angiotensin-II receptor antagonists had a non-significant effect on:

- All cause mortality [high quality]
- CV mortality [high quality]
- Hypotension [low quality] - however there was serious heterogeneity ($I^2$ 82%) seen when meta-analysing the results from I-PRESERVE and CHARM-preserved for this outcome. A possible cause for the inconsistency of results could be due to the use of the stronger drug candersartan in CHARM-preserved compared to irbesartan in I-PRESERVE.
- HF hospitalisation [high quality]
- Composite score (CV mortality and HF hospitalisation) [high quality]

Compared with placebo, angiotensin-II receptor antagonists made no difference to:

- Mean increase in creatinine [high quality]

The evidence profile below summarises the quality of the evidence and outcome data from 2 studies [97,98] comparing ARBs vs. placebo in heart failure with preserved ejection fraction (HFPEF).

## Evidence profile: ARBs vs. placebo in heart failure with preserved ejection fraction

**Question:** Should angiotensin II receptor blockers (ARBs) vs. Placebo be used for HFPEF?
**Bibliography:** Massie BM, Carson PE, McMurray JJ et al. Irbesartan in patients with heart failure and preserved ejection fraction. *New England Journal of Medicine.* 2008; 359(23):2456-2467 **I-PRESERVE** Yusuf S, Pfeffer MA, Swedberg K et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the **CHARM-Preserved Trial**. *Lancet.* 2003; 362(9386):777-781.

| Quality assessment | | | | | | | Summary of findings | | | | | Hazard ratio |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality | |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | angiotensin II receptor blockers (ARBs) | Placebo | Relative (95% CI) | Absolute | | |
| **All cause mortality (follow-up 24-49 months)** | | | | | | | | | | | | |
| 2 I-PRESERVE, CHARM PRESERVED | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision | none | 682/3581 (19%) | 680/3570 (16%)<br>21% | RR 1.00 (0.91 to 1.10) | 0 fewer per 1,000<br>0 fewer per 1,000 | ⊕⊕⊕⊕ HIGH | 0.99 (0.90 to 1.09) |
| **CV mortality (follow-up 24-49 months)** | | | | | | | | | | | | |
| 2 I-PRESERVE, CHARM PRESERVED | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision | none | 481/3581 (13.4%) | 472/3570 (11%)<br>15% | RR 1.02 (0.9 to 1.14) | 2 more per 1,000<br>2 more per 1,000 | ⊕⊕⊕⊕ HIGH | 1.00 (0.88 to 1.14) |
| **HF hospitalisation (follow-up 24-49 months)** | | | | | | | | | | | | |
| 2 I-PRESERVE, CHARM PRESERVED | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision | none | 566/3581 (15.8%) | 612/3570 (16%)<br>18% | RR 0.92 (0.83 to 1.02) | 12 fewer per 1,000<br>14 fewer per 1,000 | ⊕⊕⊕⊕ HIGH | |
| **Composite score: CV death and HF hospitalisation (follow-up 24-49 months)** | | | | | | | | | | | | |
| 2 I-PRESERVE, CHARM PRESERVED | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision | none | 761/3581 (21.3%) | 804/3570 (21%)<br>24% | RR 0.94 (0.86 to 1.03) | 12 fewer per 1,000<br>14 fewer per 1,000 | ⊕⊕⊕⊕ HIGH | |
| **Hyperkalaemia (follow-up 24-49 months)** | | | | | | | | | | | | |
| 2 I-PRESERVE, CHARM PRESERVED | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | none | 34/3581 (0.9%) | 18/3570 (0.4%)<br>0.5% | RR 1.88 (1.07 to 3.33) | 3 more per 1,000<br>4 more per 1,000 | ⊕⊕⊕O MODERATE | |
| **Raised creatinine (follow-up median 36.6 months)** | | | | | | | | | | | | |
| 1 CHARM-PRESERVED | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[2] | none | 72/1514 (4.8%) | 36/1509 (2.4%) | RR 1.99 (1.34 to 2.96) | 24 more per 1000 (from 8 more to 47 more) | ⊕⊕⊕O MODERATE | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Mean increase in creatinine (follow-up mean 49.5 months; measured with: mg/dl; range of scores: -; Better indicated by less)** | | | | | | | | | | | | |
| 1<br>I-PRESERVE | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision | none | 2067 | 2061 | - | MD 0.04 (0.02 to 0.06) | ⊕⊕⊕⊕<br>HIGH | |
| **Hypotension (follow-up 24-49 months)** | | | | | | | | | | | | |
| 2<br>I-PRESERVE, CHARM PRESERVED | randomised trial | no serious limitations | serious[3] | no serious indirectness | serious[1] | none | 97/3581 (2.7%) | 79/3570 (1%)<br>3% | RR 1.22 (0.91 to 1.64) | 2 more per 1,000<br>6 more per 1,000 | ⊕⊕OO<br>LOW | |

[1] total number of events is less than 300, 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect includes both negligible effect and appreciable benefit or appreciable harm.
[2] total number of events is less than 300
[3] 82 % heterogeneity

### 5.2.5.4 Health Economic methodological introduction

From the 2003 Guideline[22], there was no UK-based economic evaluation of the use of angiotensin-II receptor antagonists in the treatment of heart failure. One cost-effectiveness analysis from the United States was found comparing losartan with the ACE inhibitor captopril[99]. This analysis showed little difference between the cost-effectiveness ratio of these two drugs when used for symptomatic heart failure in older people.

From our review, one economic analysis developed from the UK perspective assessing an angiotensin-II receptor antagonist (ARB) in patients with chronic heart failure was identified and presented to the GDG.

McMurray et al. (2006)[100] developed an economic analysis based on the 'Assessment of Reduction in Mortality and morbidity' (CHARM) programme assessing the addition of candesartan to optimal medical treatment. Cost-effectiveness analyses reporting cost per life-year gained were conducted on the basis of CHARM-Added and CHARM-Alternative trials. These cost-effectiveness analyses were developed from three perspectives (UK, France, and Germany) and considered within-trial time horizons (median follow-up of 41 months for CHARM-Added and of 34 months for CHARM-Alternative). The health benefit considered was all-cause mortality. Costs considered were drug treatment (including 4 GP visits and 4 biochemistry tests for drug initiation and up-titration in the candesartan arm), hospital admission (all-cause admissions), and cardiovascular procedures. The sensitivity analysis increased the length of non-cardiovascular admission by 30% in the candesartan group (potential additional cost of certain adverse events [renal impairment]), added the cost of one GP visit for candesartan-related adverse events not leading to admission (renal impairment and hypotension), varied the length of hospital stay ± 20%, and used 3.5% as discount rate for UK analyses (base-case analyses used 3%).Table 5.15 presents the quality and applicability assessment of this economic analysis.

**Table 5.15: Economic study assessment**

| Study | Study quality* | Study applicability** |
|---|---|---|
| McMurray 2006[100] | Potentially serious limitations (a) | Directly applicable |

*Very serious limitations / Potentially serious limitations / Minor limitations; ** Directly applicable / Partially applicable / Not applicable

(a) Outcomes were not measured as QALYs; Short time horizons.

### 5.2.5.5 Health economic evidence statements

Table 5.16 presents UK results of the cost-effectiveness analyses developed by McMurray et al. (2006)[100]. These results considered all-cause mortality, all-cause hospital admissions, and costs related to cardiovascular procedures and drug treatments. These cost-effectiveness results show that adding candesartan to optimal medical treatment was cost-saving in CHARM-Added and cost-effective in CHARM-Alternative. The cost-effectiveness result of CHARM-Alternative has a very broad confidence interval. The breadth of the confidence interval reflects the uncertainty around the mortality reduction. An interval was not reported for the CHARM-Added result.

**Table 5.16 Cost-effectiveness results - McMurray 2006 economic analysis***

| CHARM Trial | Incremental cost (£) | Incremental effect - Life-year gained (LYG) (95%CI) | UK results – Cost/LYG (95%CI)[¥] |
|---|---|---|---|
| Alternative | £51±£771/year** | 0.078 (0.003-0.15) | £1706 (dominant[¥¥]; £709,631) |
| Added | £10±£210/year** | 0.061 (-0.002-0.12) | Dominant[¥¥] |

* When developing the analysis, unit costs in pound sterling were converted into Euro using 1 Euro = 0.67 GBP. We used the same converted rate to present results in pound sterling.

** Median follow-up of 41 months for CHARM-Added and of 34 months for CHARM-Alternative

[¥] Using the utility score proposed by Mant 2009[37] of 0.65 for patients with heart failure, we estimated the threshold in cost per LYG equivalent to the £20,000 per QALY gained proposed by NICE to be £13,000 per LYG.

[¥¥] 'Dominant' means that adding candesartan to optimal medical management is more effective and less costly than adding placebo.

The GDG expressed concerns about these results considering that the resource use was underestimated in the candesartan arm. They discussed the four GP visits and biochemistry tests for candesartan initiation and up-titration, and suggested that the number of visits and tests under-estimate the usual UK practice. In addition, the GDG noted that additional GP visits for candesartan-related complications (hypotension and renal impairment) are usual practice. Additional GP visits were calculated for candesartan-related complications in the sensitivity analysis, and this did not affect the conclusions. The variation in the sensitivity analysis that affected the results most was when increasing the length of stay for non-cardiovascular admissions by 30% in the candesartan group to account for potential additional cost related to certain adverse events (renal impairment). The effect of this was that the treatment was no longer cost-saving in CHARM-Added (results not presented).

No cost-effectiveness analysis was developed on CHARM-preserved. For this trial, the effect of the treatment was non-significant on all-cause mortality and on all-cause hospitalisations (Table 5.17). In addition, the length of stay per hospitalised patient was longer (non-significant) for the treatment arm[100].

**Table 5.17 Outcomes from CHARM-Preserved[100,101,92]**

| Mortality | | Hospital admission | |
|---|---|---|---|
| All-cause | Heart failure-related | All-cause (difference in mean admission per patient) | Heart failure-related (difference in admission per patient) |
| RR = 0.97 (95%CI 0.02, 1.14) | RR = 0.99, ns | 0.03 (95%CI -0.13, 0.20) | 0.15 |

It should be noted that the McMurray et al. (2006) study[100] used a short time horizon, and did not consider quality of life.

### 5.2.5.6 From evidence to recommendations

***Relative value placed on the outcomes considered***

Compared to placebo, ARB did not reduce all cause mortality. However, treatment with ARB led to significant reduction in the rate of heart failure hospitalisation (CHARM-Alternative and the ARCH-J trials)[92,96]. There was also a significant reduction of the composite end-point of cardiovascular mortality and heart failure hospitalisation (CHARM-alternative trial) [92].

Only one trial (Val-HeFT post-hoc analysis) [77]showed an improved quality of life score, and another trial (STRETCH) [95]showed an increased number of patients with improved NYHA functional class when treated with ARB.

Treatment with ARB resulted in significant increase in hyperkalaemia, hypotension and raised creatinine level.

The GDG were aware of two trials (ELITE II and OPTIMAAL) that provided direct comparison of ARB with ACEI in heart failure due to left ventricular systolic dysfunction[102,103]. ELITE-II compared Losartan to Captopril in patients $\geq$ 60 years with LVEF $\leq$ 40% and found similar morbidity and mortality associated with treatment with either agent. OPTIMAAL compared Losartan to Captopril in patients with significant left ventricular systolic dysfunction following Q wave myocardial infarction and found a trend for reduced mortality in the captopril arm, and no difference in morbidity. All the placebo-controlled ACEI trials except CONSENSUS-II (which was in a unique early AMI phase using intravenous ACEI), have consistently shown reduction of morbidity and mortality in heart failure due to left ventricular systolic dysfunction, in contrast with the results of the placebo-controlled ARB trials. However, such indirect comparison can be misleading. The ARB trials were performed in a different era in heart failure patients with better prognosis as a result of treatment with other effective agents such as beta-blockers. Therefore, it will have been more difficult to demonstrate survival benefit in these studies. The more recent HEAAL study[104], which was published after the cut off date for the literature searches for this guideline, did find reduced mortality and heart failure hospitalisation in people on high dose (150 mg/day) losartan as compared to low dose (50 mg/day) losartan in the treatment of heart failure due to LVSD in patients intolerant of ACEI (85% due to cough). However, the higher dose was associated with increased renal complications and hyperkalaemia.

The GDG explored the current practice of readily switching patients with heart failure with LVSD from ACEI to ARB whenever side-effects are encountered. Intractable dry cough is the only side-effect that remains unique to ACEI and is readily relieved by switching treatment to ARB. The GDG felt that in light of the the stronger evidence base (and lower cost) of ACEI, treatment should only be switched when ACEI are not tolerated.

Angio-oedema reflects true intolerance to ACEI. It can, however, occur with ARB, albeit much less frequently. The occurrence of renal impairment, hypotension or hyperkalaemia while on ACEI should initially call for reduction (when significant) of the dose of ACEI rather than an immediate switch to ARB (see Appendix J on practical recommendations). The GDG advises that every attempt is made not to stop ACEI in the presence of side-effects, and that education is provided for patient and carers. The GDG noted that some of the patients recruited into the CHARM-Alternative trial had hypotension, hyperkalaemia or renal impairment as the reason for stopping ACEI, and that many were able to tolerate the ARB candesartan. However, candesartan itself led to significantly more patients than placebo discontinuing the study medication due to hypotension, hyperkalaemia and renal impairment.

The GDG considered the impact of treatment of heart failure associated with preserved left ventricular ejection fraction, with ARB.

Two large randomised controlled trials were reviewed.[97,98] CHARM-Preserved and I-PRESERVE. ARB had no impact in this group of patients on all cause mortality, cardiovascular mortality, heart failure hospitalisation and the composite score of cardiovascular mortality and heart failure hospitalisation. These agents did not significantly

cause hypotension resulting in symptoms or in withdrawal from the trial. However, they significantly increased the incidence of hyperkalaemia and the number of patients with raised serum creatinine (though not the mean creatinine level between the placebo and the ARB treated groups). Taken alone, CHARM-Preserved trial showed a reduction of hospitalisation, but not when combined with I-PRESERVE in meta-analysis.

***Quality of evidence***

In trials looking at the impact of ARB therapy on patients with heart failure and reduced left ventricular ejection fraction, the evidence of lack of effect on all cause mortality was of high quality in all the trials, except the Val-HeFT-post-hoc analysis[93], where the evidence on the effect of all cause mortality was of low quality.

Moderate quality evidence was observed for the significant reduction in heart failure hospitalisation and in the composite score of cardiovascular mortality and heart failure hospitalisation.

Moderate quality of evidence from single trials showed that ARB therapy in these patients leads to improved quality of life scores, and increased number of patients with improved NYHA functional class. Similarly, moderate quality of evidence was observed for ARB therapy increasing the rates of hyperkalaemia, hypotension and raised creatinine level.

The appraisal of trials looking at the impact of ARB on patients with heart failure and preserved left ventricular ejection fraction produced high-quality evidence that these agents have no impact on: all cause mortality, cardiovascular mortality, composite score of cardiovascular mortality and heart failure hospitalisation or on the mean increase in serum creatinine. However, moderate quality evidence was observed for the ARB therapy resulting in a significant rise in the number of patients with raised creatinine, and in the significant increase in the incidence of hyperkalaemia.

***Trade-off between clinical benefits and harms***

The use of ARB is not justifiable in patients with heart failure and preserved left ventricular ejection fraction as there is no evidence of benefit, with evidence of potential harmful side effects (hyperkalaemia and raised creatinine level).

An ARB could be prescribed to patients with heart failure and preserved left ventricular ejection fraction if there is another indication to prescribe them, such as systemic hypertension or diabetes mellitus.

In patients with heart failure and left ventricular systolic dysfunction, the use of ARB is helpful in reducing hospitalisation, improving quality of life and improving heart failure functional class. There is also evidence from some trials of a reduction in the combined end-point of mortality and hospitalisation. However, treatment with these agents requires frequent monitoring of serum urea, electrolytes, creatinine and eGFR to guard against the potential side effects of the drugs.

***Trade-off between net health benefits and resource use***

The use of ARB in patients with heart failure and left ventricular systolic dysfunction was found to be cost effective, however the GDG noted the broad confidence interval of the results of the cost-effectiveness analysis of the CHARM-Alternative trial [100]. The breadth of the confidence interval reflects the uncertainty around the mortality reduction.

For the cost-effectiveness of ARBs in patients with heart failure and preserved ejection fraction, the GDG agreed that the evidence is not clear or conclusive in this population.

#### 5.2.5.7 Recommendations

- Consider an ARB licensed for heart failure as an alternative to an ACE inhibitor for patients with heart failure due to left ventricular systolic dysfunction who have intolerable side effects with ACE inhibitors. **[new 2010]**
- Monitor serum urea, electrolytes, creatinine and eGFR for signs of renal impairment or hyperkalaemia in patients with heart failure who are taking an ARB[12],[13]. **[new 2010]**

### *5.2.6 Angiotensin-II receptor antagonists +other vs placebo + other*

**Clinical Question:**

What is the efficacy and safety of a) angiotensin-II receptor antagonists (ARBs) plus an Angiotensin Converting Enzyme Inhibitors ( ACEIs) in comparison to ACE I plus placebo b) ARBs + ACEI + BB vs placebo + ACEI + BB in the medical management of adults with heart failure?

#### 5.2.6.1 Clinical introduction

See Clinical Introduction for ARB1 (Section 5.2.5.1) above

#### 5.2.6.2 Clinical Methodological introduction

**a) Angiotensin-II receptor antagonists (ARBs) plus Angiotensin Converting Enzyme Inhibitors (ACEI) in comparison to ACEI plus placebo**

Two studies were identified comparing ARB plus ACEI with Placebo plus ACEI (Houghton et al; Krum et al)

*Population - percentage of patients on background ACEI and BB:*

- Houghton et al: ACEI 100% BB 0%
- Val-Heft subgroup (Krum et al): ACEI 100%, BB 0%

*Intervention:*

- Valsartan up to 320mg (160mg bd) (Val-Heft subgroup analysis – Krum et al)
- Losartan up to 50mg/day (Houghton et al)

*Comparison*

- Placebo

[12] For practical information on treatment with ARBs see 'Chronic kidney disease' (NICE clinical guideline 73).

[13] For more information see Appendix J.

**b) ARBs + ACEI + betablockers (BB) vs placebo + ACEI + BB in the medical management of adults with chronic heart failure?**

*Population - percentage of patients on background ACEI and BB:*

- CHARM-added (McMurray et al): ACEI 100%, BB 55%
- Val-HeFT (Cohn et al): ACEI 92%, BB 35%
- Cocco et al: ACEI 100%, BB 100%

*Intervention:*

- Candesartan up to 32 mg/day (CHARM-added – McMurray et al)
- Valsartan up to 320 mg/day (160mg bd) (Val-HeFT– Cohn et al.)
- Valsartan up to 160 mg/day (Cocco et al.)

**c) ARBs + ACEI + betablockers (BB) vs placebo + ACEI + BB in the medical management of adults with heart failure post myocardial infarction**

The VALIANT trial [105] was designed differently to the trials used in patients with chronic heart failure (see above). Patients were not on a background of ACEI but were randomised to ARB + ACEI vs ACEI vs ARB, and most patients were on a background of beta blockers.

*Population - percentage of patients on background ACEI and BB:*

- VALIANT BB 70%

*Intervention:*

- Valsartan (up to 160mg bd) vs Valsartan (up to 80mg bd) plus captopril (up to 150 mg/day) vs captopril (up to 150 mg/day)

### 5.2.6.3 Clinical evidence statements

**a) Angiotensin-II receptor antagonists (ARBS) plus Angiotensin Converting Enzyme Inhibitors (ACEI) in comparison to ACEI plus placebo in chronic heart failure**

Compared with ACEI + placebo, ARBs + ACEI significantly reduced:

- First hospitalisation [low quality]

Compared with ACEI + placebo, ARBs + ACEI significantly improved:

- QoL (MLHQ) [moderate]

Compared with ACEI + placebo, ARBs + ACEI significantly increased:

- Hyperkalaemia [high quality]

Compared with ACEI + placebo, ARBs + ACEI had no difference on:

- Mortality [moderate quality]
- Increased serum creatinine (µmol/L) [low quality]

The evidence profile below summarises the quality of the evidence and outcome data from 2 studies[106,107]. Krum 2004 was a subgroup analysis of the Val-HeFT RCT. Both studies compared ARBs + ACEI vs. ACEI + placebo in heart failure with left ventricular systolic dysfunction (LVSD). Patients in both arms in both studies were not on a background of BB.

## Evidence Profile: ARBs + ACEI vs. ACEI + placebo in heart failure with left ventricular systolic dysfunction (LVSD)

**Question:** Should ARB + ACEI (no BB) vs Placebo + ACEI (no BB) be used for CHF?
**Bibliography:** H. Krum, P. Carson, C. Farsang, A. P. Maggioni, R. D. Glazer, N. Aknay, Y. T. Chiang, and J. N. Cohn. Effect of valsartan added to background ACE inhibitor therapy in patients with heart failure: results from Val-HeFT. European Journal of Heart Failure 6 (7):937-945, 2004. A. R. Houghton, M. Harrison, A. J. Cowley, and J. R. Hampton. Combined treatment with losartan and an ACE inhibitor in mild to moderate heart failure: results of a double-blind, randomized, placebo-controlled trial. American Heart Journal 140 (5):e25-e31, 2000. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, Olofsson B, Yusuf S, Pfeffer MA, CHARM Investigators and Committees. 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(9386):767-771.Ref ID 1

| Quality assessment | | | | | | | Summary of findings | | | | | Hazard Ratio |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality | |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | ARB + ACE (no BB) | Placebo + ACE (no BB) | Relative (95% CI) | Absolute | | |
| **Mortality (follow -up mean 23 months)** | | | | | | | | | | | | |
| 2<br>Val-Heft (subgroup Krum et al)<br>CHARM-added McMurray | randomised trial[1] | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 536/2106 (25.5%) | 555/2063 (26.9%)<br>25.4%<br>38.7% | RR 0.95 (0.85 to 1.05) | 13 fewer per 1000 (from 40 fewer to 13 more)<br>12 fewer per 1,000<br>19 fewer per 1,000 | ⊕⊕⊕O MODERATE | 0.93 (0.83 to 1.05) |
| **First hospitalisation (follow-up mean 23 months)** | | | | | | | | | | | | |
| 1<br>Val-Heft | randomised trial[1] | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 224/1532 (14.6%) | 315/1502 (21%) | RR 0.70 (0.6 to 0.81) | 63 fewer per 1000 (from 40 fewer to 84 fewer) | ⊕⊕OO LOW | |
| **Hyperkalaemia (follow-up 41 months)** | | | | | | | | | | | | |
| 1<br>Houghton et al | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision | none | 44/1276 (3.4%) | 9/1272 (0.7%) | RR 4.87 (2.39 to 9.94) | 27 more per 1000 (from 10 more to 63 more) | ⊕⊕⊕⊕ HIGH | |
| **Increased serum creatinine (umol/L) (follow-up 12 weeks; range of scores: -; Better indicated by less)** | | | | | | | | | | | | |
| 1<br>Houghton et al | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | very serious[3] | none | 10 | 10 | - | MD -2.0 (0 to 0) | ⊕⊕OO LOW | |

| Quality of Life (MLHQ) (follow-up mean 23 months; measured with: umol/L; range of scores: -; Better indicated by less) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1<br>Val-Heft | randomised trial[1] | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 2511 | 2499 | - | MD 2.78 (0 to 0) | ⊕⊕⊕O<br>MODERATE | |

[1] Subgroup analysis of the Val-HeFT RCT and prespecified subgroup analysis of CHARM-added
[2] No explanation was provided
[3] No details of SD, SE or effect size CIs given

### b) ARB + ACEI + BB vs placebo + ACEI + BB in patients with chronic heart failure

Compared with placebo + ACEI + BB, ARB + ACEI + BB had a significant reduction on:

- HF hospitalisation [moderate quality]
- Composite score (CV mortality and HF hospitalisation) [high quality]

Compared with placebo + ACEI + BB, ARB + ACEI + BB had a significantly fewer number of cases with:

- Worsened NYHA class [low quality]

Compared with placebo + ACEI + BB, ARB + ACEI + BB had no significant effect on:

- All cause mortality [moderate quality]
- Improved NYHA class [low quality]
- Unchanged NYHA class [low quality]

Compared with placebo + ACEI + BB, ARB + ACEI + BB were significantly worse for:

- Hypotension [moderate quality]
- Hyperkalaemia [high quality]
- Increased serum creatinine (number of patients) [high quality]

NYHA class

The results of one study that could not be incorporated into the meta-analysis showed[108]:

Patient NYHA class II
Candesartan 13.8% got worse vs 23.8% improved
Placebo 20.8 got worse vs 18.7% improved
NYHA III-IV
Candsartan 4.2% got worse vs 45.7% improved
Placebo 5.5% got worse vs 45.8% improved

The evidence profile below summarises the quality of the evidence and outcome data from three studies [101,109,110] comparing ARBs + ACEI + BB vs. placebo + ACEI + BB in heart failure with reduced left ventricular ejection fraction (LVEF).

## Evidence Profile

**Question:** Should ARB + ACEI + BB vs Placebo + ACEI + BB be used for CHF?
**Bibliography:** McMurray 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. G. Cocco, S. Kohn, and C. Sfrisi. Comparison of the effects of cilazapril and of the combination of cilazapril plus valsartan in patients with advanced heart failure. HeartDrug 2 (6):286-294, 2002. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. New England Journal of Medicine. 2001; 345(23):1667-1675.

| Quality assessment | | | | | | | Summary of findings | | | | | Hazard Ratio |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality | |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | ARB + ACE + BB | Placebo + ACE + BB | Relative (95% CI) | Absolute | | |
| **All cause mortality (follow-up 23 to 41 months)** | | | | | | | | | | | | |
| 2 CHARM-added Val-Heft | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 872/3787 (23%) | 896/3771 (23.8%) | RR 0.97 (0.89 to 1.05) | 7 fewer per 1000 (from 26 fewer to 12 more) | ⊕⊕⊕O MODERATE | 0.94 (0.86 to 1.03) |
| **HF Hospitalisation (no. of patients) (follow-up 23-41 months)** | | | | | | | | | | | | |
| 2 CHARM-added Val-Heft | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision[2] | none | 655/3787 (17.3%) | 811/3771 (21.5%) | RR 0.81 (0.71 to 0.92) | 41 fewer per 1000 (from 17 fewer to 62 fewer) | ⊕⊕⊕O MODERATE | |
| **Combined outcome: CV death or hospital admission for CHF (follow-up median 41 months)** | | | | | | | | | | | | |
| 1 CHARM-added | randomised trials | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision | none | 483/1276 (37.9%) | 538/1272 (42.3%) | RR 0.89 (0.81 to 0.98) | 47 fewer per 1000 (from 8 fewer to 80 fewer) | ⊕⊕⊕⊕ HIGH | |
| **Hypotension (follow-up 2-41 months)** | | | | | | | | | | | | |
| 3 CHARM- | randomised trials | serious[3] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 94/3803 (2.5%) | 0.8% | RR 1.46 (1.07 to 2.00) | 4 more per 1000 (from 1 more to 8 more) | ⊕⊕⊕O MODERATE | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| added<br>Val-Heft<br>Cocco 2002 | | | | | | | | 25% | | 115 more per 1000 (from 18 more to 250 more) | | |
| **Hyperkalaemia (follow-up median 41 months)** | | | | | | | | | | | | |
| 1<br>CHARM-added | randomised trials | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision[2] | none | 44/1276 (3.4%) | 9/1272 (0.7%) | RR 4.87 (2.39 to 9.94) | 27 more per 1000 (from 10 more to 63 more) | ⊕⊕⊕⊕ HIGH | |
| **Increased serum creatinine (number of patients) (follow-up median 41 months)** | | | | | | | | | | | | |
| 1<br>CHARM-added | randomised trials | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision | none | 100/1276 (7.8%) | 52/1272 (4.1%) | RR 1.92 (1.38 to 2.66) | 38 more per 1000 (from 16 more to 68 more) | ⊕⊕⊕⊕ HIGH | |
| **Improved NYHA class (follow-up 6wks and 23 months)** | | | | | | | | | | | | |
| 2<br>Cocco 2002<br>Val-Heft | randomised trials | serious[4] | no serious inconsistency | no serious indirectness | serious[5] | none | 592/2527 (23.4%) | 523/2515 (20.8%) | RR 1.35 (0.79 to 2.3) | 73 more per 1000 (from 44 fewer to 270 more) | ⊕⊕OO LOW | |
| **Unchanged NYHA class (follow-up 8 weeks)** | | | | | | | | | | | | |
| 1<br>Cocco 2002 | randomised trials | serious[6] | no serious inconsistency | no serious indirectness | serious[5] | none | 4/16 (25%) | 8/16 (50%) | RR 0.50 (0.19 to 1.33) | 250 fewer per 1000 (from 405 fewer to 165 more) | ⊕⊕OO LOW | |
| **Worsened NYHA class (follow-up 6 wks and 23 months)** | | | | | | | | | | | | |
| 2<br>Cocco 2002<br>Val-Heft | randomised trials | serious[4] | no serious inconsistency | no serious indirectness | serious[5] | none | 254/2527 (10.1%) | 322/2515 (12.8%) | RR 0.79 (0.67 to 0.92) | 27 fewer per 1000 (from 10 fewer to 42 fewer) | ⊕⊕OO LOW | |

[1] All studies double blind, ITT analysis and <20% dropouts, 1/2 unclear allocation concealment, 1 study unclear if ITT analysis performed
[2] <300 events
[3] All trials double blind and powered; 2/3 unclear allocation concealment, all <20% drop-outs, 1/3 ITT analysis
[4] both studies double blind, powered, unclear allocation concealment and <20% dropouts. 1 study unclear if ITT analysis,
[5] total number of events is less than 300, 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect includes both negligible effect and appreciable benefit or appreciable harm.
[6] double blind, unclear allocation concealment, appears to be no dropouts (and so appears to be ITT analysis)

**Evidence Profile: ARBs + ACEI + BB vs. placebo + ACEI + BB in heart failure with left ventricular systolic dysfunction (LVSD)**

### c) ARB + ACEI + BB vs placebo + ACEI + BB in chronic heart failure post myocardial infacrtion

The evidence profile below summarises the quality of the evidence and outcome data from one study [105] comparing ARBs + ACEI + BB vs. placebo + ACEI + BB in post-MI patients with heart failure with reduced left ventricular ejection fraction (LVEF).

Compared with placebo + ACEI + BB, ARB + ACEI + BB had a significant reduction on:

- HF hospitalisation [high quality]

Compared with placebo + ACEI + BB, ARB + ACEI + BB had no difference on:

- All cause mortality [high quality]
- Hyperkalaemia [moderate quality]

Compared with placebo + ACEI + BB, ARB + ACEI + BB were significantly worse for:

- Hypotension [high quality]

## Evidence Profile

**Question:** Should ARB + ACEI + BB vs Placebo + ACEI + BB be used for post-MI and CHF?
**Bibliography:**. M. A. Pfeffer, J. J. McMurray, E. J. Velazquez, J. L. Rouleau, L. Kober, A. P. Maggioni, S. D. Solomon, K. Swedberg, Werf F. Van de, H. White, J. D. Leimberger, M. Henis, S. Edwards, S. Zelenkofske, M. A. Sellers, and R. M. Califf. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med 349 (20):1893-1906, 2003.

| Quality assessment | | | | | | | Summary of findings | | | | | Hazard ratio |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality | |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | ARB + ACE + BB | Placebo + ACE + BB | Relative (95% CI) | Absolute | | |
| **All cause mortality (follow-up mean 23 months)** | | | | | | | | | | | | |
| 1 VALIANT | randomised trials | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision | none | 941/4885 (19.3%) | 958/4909 (19.5%) | RR 0.99 (0.91 to 1.07) | 2 fewer per 1000 (from 18 fewer to 14 more) | ⊕⊕⊕⊕ HIGH | 1.00 (97.5%CI 0.89 to 1.09) |
| **HF Hospitalisation (follow-up mean 23 months)** | | | | | | | | | | | | |
| 1 VALIANT | randomised trials | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision | none | 834/885 (94.2%) | 945/4909 (19.3%) | RR 0.89 (0.82 to 0.96) | 21 fewer per 1000 (from 8 fewer to 35 fewer) | ⊕⊕⊕⊕ HIGH | |
| **Hypokalaemia (no. of patients) (follow-up mean 23 months)** | | | | | | | | | | | | |
| 1 VALIANT | randomised trials | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | none | 12/4862 (0.2%) | 4/4879 (0.1%) | RR 3.01 (0.97 to 9.33) | 2 more per 1000 (from 0 fewer to 7 more) | ⊕⊕⊕O MODERATE | |
| **Hypotension (no of patients) (follow-up mean 23 months)** | | | | | | | | | | | | |
| 1 VALIANT | randomised trials | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision | none | 90/4862 (1.9%) | 41/4879 (0.8%) | RR 2.20 (1.53 to 3.18) | 10 more per 1000 (from 4 more to 18 more) | ⊕⊕⊕⊕ HIGH | |

### 5.2.6.4 Health Economic methodological introduction

McMurray et al. (2006)[100] developed an economic analysis based on the CHARM programme. This analysis was presented in Section 5.2.1.5.

### 5.2.6.5 From evidence to recommendations

***Relative value placed on the outcomes considered***

The question was considered in two stages: adding ARB to the combination of ACEI and beta- blockers and combining ARB with ACEI.

For the first part, there were four appraised studies. Three of the studies were of similar design adding candesartan[101] (CHARM-Added study), or Valsartan[109,110] (Val-HeFT, Cocco *et a*l) to treatment with an ACEI that was given to 92-100% of participants. In addition, beta-blockers were given to 100% of the patients in the Cocco *et al* study, 55% in CHARM-Added and 35% in the Val-HeFT study. The fourth study[105] (VALIANT) was in patients with heart failure due to LVSD following myocardial infarction. The design was more complex in that there were three arms in the study: ACEI, Valsartan or ACEI + Valsartan. In the VALIANT study 77% of the patients were on beta-blockers.

The addition of ARB to the combined ACEI and BB in patients with heart failure and LVSD did not affect all cause mortality but did significantly reduce heart failure hospitalisation, and the combined score of heart failure hospitalisation and mortality.

This intervention led to significantly less chance of worsening NYHA functional class. Adding ARB to this combination significantly increased the incidence of hyperkalaemia, hypotension and raised serum creatinine.

There was some concern raised after the publication of the Val-HeFT study [110] about the safety of combining ARB with beta- blockers in patients with heart failure. This led to a safety warning in the 2003 NICE guidelines on heart failure. However, given the results of the other studies that used both Candesartan [101] (CHARM-Added) and Valsartan [105] (VALIANT), the GDG concluded this combination could be used safely.

The second part of the question addressed combining ARB with ACEI. Two studies were appraised: Krum et al (sub-study of Val-HeFT trial)[106], and Houghton *et al*[107]. These used Valsartan and Losartan, respectively.

Compared to placebo, the addition of Valsartan to ACEI in the Krum *et al* trial[106] did not impact on all cause mortality, but it significantly reduced the rate of first hospitalisation. This addition also resulted in significant improvement in the quality of life. There was no significant impact of adding Losartan in the Houghton *et al* study[107] on the incidence of hyperkalaemia or increased serum creatinine.

***Quality of evidence***

There is high-quality evidence that adding ARB to the combination of ACEI and beta-blockers results in significantly reduced combined score of cardiovascular mortality and heart failure hospitalisation; and for increased risk of hyperkalaemia.

With regards to the impact of this addition on all cause mortality, heart failure hospitalisation, hypotension, and the number of patients with raised serum creatinine, the evidence is of moderate quality. The evidence supporting the remainder of the statements was of low quality.

The evidence behind the statements derived from the Houghton *et al* study[107] of the addition of ARB to ACEI was of moderate quality. The main statements derived from the results of the Krum study[106] were based on low quality evidence. The latter is particularly related to the fact that this study was a post-hoc analysis.

***Trade-off between clinical benefits and harms***

The addition of ARB to other drugs for heart failure with LVSD did not reduce all cause mortality, but the trials were not powered to detect such an effect. However, another analysis (Young et al) from the CHARM programme combined the results of CHARM-Added and CHARM-Alternative. This was powered to look at the impact of ARB on mortality in heart failure patients with reduced left ventricular ejection fraction. It showed a statistically significant reduction of all cause mortality and cardiovascular mortality. This was in addition to the significant reduction of heart failure hospitalisation.

ARBs reduce the combined score of cardiovascular mortality and heart failure hospitalisation, as well as reducing the rate of hospitalisation and improving quality of life score. Against these benefits are the potential risks of hyperkalaemia, hypotension and raised serum creatinine. The latter three potential harms call for frequent checks to be made on the renal profile and the electrolyte balance when patients are given these agents. These harms have also to be considered when prescribing these agents to heart failure patients with significant renal dysfunction or borderline low systolic blood pressure. Further details regarding the issue of monitoring and adjusting the doses of ARB are in Appendix J. The GDG considered whether some patients with heart failure and LVSD might be prescribed ACEI, beta-blockers, ARB and an aldosterone antagonist. Although some patients in the CHARM-Added trial were on quadruple therapy, these were the minority. The GDG does not believe there is sufficient evidence to support the widespread use of quadruple therapy. Similarly, even in the absence of beta-blockers the GDG does not recommend using triple therapy of ACEI with ARB and aldosterone antagonists for safety concerns (risks of hyperkalaemia and renal impairment). A similar view was adopted by the Chronic Kidney Disease NICE guidance where such combination of ACEI/ACEI and AA was discouraged.

***Trade-off between net health benefits and resource use***

The use of ARB in patients with heart failure and left ventricular systolic dysfunction added to ACEI and beta-blockers was found to be cost-saving in the reviewed cost-effectiveness analysis based on CHARM-Added[100].

A confidence interval was not reported with this result. The all-cause mortality reduction in the CHARM-Added trial, although not statistically significant, was larger than that recorded in our meta-analysis when the study was combined with other trials (RR=0.91 vs RR=0.98) (Section 5.2.5.4). Had the meta-analysis been used ARBs might not appear cost-effective.

### 5.2.6.6 Recommendation

The GDG drafted a recommendation on the use of angiotensin II receptor antagonists as second-line treatment after considering evidence for Aldosterone antagonists and hydralazine in combination with nitrates. See Recommendations R28 and R29.

## Drugs not within scope of partial update

There were agents that were outside the scope of the partial update. These included Aspirin and HMG-CoA reductase inhibitors (statins). For more information refer to Appendix M, the 2003 Guideline[22]:

- Aspirin (7.2.9)
- Statins (7.2.10)

For the statins, the reader is referred to

- Lipid Modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease (NICE Clinical Guideline No.67 (2008)). Available from www.nice.org.uk/CG67.

- Statins for the prevention of cardiovascular events (NICE Technology Appraisal No.94 (2006) Available from www.nice.org.uk/TA094.

The GDG was aware of two large randomized controlled trials of statins in patients with heart failure that were published recently. These were: Effect of rosuvastatin in patients with chronic heart failure (GISSI-HF trial group)[111], and the CORONA study: [104]. These trials randomized 4574 patients with heart failure and 5011 patients over the age of 60 years with systolic heart failure of ischaemic origin, respectively, to have 10 mg rosuvastatin or placebo. The statin did not have an impact on any of the trials' outcomes other than reducing hospitalisation in the CORONA study. Therefore, it is unlikely that statins would be beneficial in heart failure. The GDG felt that in the light of this evidence, the recommendation on statin use from the 2003 guideline should be deleted.

The GDG, when discussing the GISSI-HF trial of rosuvastatin in heart failure, also noted the other part of the trial that looked at the effects of n-3 polyunsaturated free fatty acid ethyl esters (PUFA) in patients with chronic heart failure[111]. This trial randomized 6975 patients with heart failure to receive either 1 g n-3 PUFA or placebo. This treatment resulted in reduction of both mortality and hospitalisation. The GDG had not formally reviewed the evidence on this topic, n-3 PUFA is not licensed for use in heart failure at this stage and the topic remains outside the scope. Therefore the GDG did not make a recommendation.

## Recommendations

### *5.2.7 All recommendations for the pharmacological treatment of heart failure*

#### Medicines adherence

For more information refer to NICE guideline:

- Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence. NICE clinical guideline 76 (2009). Available from www.nice.org.uk/guidance/CG76.

R26 Dosing regimens should be kept as simple as possible, and the healthcare professional should ensure that the patient and carer are fully informed about their medication. [2003]

#### Heart failure due to left ventricular systolic dysfunction

##### First-line treatment

See also recommendations R30 – R34 on the use of ACE inhibitors and beta-blockers for first-line treatment. See recommendations R39 – R40 for alternative first-line treatments for patients who are intolerant of ACE inhibitors. See recommendation R38 for alternative first-line treatments for patients who are intolerant of ACE inhibitors and ARBs.

R27 Offer both angiotensin-converting enzyme (ACE) inhibitors and beta-blockers licensed for heart failure to all patients with heart failure due to left ventricular systolic dysfunction. Use clinical judgement when deciding which drug to start first. **[new 2010] KPI**

##### Second-line treatment

See also recommendations R35 - R37 and R40 on second-line treatments.

R28 Seek specialist advice before offering second-line treatment to patients with heart failure due to left ventricular systolic dysfunction. **[new 2010]**

R29 Seek specialist advice and consider adding one of the following if a patient remains symptomatic despite optimal therapy with an ACE inhibitor and a beta-blocker:

- an aldosterone antagonist licensed for heart failure (especially if the patient has moderate to severe heart failure [NYHA[14] class III-IV], or has had an MI within the past month) or
- an angiotensin II receptor antagonist (ARB) licensed for heart failure[15] (especially if the patient has mild to moderate heart failure [NYHA class II-III]) or
- hydralazine in combination with nitrate (especially if the patient is of African or Caribbean origin[16] and has moderate to severe heart failure [NYHA class III-IV]). **[new 2010] KPI**

### ACE inhibitors (first-line treatment)

See also recommendation R27.

R30 Start ACE inhibitor therapy at a low dose and titrate upwards at short intervals (for example, every 2 weeks) until the optimal tolerated or target dose is achieved. **[2010]**

R31 Measure serum urea, creatinine, electrolytes and eGFR at initiation of an ACE inhibitor and after each dose increment[17] [18] **[2010]**

### Beta-blockers (first-line treatment)

See also recommendation R27.

R32 Offer beta-blockers licensed for heart failure to all patients with heart failure due to left ventricular systolic dysfunction, including:

- older adults **and**
- patients with:
  - peripheral vascular disease
  - erectile dysfunction
  - diabetes mellitus
  - interstitial pulmonary disease and
  - chronic obstructive pulmonary disease (COPD) without reversibility. **[new 2010] KPI**

R33 Introduce beta-blockers in a 'start low, go slow' manner, and assess heart rate, blood pressure, and clinical status after each titration. **[2010]**

R34 Switch stable patients who are already taking a beta-blocker for a comorbidity (for example, angina or hypertension), and who develop heart failure due to left ventricular systolic dysfunction, to a beta-blocker licensed for heart failure. **[new 2010]**

### Aldosterone antagonists (second-line treatment)

See also recommendations R28 and R29.

R35 In patients with heart failure due to left ventricular systolic dysfunction who are taking aldosterone antagonists, closely monitor potassium and creatinine levels and eGFR.

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[14] The New York Heart Association classification of heart failure.

[15] Not all ARBs are licensed for use in heart failure in combination with ACE inhibitors

[16] This does not include mixed race.

[17] For practical recommendations on treatment with ACE inhibitors see 'Chronic kidney disease' (NICE clinical guideline 73).

[18] For more information see Appendix J.

Seek specialist advice if the patient develops hyperkalaemia or renal function deteriorates[19]. **[new 2010]**

R36 For patients who have had an acute MI and who have symptoms and/or signs of heart failure and left ventricular systolic dysfunction, treatment with an aldosterone antagonist licensed for post-MI treatment should be initiated within 3-14 days of the MI, preferably after ACE inhibitor therapy. (This recommendation is from 'MI: secondary prevention' NICE clinical guideline 48.) **[2007]**

R37 Patients who have recently had an acute MI and have clinical heart failure and left ventricular systolic dysfunction, but who are already being treated with an aldosterone antagonist for a concomitant condition (for example, chronic heart failure), should continue with the aldosterone antagonist or an alternative, licensed for early post-MI treatment. (This recommendation is from 'MI: secondary prevention', NICE clinical guideline 48.)

### Hydralazine in combination with nitrate (alternative first-line treatment)

See also recommendations R28 and R29 for the use of hydralazine in combination with nitrate as second-line treatment.

R38 Seek specialist advice and consider hydralazine in combination with nitrate for patients with heart failure due to left ventricular systolic dysfunction who are intolerant of ACE inhibitors and ARBs. **[new 2010]**

### Angiotensin II receptor antagonists (second-line or alternative first-line treatment)

See also recommendations R28 and R29 for the use of ARBs as second-line treatment.

R39 Consider an ARB licensed for heart failure as an alternative to an ACE inhibitor for patients with heart failure due to left ventricular systolic dysfunction who have intolerable side effects with ACE inhibitors. **[new 2010]**

R40 Monitor serum urea, electrolytes, creatinine and eGFR for signs of renal impairment or hyperkalaemia in patients with heart failure who are taking an ARB[20],[21]. **[new 2010]**

### Digoxin

R41 Digoxin is recommended for:

- worsening or severe heart failure due to left ventricular systolic dysfunction despite first- and second-line treatment for heart failure.[22] **[2003, amended 2010**]

[19] For more information see Appendix J.

[20] For practical recommendations on treatment with ARBs see 'Chronic kidney disease' (NICE clinical guideline 73).

[21] For more information see Appendix J.

[22] See 'Atrial fibrillation' (NICE clinical guideline 36) for recommendations on the use of digoxin in patients with atrial fibrillation.

## All types of heart failure

### Diuretics

R42 Diuretics should be routinely used for the relief of congestive symptoms and fluid retention in patients with heart failure, and titrated (up and down) according to need following the initiation of subsequent heart failure therapies. **[2003]**

R43 The diagnosis and treatment of heart failure with preserved ejection fraction should be made by a specialist, and other conditions that present in a similar way may need to be considered. Patients in whom this diagnosis has been made should usually be treated with a low to medium dose of loop diuretics (for example, less than 80 mg furosemide per day). Patients who do not respond to this treatment will require further specialist advice. **[2003]**

### Calcium channel blockers

R44 Amlodipine should be considered for the treatment of comorbid hypertension and/or angina in patients with heart failure, but verapamil, diltiazem or short-acting dihydropyridine agents should be avoided. **[2003]**

### Amiodarone

R45 The decision to prescribe amiodarone should be made in consultation with a specialist. **[2003]**

R46 The need to continue the amiodarone prescription should be reviewed regularly. **[2003]**

R47 Patients taking amiodarone should have a routine 6-monthly clinical review, including liver and thyroid function test, and including a review of side effects. **[2003]**

### Anticoagulants[23]

R48 In patients with heart failure in sinus rhythm, anticoagulation should be considered for those with a history of thromboembolism, left ventricular aneurysm, or intracardiac thrombus. **[2003]**

### Aspirin

R49 Aspirin (75–150 mg once daily) should be prescribed for patients with the combination of heart failure and atherosclerotic arterial disease (including coronary heart disease). **[2003]**

### Inotropic agents

R50 Intravenous inotropic agents (such as dobutamine, milrinone or enoximone) should only be considered for the short-term treatment of acute decompensation of chronic heart failure. This will require specialist advice. **[2003]**

### Heart failure due to valve disease

R51 Patients with heart failure due to valve disease should be referred for specialist assessment and advice regarding follow-up. **[2003]**

R52 ACE inhibitor therapy should not be initiated in a patient with a clinical suspicion of haemodynamically significant valve disease, until the valve disease has been assessed by a specialist. **[2003]**

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[23] See also ‘Atrial fibrillation’ (NICE clinical guideline 36) for recommendations on the use of anticoagulants in patients with atrial fibrillation

### General

#### Age

R53 The management of heart failure should be determined by clinical criteria, irrespective of the age of the patient. **[2003]**

R54 Tolerance of drugs may be lower and side effects require closer and more frequent monitoring in older patients. **[2003]**

#### Gender

R55 The principles of pharmacological management of heart failure should be the same for men and women. **[2003]**

R56 In women of reproductive age who have heart failure, contraception and pregnancy should be discussed. If pregnancy is being considered or occurs, specialist advice should be sought. Subsequently, specialist care should be shared between the cardiologist and obstetrician. **[2003]**

R57 The potential teratogenic effects of drugs should be considered. **[2003]**

### Comorbidities

R58 Manage co morbidities according to:

- 'Hypertension', NICE clinical guideline 34
- 'MI: secondary prevention', NICE clinical guideline 48
- 'Type 2 diabetes', NICE clinical guideline 87

and other relevant NICE guidance. This is particularly important in heart failure with preserved ejection fraction. **[new 2010]**

## 5.3 Invasive procedures

### *5.3.1 Introduction*

Although drug therapy is the mainstay of treatment of heart failure, some patients will also benefit from diagnostic or interventional invasive procedures. These procedures are organised by the specialist. This guideline can only give general advice, and specialist advice is strongly recommended where such procedures might be considered.

## Procedures within the scope of the update

### *5.3.2 Cardiac resynchronisation therapy*

Cardiac resynchronisation therapy (CRT) is one of the major new advances in the management of heart failure, resulting in reduced morbidity and increased survival of heart failure patients with dys-synchrony. The GDG were aware of new advances in the evidence-base for CRT, widening the indications for these devices to involve patients with less severe heart failure. This is the basis of a pending review for the existing guidance in 2010. For more information refer to:

- Cardiac resynchronisation therapy for the treatment of heart failure (NICE technology appraisal guidance 120 **[2007]**. (Available from www.nice.org.uk/guidance/TA120)

Please refer to the NICE website for updates on the review status of this appraisal.

### *5.3.3 Implantable cardioverter-defibrillators (ICDs)*

The 2003 guideline included recommendations from NICE Technology Appraisal No 11 (Guidance on the use of implantable cardioverter defibrillators for arrhythmias). These have been superseded by Technology Appraisal No 95 (2006). However, that guidance did not cover the patients with non-ischaemic dilated cardiomyopathy. For more information refer to:

- Implantable cardioverter defibrillators for arrhythmias (NICE technology appraisal guidance 95 **[2006]**. (Available from www.nice.org.uk/guidance/TA95)

NICE will consult on review plans for this guidance in August 2010. Please refer to the NICE website for updates on the review status of this appraisal.

## Procedures outside the scope of the update

Other interventional procedures considered in the 2003 guideline were outside the scope of the partial update (2010). For more information please refer to the following sections of Appendix M, the 2003 Guideline [22].

- Coronary revascularisation (7.4.1)
- Cardiac transplantation (7.4.2)
- Ventricular assist devices (7.4.3)
- Mitral valve surgery and cardiomyoplasty (7.4.6)

## Recommendations

### *5.3.4 Recommendations for invasive procedures*

#### Coronary revascularisation

R59 Coronary revascularisation should not be routinely considered in patients with heart failure due to systolic left ventricular impairment, unless they have refractory angina. **[2003]**

#### Cardiac transplantation

R60 Specialist referral for transplantation should be considered in patients with severe refractory symptoms or refractory cardiogenic shock. **[2003]**

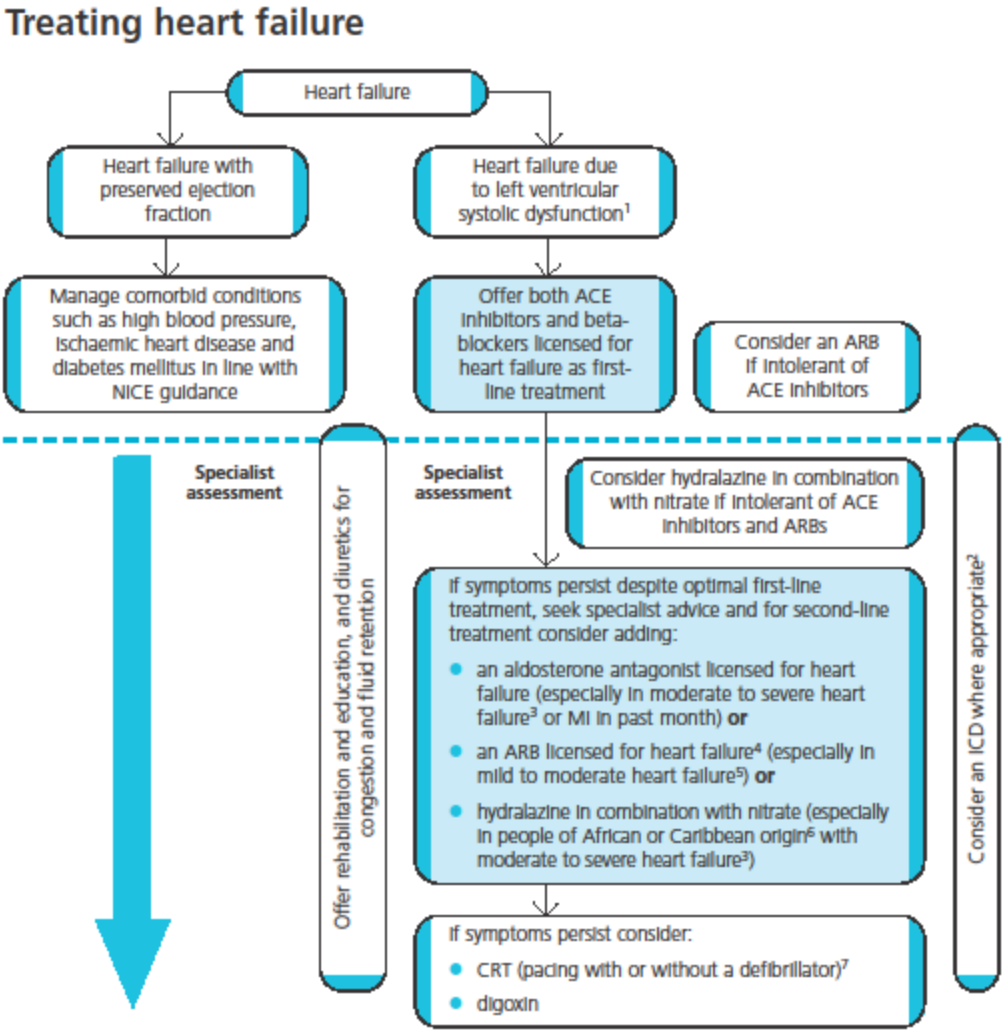
#### Cardiac resynchronisation therapy

Refer to 'Cardiac resynchronisation therapy for the treatment of heart failure' (NICE technology appraisal guidance120 **[2007]**). Please refer to the NICE website for updates on the review status of this appraisal.

#### Implantable cardioverter-defibrillators (ICDs)

Refer to the 'Implantable cardioverter defibrillators for arrhythmias' (NICE technology appraisal guidance 95 **[2006]**). Please refer to the NICE website for updates on the review status of this appraisal.

## 5.4 Treatment algorithm




[1] For more information on drug treatment see appendix J and 'Chronic kidney disease' (NICE clinical guideline 73).
[2] Consider an ICD in line with 'Implantable cardiovascular defibrillators for arrhythmias' (NICE technology appraisal guidance 95).
[3] NYHA class III–IV.
[4] Not all ARBs are licensed for use in heart failure in combination with ACE inhibitors.
[5] NYHA class II–III.
[6] This does not include mixed race. For more information see the full guideline at www.nice.org.uk/guidance/CG108
[7] Consider CRT in line with 'Cardiac resynchronisation therapy for the treatment of heart failure' (NICE technology appraisal guidance 120).

# 6 Rehabilitation in chronic heart failure

## 6.1 Clinical introduction

**What is the safety and efficacy of exercise based cardiac rehabilitation in adults with chronic heart failure?**

Heart failure has adverse physical and psychological effects. Fatigue and dyspnoea are major obstacles to a patient's ability to exercise. Depression and anxiety associated with heart failure can further impair both the ability and motivation to exercise. Rehabilitation aims to deliver education and improve the patient's exercise tolerance and life-style. Since the publication of the 2003 guidance on heart failure, several studies into the impact of rehabilitation programmes on heart failure patients have been published.

**Reasons for Review**

The main thrust of the existing guidance on rehabilitation in heart failure from 2003 is based on common sense and the role of rehabilitation in other cardiac conditions. There have, however, been a number of studies on the use of rehabilitation programmes for patients with heart failure which may lead to more specific recommendations.

## 6.2 Clinical methodological introduction

**Population:** all chronic heart failure

**Intervention:** exercise based cardiac rehabilitation

**Comparison:** standard care including nurse specialist care

**Outcomes:** all cause death up to 5 years, all cause hospitalisation, quality of life (Minnesota Living with Heart Failure Questionnaire (MLHF)), improvement in exercise tolerance (6 minute walking test (6MWT)) and improvement in New York Heart Association (NYHA) functional class.

Low quality and non-randomised controlled trials were excluded from the review (e.g. no allocation concealment, no blinding and no intention to treat analysis (ITT) or high drop out rates). The blinding of participants and those giving the intervention was not possible. However the majority of studies did not state whether end-point assessments were carried out by a person blinded to the intervention given.

Twelve randomised-controlled trials (RCT) were identified comparing **exercise based cardiac rehabilitation vs. standard care.**[112-123]. Table 6.1 below summarises the population, intervention and outcomes for each of the studies.

One study was identified comparing care from a specialist nurse plus exercise based cardiac rehabilitation with specialist nurse care only [124].

# SUMMARY OF INCLUDED STUDIES exercise based cardiac rehab vs standard care

**Table 6.1: Summary of studies**

| STUDY | POPULATION | INTERVENTION | COMPARISON | OUTCOMES |
|---|---|---|---|---|
| O'CONNOR 2009 (HF-ACTION trial) | - LVEF ≤35%<br>- NYHA class II-IV<br>- median age 59 years<br>- N=2331 | - Structured supervised group exercise phase: 3 sessions/week of walking, treadmill or stationary cycling<br>- Home exercise phase after 36 sessions (3 months): cycling or treadmill 5 times/week<br>- telephone follow-up | - usual care: no formal exercise programme, given educational leaflet which included information about exercise.<br>- telephone calls to give comparable level of attention as per the exercise group<br>- 8% of patients were doing their own continuous exercise | - all cause death<br>- CV death<br>- all cause hospitalisation<br>- median 6MWT (12 months follow-up)<br>- change in NYHA class Median 30 months |
| COVERA 2004 | - LVEF ≤40%<br>- NYHA class II-IV<br>- mean age 61.3-63.8 years<br>- N=79 | - Home walking exercise 1/day for 5 days/week<br>- pedometer use<br>- nurse home visits and reviews | - control group: maintained normal exercise and measured with pedometer<br>- nurse home visits and reviews | - all cause death<br>- all cause hospitalisation<br>- mean 6MWT (12 week follow up) |
| NILSSON 2008 | - LVEF <40% or ≥40% with clinical symptoms of HF<br>- NYHA class II-IIIB<br>- mean age 69-72<br>- N=80 | - standard care plus group based high intensity 16 week aerobic interval training (2days/week) each 50 mins; followed by 15-30 mins counselling by physical therapist<br>- 4 individual counselling sessions with CHF nurse | - Standard care: outpatients monitoring by nurse specialist with cardiologist supervision. Follow up in primary care. | - mean Qol score<br>- mean 6MWT ( 4 month follow up) |
| NILSSON 2008 (follow up) | AS ABOVE | AS ABOVE | AS ABOVE | - mean Qol score<br>- mean 6MWT (12 month follow up) |
| AUSTIN 2005 | - LVEF ≤40%<br>- NYHA class II-III<br>- mean age 72<br>- N=200 | - standard care plus 8 week cardiac rehabilitation programme by a nurse specialist 2/week for 2.5 hrs<br>- followed by 16 weeks of community based weekly 1hr sessions of aerobic endurance training | - standard care: 8 weekly outpatient monitoring of clinical status by nurse specialist.<br>- advice and treatment self monitoring information | - all cause death<br>- all cause hospitalisation<br>- mean Qol score<br>- mean 6MWT<br>- NYHA class (follow up: 24 weeks) |

| STUDY | POPULATION | INTERVENTION | COMPARISON | OUTCOMES |
|---|---|---|---|---|
| | | and low resistance/ highly repetitive muscular strength work<br>- exercise at home encouraged 3/week<br>- weekly education sessions<br>- optional counselling from dietician, psychotherapist and occupational therapist. | | |
| AUSTIN 2008 (follow up) | AS ABOVE<br><br>N=112 | 5-year follow-up of previous 24-week trial (see above) | 5-year follow-up of previous 24-week trial (see above) | - all cause death<br>- all cause hospitalisation<br>- mean QoI score<br>- mean 6MWT<br>- NYHA class<br>(follow up: 5 years) |
| CIDER 2003 | - LVEF <45%<br>- NYHA class II-III<br>- mean age 70-75 years<br>- N=25 | - Hydrotherapy: 45 min sessions in pool, 3/week over 8 weeks.<br>- Exercise used muscles required for activities of daily living.<br>- Improving aerobic capacity, peripheral muscle strength and endurance.<br>- Heart rate monitors used. | - control group: instructed to live life as normal and not increase physical activity during the 8 weeks | - mean QoI score<br>- mean 6MWT<br>(follow up: 8 weeks) |
| COLLINS 2004 | - LVEF <40%<br>- NYHA class II-III<br>- mean age 62-66 years<br>- N=31 | - Rehabilitation programme: supervised moderate aerobic exercise programme<br>- Included polestriding and treadmill walking: 3/week with duration increasing to 45-50 mins by week 12.<br>- Exercise physiotherapist or specialist nurse supervised sessions. | - control group: seen bi-weekly by nurse, and asked not to change their level of exercise. | - mean change in QoI score (follow up: 12 weeks) |
| SARULLO 2006 | - LVEF <40%<br>- NYHA class II-III<br>- mean age 53 years | - Supervised physical training programme: bicycle ergometer 30 mins 3/week | - control group: no change to physical activity | - mean QoI score<br>- NYHA class<br>(follow up: 3 months) |

| STUDY | POPULATION | INTERVENTION | COMPARISON | OUTCOMES |
|---|---|---|---|---|
| | - N=60 | | | |
| DRACUP 2007 | - LVEF ≤40%<br>- NYHA class II-IV<br>- mean age 53-54 years<br>- N=173 | - Low level aerobic and resistive/strength training programme.<br>- walking 4/week, increasing to 45 mins at 12 weeks<br>- Resistance programme 3/week on days they did not walk. | - control group: no change to physical activity | - all cause death<br>- all cause hospitalisation (follow up: 1 year)<br>- mean QoI score<br>- mean 6MWT (follow up: 6 months) |
| WITHAM 2005 | - LVEF: not reported (just those with LVSD)<br>- NYHA class II-III<br>- mean age 80-81<br>- N=82 | - Physiotherapist delivered exercise<br>- supervised phase (0-3 months): outpatients of small groups 2/week mainly aerobic and weights (resistance/strength)<br>- Home exercise phase (3-6 months): 2-3/week with weekly telephone calls with physio who set new targets for activity. | - control group: usual care, no restriction of their exercise activities | - mean 6MWT (follow up: 6 months) |
| BELARDINELLI 1999 (from OLD GUIDELINE) | - LVEF ≤ 40%<br>- NYHA class not reported<br>- mean age 53-56 years<br>- N=99 | - 2 phases of supervised exercise training<br>- phase 1: 3/week for 8 weeks: sessions were 1 hr including 40 mins on cycle ergometer<br>- phase 2: 12 months maintenance programme 2 sessions/week | - Control group: no exercise. | - CV death<br>- HF hospitalisation<br>- Mean QoI score (follow-up: 14 months) |

## 6.3 Clinical evidence statements

### a) Exercise based cardiac rehabilitation vs. standard care.

Compared with standard care, exercise rehabilitation significantly reduced:

- HF hospitalisation (up to 4.4 years) [moderate quality]

Compared with standard care, exercise rehabilitation significantly improved:

- Quality of Life (QoL) (up to 5 year follow-up) [moderate quality]*
- Mean 6MWD (up to 6 months) [moderate quality]* and 12 months [high quality]

There was no significant difference between exercise rehabilitation and standard care for:

- All cause mortality (up to 30 months) and at 5 year follow-up [moderate quality]
- All cause hospitalisation (up to 30 months) [very low quality]*
- CV death (up to 4.4 years) [very low quality]*
- Quality of life (up to 6 months) [high quality]
- Mean change in QoL (up to 3 months) [low quality]
- Mean 6MWT (at 5 year follow-up) [moderate quality]

Change in NYHA class

O'Connor 2009 (follow-up median 30 months):

- Improvement (by 1 class): standard group 25%; experimental group 30%

Austin 2005 (follow up: 24 weeks):

- Deterioration (by 1 class): standard group: 8/94; experimental group: 3/85
- No change: standard group: 76/94; experimental group: 44/85
- Improvement (by 1 class): standard group: 9/94; experimental group: 35/85
- Improvement (by 2 classes): standard group: 1/94; experimental group: 3/85

Austin 2008 (follow up: 5 years):

- Deterioration (by 1 class): standard group: 31%; experimental group: 33%
- No change: standard group: 51%; experimental group: 37%
- Improvement (by 1 class): standard group: 9%; experimental group: 25%

Sarullo 2006 (3 months):

- Exercise: decreased from 2.6 (0.1) to 1.06 (0.1); Control: decreased from 2.5 (0.1) to 2.4 (0.2) ; MD between groups at 3 months: -1.34, p=0.0001

***NOTE:** for these outcome measures there was significant heterogeneity between the trials when pooled into meta-analyses. Possible sources of heterogeneity are likely to be due to the huge variation between interventions between the trials (for example, hospital-based rehabilitation, home-based rehabilitation, different exercise modalities) and differences in follow-up time.*

**Evidence profile**

The evidence profile below summarises the quality of the evidence and outcome data from 12 randomised-control trials (RCT) [112-123] comparing **exercise based cardiac rehabilitation vs. standard care.**

## Evidence profile - exercise based cardiac rehabilitation vs. standard care

**Question:** Should Exercise based cardiac rehabilitation vs standard care
**Bibliography:** Austin J, Williams R, Ross L et al. Randomised controlled trial of cardiac rehabilitation in elderly patients with heart failure. *European Journal of Heart Failure.* 2005; 7(3):411-417.; Austin J, Williams WR, Ross L et al. Five-year follow-up findings from a randomized controlled trial of cardiac rehabilitation for heart failure. *European Journal of Cardiovascular Prevention & Rehabilitation.* 2008; 15(2):162-167; Belardinelli R, Georgiou D, Cianci G et al. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. [see comments.]. *Circulation.* 1999; 99(9):1173-1182; Cider A, Schaufelberger M, Sunnerhagen KS et al. Hydrotherapy--a new approach to improve function in the older patient with chronic heart failure. *European Journal of Heart Failure.* 2003; 5(4):527-535; Corvera-Tindel T, Doering LV, Woo MA et al. Effects of a home walking exercise program on functional status and symptoms in heart failure. *American Heart Journal.* 2004; 147(2):339-346; Dracup K, Evangelista LS, Hamilton MA et al. Effects of a home-based exercise program on clinical outcomes in heart failure. *American Heart Journal.* 2007; 154(5):877-883; Nilsson BB, Westheim A, Risberg MA. Long-term effects of a group-based high-intensity aerobic interval-training program in patients with chronic heart failure. *American Journal of Cardiology.* 2008; 102(9):1220-1224; C. M. O'Connor, D. J. Whellan, K. L. Lee, S. J. Keteyian, L. S. Cooper, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. Journal of the American Medical Association 301 (14):1439-1450, 2009.

| Quality assessment | | | | | | | Summary of findings | | | | | Hazard ratio |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality | |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | Exercise based cardiac rehabilitation | standard care | Relative (95% CI) | Absolute | | |
| **All cause mortality (follow-up 3-30 months)** | | | | | | | | | | | | |
| 4<br>AUSTIN 2005<br>CORVERA 2004<br>DRACUP 2007<br>O'CONNOR 2009 | randomised trial | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision[2] | none | 205/1373 (14.9%) | 211/1389 (15.2%) | RR 0.98 (0.82 to 1.17) | 3 fewer per 1000 (from 27 fewer to 26 more) | ⊕⊕⊕O MODERATE | 0.98 (0.81 to 1.19) |
| **All cause mortality (follow-up 5 years)** | | | | | | | | | | | | |
| 1<br>AUSTIN 2005 | randomised trial | no serious limitations[3] | no serious inconsistency | no serious indirectness | serious[2] | none | 31/100 (31%) | 38/100 (38%) | RR 0.82 (0.56 to 1.20) | 68 fewer per 1000 (from 167 fewer to 76 more) | ⊕⊕⊕O MODERATE | 0.78 (0.48 to 1.25) |
| **CV mortality up (follow-up mean 30 months-4.4 years)** | | | | | | | | | | | | |
| 2<br>BELARDINELLI 1999<br>O'CONNOR 2009 | randomised trial | serious[4] | serious[5] | no serious indirectness | serious[6] | none | 140/1209 (11.6%) | 163/1221 (13.3%) | RR 0.69 (0.34 to 1.40) | 40 fewer per 1000 (from 90 fewer to 70 more) | ⊕OOO VERY LOW | 0.86 (0.69 to 1.08) |
| **All cause hospitalisation (follow-up 3-30 months)** | | | | | | | | | | | | |
| 4<br>AUSTIN 2005<br>CORVERA 2004<br>DRACUP 2007<br>O'CONNOR 2009 | randomised trial | serious[1] | serious[7] | no serious indirectness | serious[6] | none | 778/1373 (56.7%) | 834/1389 (60%)<br>11%<br>65% | RR 0.77 (0.53 to 1.12) | 138 fewer per 1000 (from 282 fewer to 72 more)<br>25 fewer per 1,000<br>149 fewer per 1,000 | ⊕OOO VERY LOW | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **HF hospitalisation (follow-up mean 4.4 years)** | | | | | | | | | | | |
| 1<br>BELARDINELLI 1999 | randomised trial | no serious limitations[8] | no serious inconsistency | no serious indirectness | serious[2] | none | 5/50 (10%) | 14/49 (28.6%) | RR 0.35 (0.14 to 0.90) | 186 fewer per 1000 (from 29 fewer to 246 fewer) | ⊕⊕⊕O MODERATE | |
| **Mean QoL score (follow-up 2-6 months; measured with: Minnesota Living with Heart Failure Questionnaire; range of scores: 0-105; Better indicated by less)** | | | | | | | | | | | |
| 4<br>CIDER 2003<br>DRACUP 2007<br>NILSSON 2008<br>SARULLO 2006 | randomised trial | no serious limitations[9] | no serious inconsistency | no serious indirectness | serious[10] | none | 141 | 147 | - | MD -0.96 (-7.36 to 5.44) | ⊕⊕⊕O MODERATE | |
| **Mean QoL score (follow-up 1-5 years; measured with: Minnesota Living with Heart Failure Questionnaire; range of scores: 0-105; Better indicated by less)** | | | | | | | | | | | |
| 3<br>AUSTIN 2008<br>BELARDINELLI 1999<br>NILSSON 2008 | randomised trial | no serious limitations[11] | serious[12] | no serious indirectness | serious[10] | none | 147 | 144 | - | MD -6.67 (-13.20 to -0.14) | ⊕⊕OO LOW | |
| **Mean change in QoL (follow-up 12 weeks; measured with: Minnesota Living with Heart Failure Questionnaire; range of scores: 0-105; Better indicated by less)** | | | | | | | | | | | |
| 1<br>COLLINS 2004 | randomised trial | serious[13] | no serious inconsistency | no serious indirectness | serious[10] | none | 15 | 16 | - | MD -3.10 (-12.65 to 6.45) | ⊕⊕OO LOW | |
| **Mean 6MWT (follow-up 2-6 months; measured with: 6 minute walking test (metres); range of scores: -; Better indicated by more)** | | | | | | | | | | | |
| 5<br>CIDER 2003<br>CORVERA 2004<br>DRACUP 2007<br>NILSSON 2008<br>WITHAM 2005 | randomised trial | no serious limitations[14] | serious[15] | no serious indirectness | no serious imprecision | none | 224 | 215 | - | MD 40.04 (8.12 to71.95) | ⊕⊕⊕O MODERATE | |
| **Mean 6MWT up (follow-up 12 months; measured with: 6 minute walking test (metres); range of scores: -; Better indicated by more)** | | | | | | | | | | | |
| 1<br>NILSSON 2008 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision | none | 40 | 40 | - | MD 63.00 (15.3 to 110.7) | ⊕⊕⊕⊕ HIGH | |
| **Mean 6MWT up (follow-up 5 years; measured with: 6 minute walking test (metres); range of scores: -; Better indicated by more)** | | | | | | | | | | | |
| 1<br>AUSTIN 2008 | randomised trial | no serious limitations[16] | no serious inconsistency | no serious indirectness | serious[17] | none | 224 | 215 | - | MD 29.70 (-15 to 74.4) | ⊕⊕⊕O MODERATE | |

[1] unclear allocation concealment 3/4; unclear blinding 3/4 (1 single blind); uneven drop out across arms 1/4 (15% control vs. 6% in training)
[2] total number of events is less than 300;
[3] 43% drop out-but 5 yr follow up
[4] Unclear allocation concealment 2/2; unclear blinding 2/2
[5] significant heterogeneity I=76%, chi-squared p=0.04.
[6] total events <300; 95% CI around the pooled or best estimate of effect includes both negligible effect and appreciable benefit or appreciable harm.
[7] serious heterogeneity I=70%, Chi-squared p=0.02
[8] unclear allocation concealment and blinding
[9] unclear allocation concealment 2/4; unclear blinding 3/4 (1 single blind)
[10] 95% confidence interval includes no effect and the upper or lower confidence limit crosses the minimal important difference (MID), either for benefit of harm (5 points)
[11] 1/3 unclear allocation concealment; 3/3 unclear blinding; 1/3 43% drop out but 5 yr follou up; 1/3 unclear ITT
[12] serious heterogeneity I=50%

[13] unclear allocation concealment; unclear blinding; unclear ITT
[14] 3/5 unclear allocation concealment; 4/5 unclear blinding
[15] serious heterogeneity I=64%
[16] unlclear blinding; 45% drop-out but 5 yr follow up
[17] the upper or lower confidence limit crosses an effect size of 0.5 in either direction.

### b) Specialist nurse care plus exercise training with specialist nurse care only

There was no significant difference between patients receiving specialist care plus exercise based cardiac rehabilitation with specialist nurse care only for the following outcomes:

- All cause hospitalisation (12 month follow-up) [moderate quality]
- Hospitalisation (cardiac) (12 month follow-up) [moderate quality]
- ISWT/m (6 month follow-up) [moderate quality]
- MLHF (12 month follow-up) [high quality]

**Evidence profile**

The evidence profile below summarises the quality of the evidence and outcome data from the RCT comparing **specialist nurse care plus exercise based cardiac rehabilitation vs. specialist nurse care**[124].

## Evidence profile: specialist nurse care plus exercise based cardiac rehabilitation vs. specialist nurse care

**Question:** Should specialist plus exercise vs specialist be used for chronic heart failure?
**Bibliography:** Jolly K, Taylor RS, Lip GY et al. A randomized trial of the addition of home-based exercise to specialist heart failure nurse care: the Birmingham Rehabilitation Uptake Maximisation study for patients with Congestive Heart Failure (BRUM-CHF) study. *European Journal of Heart Failure.* 2009; 11(2):205-213.

| Quality assessment | | | | | | | Summary of findings | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality | Importance |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | specialist plus exercise | specialist | Relative (95% CI) | Absolute | | |
| **All cause hospitalisation (follow-up 12 months)** | | | | | | | | | | | | |
| 1 Jolly 2009 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious | none | 16/85 (18.8%) | 20/84 (23.8%)<br>0% | RR 0.79 (0.44 to 1.42) | 50 fewer per 1000 (from 133 fewer to 100 more)<br>0 fewer per 1,000 | ⊕⊕⊕O MODERATE | |
| **Hospitalisation (cardiac) (follow-up 12 months)** | | | | | | | | | | | | |
| 1 Jolly 2009 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | very serious[1] | none | 11/85 (12.9%) | 11/84 (13.1%)<br>0% | RR 0.99 (0.45 to 2.15) | 1 fewer per 1000 (from 72 fewer to 151 more)<br>0 fewer per 1,000 | ⊕⊕OO LOW | |
| **ISWT/m (follow-up 6 months; range of scores: -; Better indicated by less)** | | | | | | | | | | | | |
| 1 Jolly 2009 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[2] | none | 85 | 84 | - | MD 20.77 (-17.83 to 59.37) | ⊕⊕⊕O MODERATE | |
| **Minnesota Living with Heart Failure (follow-up 12 months; range of scores: -; Better indicated by less)** | | | | | | | | | | | | |
| 1 Jolly 2009 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision | none | 85 | 84 | - | MD 2.70 (-4.23 to 9.63) | ⊕⊕⊕⊕ HIGH | |

[1] 95% confidence interval around the pooled or best estimate of effect includes both negligible effect and appreciable benefit or appreciable harm. Less than 300 events
[2] 95% CI includes no effect and the upper or lower confidence limit crosses an effect size of 0.5 in either direction.

## 6.4 Health Economic methodological introduction

From the 2003 Guideline [22] no conclusion was made in light of the included cost-effectiveness analysis assessing a rehabilitation programme for patients with heart failure (Georgiou 2001[125]). In addition, the 2003 Guideline[22] reviewed evidence from other disease areas which suggested that if a rehabilitation programme can reduce the risk of hospitalisation, they often represent a very cost effective use of resources.

We conducted a second review of the cost-effectiveness analysis[125] assessing exercise-based cardiac rehabilitation in patients with chronic heart failure.

Georgiou et al. (2001)[125] presented a cost-effectiveness analysis of long-term moderate exercise training in patients with stable chronic heart failure (n=99). The decision-analytic model was based on the Belardinelli 1999 RCT[123] and reported cost per life-year gained. The Belardinelli 1999 study[123] was conducted in a population of NYHA class II-III heart failure patients aged from 55 to 64 years. The Georgiou 2001 economic analysis[125] covered the period of the Belardinelli 1999 trial (1,639 days) plus 10 years, and was developed from a societal perspective (included direct medical costs and patient-level costs). The treatment group attended a 14-month-long healthcare-based physical rehabilitation program: 3 sessions/week for 8 weeks followed by 2 sessions/week for 12 months; 1 hour/session (20 minutes for warm-up and stretching, and 40 minutes on an electronically braked cycle ergometer). Hospitalisation and mortality rates for the treatment and the control cohorts for the within-trial period were taken from Belardinelli 1999[123]. The same hospitalisation and mortality rates were used for both cohorts after the trial period. The mortality rate used post-trial was from the *National Health and Nutrition Examination I – Epidemiologic follow-up Survey (1982 – 1986)*[126], which was adjusted with sex-specific rates, and increased by 23% to account for ACEI intake introduced after the National Survey (Pfeffer 1992[127]; Garg 1995[128]). The cost components incorporated in to the analysis were (1) cost of exercise training (equipment, rented place, trainer salary); (2) cardiopulmonary stress test cost including the physician component of interpretation and exercise prescription; (3) hospitalisation cost; and (4) the patient-level cost of wages lost for attending training sessions. The sensitivity analysis varied (a) the survival probabilities for the within-trial period; (b) the survival probabilities post-trial varying the ACEI survival rate adjustment; and (c) the within-trial rates of hospitalisation. Future costs and benefits were discounted at 3% per annum. Table 6.2 gives the quality and applicability assessment of this economic analysis.

**Table 6.2: Economic study assessment**

| Study | Study quality* | Study applicability** |
|---|---|---|
| Georgiou 2001[125] | Potentially serious limitations (a) | Partially applicable (b) |

*Very serious limitations / Potentially serious limitations / Minor limitations; ** Directly applicable / Partially applicable / Not applicable

(a) Small cohort size; Outcomes were not measured as QALYs.

(b) The analysis was developed from a US perspective.

## 6.5 Health economic evidence statements

Results of the Georgiou 2001 cost-effectiveness analysis[125] are presented in Table 6.3. The study showed that an exercise training programme like the one used in the Belardinelli 1999 study[123] is highly cost-effective for patients with chronic heart failure in the US, even using conservative assumptions and estimates, and considering wages lost. Removing the lost wages from the base-case analysis showed an ICER of £258 per life-year gained, again

highly cost-effective. However, this analysis was developed from a US perspective and the generalisation of these results to a UK context is questionable. Limitations of the analysis were that (1) the study assessed a predominantly male population aged between 55 and 64 years of NYHA class II-III heart failure patients, to which the results of the analysis are applicable; (2) the Bellardinelli RCT[123] has small cohort sizes (n=50 in the treatment group and n=49 in the control group); and (3) the study did not report QALYs.

**Table 6.3: Results – Georgiou 2001 economic analysis***

| Incremental cost (£) | Incremental effects | ICER | Uncertainty |
|---|---|---|---|
| £2106 | Life expectancy (years): 1.82 | Base-case analysis: £1157 per life-year gained (LYG)** | Sensitivity analyses:<br>(1) Patient-level cost removed: £258 per LYG;<br>(2) Within-trial survival rates varied: £5400 to £660 per LYG;<br>(3) Post-trial survival rates varied: £1108 to £1211 per LYG;<br>(4) Hospitalisation rates varied: £1548 to £781 per LYG |

* Costs were converted into pound sterling using Purchasing Power Parities[81]

** Using the utility score proposed by Mant 2009[37] of 0.65 for patients with heart failure, we estimated the threshold in cost per LYG, equivalent to the £20,000 per QALY gained proposed by NICE, to be £13,000 per LYG.

The Georgiou 2001 economic analysis[125] was included in a 2006 review by Hagberg et al.[129] of cost-effectiveness studies of healthcare-based interventions aimed at improving physical activity in different populations and perspectives. The Georgiou 2001 study[125] was the only included study developed on patients with chronic heart failure. The Hagberg 2006 review[129] suggested that healthcare-based rehabilitation programmes are likely to be cost-effective in different populations and for different healthcare systems, including the UK NHS (in almost every study included in the review, the rehabilitation program was found to be cost-effective).

## 6.6 From evidence to recommendations

### Relative value placed on the outcomes considered

The GDG considered the issue of rehabilitation after careful consideration of the concerns expressed by the patient members about the availability of rehabilitation programmes and the patchy adherence to the previous NICE guideline. The GDG believe that of the three main components of any rehabilitation programme exercise is the most important intervention since the education and counselling are usually incorporated into standard care. Therefore, the GDG elected to review the role of exercise-based rehabilitation programmes in the management of patients with heart failure, while acknowledging the importance of psychosocial aspects of rehabilitation. In terms of assessment of objective physical function, the GDG preferred the well validated 6 minute walking test to formal cardio-pulmonary exercise testing given the easy access to the former, and its applicability to a wider population of heart failure patients, particularly the elderly.

The GDG reviewed the evidence derived from 13 randomised controlled trials, which used exercise based programme of rehabilitation. These were published between 1999 and 2009. The programmes were heterogeneous but all included structured exercise that ranged from walking to intensive gym based activity including resistance and aerobic exercises. One study looked at exercises within the swimming pool. The studies looked at a wide range of patient age groups, including older people. All included patients with symptomatic heart failure, mostly NYHA class II-III, though three trials included a few patients with NYHA class IV[112,117,121]. The GDG were reluctant to make positive recommendations on the basis of

these small numbers for this subgroup because of their inherent instability. Only one trial (n=80) included patients with heart failure with preserved left ventricular ejection fraction (and also included patients with LVSD).[113] Despite the paucity of direct evidence in HFPEF, the GDG decided that their rehabilitation recommendations should relate to all patients with heart failure who do not have a contra-indication, since symptoms and prognosis of patients with HFPEF do not differ significantly from those with heart failure due to LVSD. Also, the GDG recognised that patients with HFPEF may have dysfunction of the longitudinal axis of the left ventricle which is frequently not detected by most measurements of the left ventricular ejection fraction. The GDG did not wish to inadvertently promote inequity by restricting any recommendations to patients with LVSD.

The GDG noted that the majority of the programmes included group exercises which also provided the patients with support and educational opportunities, through formal counselling, as well as iterative learning about their condition and how to cope with it. The trials included assessment of patient suitability prior to entry. The GDG discussed these criteria and concluded that most patients should be included following assessment and determination of the most suitable training programme for their needs.

The GDG was aware that some rehabilitation programmes in the NHS were designed specifically to meet the needs of patients with chronic heart failure whereas others incorporate heart failure patients within their existing cardiac rehabilitation programmes (post- myocardial infarction and post-cardiac surgery).

***Quality of evidence***

The evidence was of high quality with regards to the 6 minute walking test (12 months) and for the Minnesota Living with Heart Failure Questionnaire (6 months).

The evidence quality was moderate with regards to:

- Heart failure hospitalisation
- Quality of life (5 years)
- 6 minute walk test at (6 months and 5 years)
- All cause mortality

The remainder of the evidence was of either low or very low quality. Several of the studies recruited small number of patients and this was reflected by the wide confidence intervals of the reported results.

***Trade-off between clinical benefits and harm***

The GDG looked at the issues of hospitalisation. A direct link between hospitalisation and exercise was reported by O'Connor (the largest trial), in 1% of the patients being hospitalised within 3 hours of the exercise programme[112]. Overall, there was no evidence of increased (or reduced) mortality of patients with significant heart failure recruited to the exercise based rehabilitation programme, confirming the safety of exercise in this high risk patient group. In addition, there are clear benefits on the exercise tolerance, on the functional class (NYHA) and on reducing heart failure hospitalisation.

***Trade-off between net health benefits and resource use***

The GDG reviewed the cost effectiveness analysis by Georgiou[125] from 2001. This showed that the exercise based rehabilitation programme in heart failure was cost effective; the incremental cost-effectiveness ratio (ICER) was £258 per life year gained when considering direct medical costs only. The GDG believed that the analysis had short comings in terms of its small population size of mainly young male patients (reducing the ability to generalise the conclusions) and the fact it was conducted from a US perspective. The Georgiou 2001[125] economic analysis was the only one assessing patients with heart failure included in the 2006 review by Hagberg[129] of cost-effectiveness studies of healthcare-based interventions

aimed at improving physical activity. With regard to the limitations of the Georgiou cost effectiveness analysis[125] and to the limited applicability of the results to the UK NHS, the conclusions of the Hagberg 2006 review were reassuring, showing that healthcare-based rehabilitation programs are likely to be cost-effective in different populations and for different healthcare systems including the UK NHS (in almost every study included in the review the rehabilitation program was found to be cost-effective).

## 6.7 Recommendations for rehabilitation

R61 Offer a supervised group exercise-based rehabilitation programme designed for patients with heart failure.

- Ensure the patient is stable and does not have a condition or device that would preclude an exercise-based rehabilitation programme*.
- Include a psychological and educational component in the programme[24].
- The programme may be incorporated within an existing cardiac rehabilitation programme. **[new 2010] KPI**

[24] The conditions and devices that may preclude an exercise-based rehabilitation programme include: uncontrolled ventricular response to atrial fibrillation, uncontrolled hypertension, and high-energy pacing devices set to be activated at rates likely to be achieved during exercise.

# 7 Monitoring

Heart failure is a progressive disease characterised by high re-hospitalisation rates [130]; [131] and complications that can lead to a decline in renal, hepatic and neurological function. The guidance in 2003 recognised the importance of monitoring patients with heart failure. Monitoring facilitates continuing education for patients and their carers and improved communication between the patient and the heart failure team enabling earlier detection of complications, including anxiety and depression. Early intervention may reduce re-hospitalisation and enables adjustment of therapy to accommodate change in the patient's clinical condition.

This update focuses on the use of natriuretic peptides and tele-monitoring in monitoring heart failure patients

**The topics within monitoring that were outside the scope of the partial update were:**

1. Clinical review. For more information please refer to Section 8.1 of the 2003 Guideline [22].
2. Review of management plan – including medication. For more information please refer to Section 8.2 of the 2003 Guideline [22].
3. Serial cardiac imaging. For more information please refer to Section 8.3 of the 2003 guidleine [22].
4. Therapeutic drug monitoring of serum digoxin concentrations. For more information please refer to Section 8.4 of the 2003 Guideline [22]

## 7.1 Serial measurement of circulating natriuretic peptide concentration

**Does serial BNP monitoring improve outcome compared to standard care in adults with chronic heart failure?**

### *7.1.1 Clinical introduction*

In 2003 the guideline development group noted that serial measurement of plasma NTproBNP concentrations had been shown in one small RCT to reduce the risk of decompensation [132]**.** However, this was insufficient to produce a recommendation on the use of natriuretic peptides in the monitoring of heart failure patients.

**Reason for review**

The emergence of new studies on the use of natriuretic peptides in monitoring patients with heart failure,.

### *7.1.2 Clinical methodological introduction*

Five randomised controlled trials (RCT) were identified on patients with chronic heart failure[132,133], [134], [135], [136].

Four of the trials compared BNP-guided therapy with clinically-guided therapy (see under 'comparison' in the table below)[132,133], [134], [135]. For details see Table 7. below. One trial used the BNP level to up-titrate beta-blocker dosage only[133]. One trial compared BNP-guided therapy with either clinically-guided therapy or usual care provided by a primary care physician[136]. The latter comparison is presented separately below.

**Table 7.1: Trials comparing BNP-guided therapy with clinically guided therapy**

| Study | Population | Intervention | Comparison |
|---|---|---|---|
| Lainchbury 2010<br>BATTLESCARRED | ▪ Included patients with persevered LVEF mean 40%<br>▪ Symptomatic HF. 75% NYHA II or III<br>▪ Inclusion criteria included NT-proBNP > 50 pmol/L<br>▪ Age (median) 76 yrs<br>▪ Age subgroups: ≤75 yrs; >75 yrs) | -Treatment was altered according to a drug algorithm if NT-proBNP level > 150 pmol/L and/or heart failure score was ≥ 2 (derived from Framlingham method of diagnosis) | -Treatment was altered if the heart failure score was ≥ 2 (derived from Framlingham method of diagnosis) |
| Beck-da-Silva, 2005 | ▪ (LVEF) of 40% or less<br>▪ Symptomatic HF (New York Heart Association class II- IV) for at least 3 months or previous hospital admission due to HF<br>▪ Age (mean) : 65 yrs<br>▪ < 50% males | -beta- blocker dosage up-titrated according to plasma BNP levels plus standard care | -beta- blocker dosage up-titrated according standard care |
| Troughton, 2000 | ▪ LVSD (LVEF <40% on echo)<br>▪ Established symptomatic HF (NYHA class II-IV)<br>▪ Age (range): 35- 85 yrs<br>▪ <50% females | -NT-proBNP guided treatment<br>-The treatment target was NT-proBNP below 200pmol/l<br>-If the targets were not achieved drug treatment was intensified according to a strict and predetermined stepwise protocol | -Treatment guided by standardised clinical assessment<br>-The treatment target was clinically compensated heart failure according to an objective score |
| Jourdain, 2007<br>STARS-BNP | ▪ Symptomatic (New York Heart Association functional class II to III) systolic heart failure defined by left ventricular ejection fraction (LVEF) <45%<br>▪ Age (mean): 65 yrs<br>▪ <50% females | -Medical therapy was increased with the aim of lowering plasma BNP levels (target <100 pg/ml)<br>- Each class of therapy modified according to the judgement of the investigator. | -Medical therapy was adjusted on the basis of the physical examination and usual para clinical and biological parameters. |
| Pfisterer, 2009<br>TIME-CHF | ▪ Dyspnea (New York Heart Association class ≥ II with current therapy), a history of hospitalisation for heart failure within the last | -BNP guided plus symptom guided medical therapy.<br>-Medical therapy to reduce BNP level to 2 | - Symptom guided medical therapy.<br>-Medical therapy to reduce symptoms to |

| | | | |
|---|---|---|---|
| | year<br>▪ Age (mean): 76 yrs<br>▪ <50% females<br>▪ Age subgroups: <75 yrs; ≥75 yrs) | times or less the upper limit of normal (<400 pg/ml in patients <75 years and <800 pg/ml in patients ≥75 years) and symptoms to NYHA class of II or less. | NYHA class of II or less. |

The Beck-da-Silva trial of 2005 [133] concentrated on uptitrating beta-blockers according to the serial level of natriuretic peptides. In the remaining four trials the investigators had either to follow a treatment algorithm or were given the choice of medical intervention needed. In the TIME-CHF trial [135] and BATTLESCARRED trial [136] the uptitration of therapy in the natriuretic peptide guided therapy was driven by either the natriuretic peptide level or by the patients' symptoms. In the studies of Jourdain (2007) [134] and Pfisterer (2009) [135] the investigators in the natriuretic peptide guided therapy had to work towards a target level for the natriuretic peptide.

### BNP-guided therapy vs clinically-guided therapy - Sub-group analysis by age

Two of the trials reported pre-specified sub-group analysis based on age: BATTLESCARRED (≤75 yrs vs >75 yrs) [136] and TIME-CHF (<75 yrs vs ≥75 yrs) [135].

### BNP-guided compared with usual care

The trial comparing BNP-guided therapy (see Table 7.2 below for details) with usual care is presented below [136]

**Table 7.2: BNP guided therapy vs usual care**

| Study | Population | Intervention | Comparison |
|---|---|---|---|
| Lainchbury 2010 BATTLESCARRED | ▪ Included patients with persevered LVEF mean 40%<br>▪ Symptomatic HF. 75% NYHA II or III<br>▪ Inclusion criteria included NT-proBNP > 50 pmol/L<br>▪ Age (median) 76 yrs<br>▪ Age subgroups: ≤75 yrs; >75 yrs) | Treatment was altered according to a drug algorithm if NT-proBNP level > 150 pmol/L and/or heart failure score was ≥ 2 (derived from Framlingham method of diagnosis) | *Usual care*<br><br>Managed in primary care with or without additional visits to a hospital cardiologist or specialised heart failure clinic |

### BNP-monitoring vs usual care – Sub-group analysis by age

The trial reporting on BNP-guided monitoring compared with usual care also reported the results of a pre-specified age sub-group analysis (≤75 yrs vs >75 yrs)

### *7.1.3 Clinical evidence statements*

Compared to clinically-guided therapy, BNP-guided therapy resulted in a significant reduction in:

- Hospitalisation (heart failure) (no. of patients) – 9.5 to 15 months [moderate quality]

There was no significant difference between BNP-guided therapy and clinically-guided therapy for the outcomes:

- Mortality (all cause) – 9.5 to 18 months [moderate quality]
- Mortality (all cause) – 3 yrs [moderate quality]
- Mortality (heart failure (HF) – 3 to 15 months [low quality]
- Hospitalisation (all cause) (no. of patients) – 3 to 15 months [low quality]
- Hospitalisation (heart failure) (no. of patients) – 3 yrs [moderate quality]
- Quality of life (Minnesota Living with Heart Failure) – 12 to 18 months [moderate quality]

The evidence profile below summarises the quality of the evidence and outcome data for the five randomised-control trials comparing BNP-guided therapy with clinically-guided therapy in patients with chronic heart failure.

## Evidence Profile: BNP guided therapy vs clinically guided therapy in patients with chronic heart failure

**Question:** Should Drug treatment guided by BNP-guided therapy vs clinically-guided therapy by clinically-guided care be used for CHF?
**Bibliography:** Beck-da-Silva L, de BA, Fraser M et al. BNP-guided therapy not better than expert's clinical assessment for beta-blocker titration in patients with heart failure. Congestive Heart Failure. 2005; 11(5):248-253; Troughton RW, Frampton CM, Yandle TG et al. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. Lancet. 2000; 355(9210):1126-1130. ; Jourdain P, Jondeau G, Funck F et al. Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure: the STARS-BNP Multicenter Study. Journal of the American College of Cardiology. 2007; 49(16):1733-1739.; Pfisterer M, Buser P, Rickli H et al. BNP-guided vs symptom-guided heart failure therapy: the Trial of Intensified vs. Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) randomized trial. Journal of the American Medical Association. 2009; 301(4):383-392; **Lainchbury JG, Troughton RW, Strangman KM *et al*.** N-Terminal Pro–B-Type Natriuretic Peptide-Guided Treatment for Chronic Heart Failure: Results From the BATTLESCARRED (NT-proBNP–Assisted Treatment To Lessen Serial Cardiac Readmissions and Death) Trial. ***J Am Coll Cardiol* 2010;55:53-60.)**

| Quality assessment | | | | | | | Summary of findings | | | | | Hazard ratio |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality | |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | Drug treatment guided by BNP Monitoring | drug treatment guided by clinically-guided care | Relative (95% CI) | Absolute | | |
| **Mortality (all causes) (follow-up 9.5-18 months)** | | | | | | | | | | | | |
| 3<br>BATTLESCARRED 2010<br>STARS-BNP 2007<br>TIME-CHF 2007 | randomised trial | no serious limitations[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 58/482 (12%) | 77/479 (10%)<br>22% | RR 0.75 (0.55 to 1.02) | 25 fewer per 1,000<br>54 fewer per 1,000 | ⊕⊕⊕O MODERATE | 0.73 (0.52 to 1.03) |
| **Mortality (all cause) (follow-up 3 years)** | | | | | | | | | | | | |
| 1<br>BATTLESCARRED 2010 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[3] | none | 40/121 (33.1%) | 40/121 (33.1%)<br>0% | RR 1.00 (0.70 to 1.43) | 0 fewer per 1000 (from 99 fewer to 142 more)<br>0 fewer per 1,000 | ⊕⊕⊕O MODERATE | 1.00 (0.65 to 1.55) |
| **Mortality (HF) (follow-up 3 to 15 months)** | | | | | | | | | | | | |
| 2<br>Beck-de-Silva 2005<br>STARS-BNP | randomised trial | serious[4] | no serious inconsistency | no serious indirectness | serious[3] | none | 4/131 (3.1%) | 11/130 (8%)<br>10% | RR 0.36 (0.12 to 1.10) | 51 fewer per 1,000<br>64 fewer per 1,000 | ⊕⊕OO LOW | 0.35 (0.11to1.11) |
| **Hospitalisation (all cause) (no. of patients) (follow-up 3 to 15 months)** | | | | | | | | | | | | |
| 2<br>STARS-BNP 2007<br>Beck-de-Silva 2005 | randomised trial | serious[4] | no serious inconsistency | no serious indirectness | serious[3] | none | 54/131 (41.2%) | 64/130 (20%)<br>55% | RR 0.84 (0.65 to 1.09) | 32 fewer per 1,000<br>88 fewer per 1,000 | ⊕⊕OO LOW | |
| **Hospitalisation (heart failure) (no. of patients) (follow-up 9.5-15 months)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4<br>BATTLESCARRED 2010<br>TIME-CHF 2009<br>STARS-BNP 2007<br>Troughton 2000 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[5] | none | 86/515 (16.7%) | 131/515 (12%)<br>24% | RR 0.66 (0.52 to 0.84) | 40 fewer per 1,000<br>81 fewer per 1,000 | ⊕⊕⊕O MODERATE | |
| **Hospitalisation (heart failure) (no. of patients) (follow-up 3 years)** | | | | | | | | | | | | |
| 1<br>BATTLESCARRED 2010 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[3] | none | 44/121 (36.4%) | 49/121 (40.5%) | RR 0.90 (0.65 to 1.24) | 41 fewer per 1000 (from 142 fewer to 97 more) | ⊕⊕⊕O MODERATE | |
| **Quality of Life (MLHF) (follow-up 12-18 months; range of scores: 0-105; Better indicated by less)** | | | | | | | | | | | | |
| 2<br>BATTLESCARRED 2010<br>TIME-CHF 2009 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[3,6] | none | 372 | 369 | - | MD 1.30 (-1.63 to 4.22) | ⊕⊕⊕O MODERATE | |

[1] 2/3 unclear allocation concealment. 2/3 single blind. 2/3 ITT reported. Largest trial > 50% total population double blind and ITT analysis
[2] 95% confidence interval around the best estimate of effect includes both negligible effect and appreciable benefit or appreciable harm.
[3] 95% confidence interval around the best estimate of effect includes both negligible effect and appreciable benefit or appreciable harm. total number of events is less than 300.
[4] 2/2 Allocation concealment not reported. 1/2 Blinding not reported. 1/2 ITT not reported.
[5] Total number of events less than 300.
[6] 95% CI > 5 points (minimaly important difference)

**BNP-guided therapy vs clinically-guided therapy - Sub-group analysis by age**

BNP-guided therapy, compared to clinically-guided therapy resulted in a significant reduction of:

- 75 yrs or less- Mortality (all cause) - 18 mths to 3 yrs [moderate quality]

There was no significant difference between BNP-guided therapy and clinically-guided therapy for the outcomes:

- 76 yrs or more - Mortality (all cause) - 18 mths to 3 yrs [moderate quality]
- 76 yrs or more - Hospitalisation (heart failure) (no. of patients) – 18 mths to 3 yrs [moderate quality]
- 75 yrs or less - Hospitalisation (heart failure) (no. of patients) – 18 mths to 3 yrs [moderate quality]

The evidence profile below summarises the quality of the evidence and outcome data for the two randomised-control trials comparing BNP-guided therapy with clinically-guided therapy in patients with chronic heart failure by age sub-group

## Evidence Profile: BNP guided therapy vs clinically guided therapy in patients with chronic heart failure by age group

**Author(s):**
**Date:** 2009-09-23
**Question:** Should BNP-guided vs clinically-guided be used for chronic heart failure?
**Settings:**
**Bibliography:** **Lainchbury JG, Troughton RW, Strangman KM *et al*.** N-Terminal Pro–B-Type Natriuretic Peptide-Guided Treatment for Chronic Heart Failure: Results From the BATTLESCARRED (NT-proBNP–Assisted Treatment To Lessen Serial Cardiac Readmissions and Death) Trial. ***J Am Coll Cardiol*** **2010;55:53-60.)**

| Quality assessment | | | | | | | Summary of findings | | | | | Hazard ratio |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality | |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | BNP-guided | clinically-guided | Relative (95% CI) | Absolute | | |
| **76 yrs or more - Mortality (all cause) - 18 mths to 3 yrs (follow-up 1.5-3 years)** | | | | | | | | | | | | |
| 2<br>BATTLESCARRED 2010<br>TIME-CHF 2009 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | None | 64/206 (31.1%) | 60/212 (25%)<br>35% | RR 1.10 (0.82 to 1.47) | 25 more per 1,000<br>35 more per 1,000 | ⊕⊕⊕O<br>MODERATE | 1.14 (0.80 to 1.63) |
| **75 yrs or less - Mortality (all cause) - 18 mths to 3 yrs (follow-up 1.5-3 years)** | | | | | | | | | | | | |
| 2<br>BATTLESCARRED 2010<br>TIME-CHF 2009 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | None | 11/108 (10.2%) | 11/102 (20%)<br>31% | RR 0.49 (0.30 to 0.79) | 50 fewer per 1,000<br>158 fewer per 1,000 | ⊕⊕⊕O<br>MODERATE | 0.45 (0.26 to 0.78) |
| **76 yrs or more - Hospitalisation (HF) - 18 mths to 3 yrs (follow-up 1.5-3 years)** | | | | | | | | | | | | |
| 2<br>BATTLESCARRED 2010<br>TIME-CHF 2009 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | None | 53/206 (25.7%) | 56/212 (20%)<br>41% | RR 0.98 (0.72 to 1.34) | 3 fewer per 1,000<br>8 fewer per 1,000 | ⊕⊕⊕O<br>MODERATE | |
| **75 yrs or less - Hospitalisatioj (HF) - 18 mths to 3 yrs (follow-up 1.5-3 years)** | | | | | | | | | | | | |
| 2<br>BATTLESCARRED 2010<br>TIME-CHF 2009 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | None | 26/166 (15.7%) | 38/157 (16%)<br>40% | RR 0.65 (0.42 to 1.00) | 56 fewer per 1,000<br>140 fewer per 1,000 | ⊕⊕⊕O<br>MODERATE | |

[1] < 300 events

### BNP-guided compared with usual care

Compared to usual care, BNP-guided therapy resulted in a significant reduction of:

- Mortality (all cause) – one year [moderate quality]

There was no significant difference between BNP-guided therapy and standard care for the outcomes:

- Mortality (all cause) – three years [moderate quality]
- Hospitalisation (heart failure) (no. of patients) – one year [moderate quality]
- Hospitalisation (heart failure) (no. of patients) – three years [moderate quality]

The evidence profile below summarises the quality of the evidence and outcome data for the one randomised-control trial comparing BNP guided monitoring with usual care in patients with chronic heart failure.

## Evidence Profile: BNP guided therapy vs usual care in patients with chronic heart failure

**Question:** Should BNP-guided vs Usual care be used for chronic heart failure?
**Bibliography: Lainchbury JG, Troughton RW, Strangman KM *et al*.** N-Terminal Pro–B-Type Natriuretic Peptide-Guided Treatment for Chronic Heart Failure: Results From the BATTLESCARRED (NT-proBNP–Assisted Treatment To Lessen Serial Cardiac Readmissions and Death) Trial. ***J Am Coll Cardiol*** **2010;55:53-60.)**

| Quality assessment | | | | | | | Summary of findings | | | | | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality | |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | BNP-guided | Usual care | Relative (95% CI) | Absolute | | |
| **Mortality (all cause) - one year (follow-up 12 months)** | | | | | | | | | | | | |
| 1 BATTLESCARRED 2010 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious | none | 11/121 (9.1%) | 23/122 (18.9%) | RR 0.48 (0.25 to 0.95) | 98 fewer per 1000 (from 9 fewer to 142 fewer) | ⊕⊕⊕O MODERATE | |
| **Mortality (all cause) - three years (follow-up 3 years)** | | | | | | | | | | | | |
| 1 BATTLESCARRED 2010 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | none | 40/121 (33.1%) | 40/122 (32.8%)<br>0% | RR 1.01 (0.7 to 1.44) | 3 more per 1000 (from 98 fewer to 144 more)<br>0 more per 1,000 | ⊕⊕⊕O MODERATE | |
| **Hospitalisation (heart failure) - one year (follow-up 12 months)** | | | | | | | | | | | | |
| 1 BATTLESCARRED 2010 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | none | 29/121 (24%) | 26/122 (21.3%) | RR 1.12 (0.71 to 1.79) | 26 more per 1000 (from 62 fewer to 168 more) | ⊕⊕⊕O MODERATE | |
| **Hospitalisation (heart failure) - three years (follow-up 3 years)** | | | | | | | | | | | | |
| 1 BATTLESCARRED 2010 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | none | 44/121 (36.4%) | 41/122 (33.6%)<br>0% | RR 1.08 (0.77 to 1.53) | 27 more per 1000 (from 77 fewer to 178 more)<br>0 more per 1,000 | ⊕⊕⊕O MODERATE | |

[1] < 300 events

### BNP-monitoring vs usual care - Sub-group analysis by age

Compared to standard care, BNP monitoring resulted in a significant reduction of:

- 75 yrs or less – Mortality (all cause) – three years (p=0.05) [moderate quality]

There was no significant difference between BNP monitoring and standard care for the outcomes:

- 76 yrs or more – Mortality (all cause) – three years [moderate quality]
- 76 yrs or more – Hospitalisation (heart failure) – one year [moderate quality]
- 75 yrs or less – Hospitalisation (heart failure) - one year [moderate quality]
- 76 yrs or more – Hospitalisation (heart failure) – three years [moderate quality]
- 75 yrs or less – Hospitalisation (heart failure) – three years [moderate quality]

The evidence profile below summarises the quality of the evidence and outcome data for the one randomised-control trials comparing BNP-guided therapy with usual care by age sub-group in patients with chronic heart failure.

## Evidence Profile: BNP guided therapy vs usual care by age subgroup in patients with chronic heart failure

**Question:** Should BNP-guided monitoring vs Usual care be used for chronic heart failure?
**Bibliography: Lainchbury JG, Troughton RW, Strangman KM *et al*.** N-Terminal Pro–B-Type Natriuretic Peptide-Guided Treatment for Chronic Heart Failure: Results From the BATTLESCARRED (NT-proBNP–Assisted Treatment To Lessen Serial Cardiac Readmissions and Death) Trial. ***J Am Coll Cardiol* 2010;55:53-60.)**

| Quality assessment | | | | | | | Summary of findings | | | | | Hazard ratio |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality | |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | BNP-guided monitoring | Usual care | Relative (95% CI) | Absolute | | |
| **76 yrs or more - Mortality (all cause) - three yrs (follow-up 3 years)** | | | | | | | | | | | | |
| 1 BATTLESCARRED 2010 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious | None | 31/63 (49.2%) | 20/58 (34.5%) | RR 1.43 (0.92 to 2.20) | 148 more per 1000 (from 28 fewer to 414 more) | ⊕⊕⊕O MODERATE | 1.56 (0.90 to 2.71) |
| **75 yrs or less - Mortality (all cause) - three yrs (follow-up 3 years)** | | | | | | | | | | | | |
| 1 BATTLESCARRED 2010 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | None | 9/58 (15.5%) | 20/64 (31.3%) | RR 0.50 (0.25 to 1.00) | 188 fewer per 1000 (from 6 fewer to 260 fewer) | ⊕⊕⊕O MODERATE | 0.47 (0.22 to 1.0) |
| **76 yrs or more - Hospitalisation (HF) - one year (follow-up 1 years)** | | | | | | | | | | | | |
| 1 BATTLESCARRED 2010 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | None | 16/63 (25.4%) | 8/58 (13.8%) | RR 1.84 (0.85 to 3.98) | 116 more per 1000 (from 21 fewer to 411 more) | ⊕⊕⊕O MODERATE | |
| **75 yrs or less - Hospitalisation (HF) - one year (follow-up 1 years)** | | | | | | | | | | | | |
| 1 BATTLESCARRED 2010 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | None | 13/58 (22.4%) | 18/64 (28.1%) | RR 0.80 (0.43 to 1.48) | 56 fewer per 1000 (from 160 fewer to 135 more) | ⊕⊕⊕O MODERATE | |
| **76 yrs or more - Hospitalisation (HF) - three yrs (follow-up 3 years)** | | | | | | | | | | | | |
| 1 BATTLESCARRED 2010 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | None | 27/63 (42.9%) | 18/58 (31%) | RR 1.38 (0.86 to 2.23) | 118 more per 1000 (from 124 fewer to 381 more) | ⊕⊕⊕O MODERATE | |
| **75 yrs or less - Hospitalisation (HF) - three yrs (follow-up 3 years)** | | | | | | | | | | | | |
| 1 BATTLESCARRED 2010 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious[1] | none | 17/58 (29.3%) | 23/64 (35.9%) | RR 0.82 (0.49 to 1.37) | 65 fewer per 1000 (from 183 fewer to 133 more) | ⊕⊕⊕O MODERATE | |

[1] < 300 events

### *7.1.4 Health Economic Methodological introduction*

From the 2003 Guideline[22], no relevant economic evidence relating to serial natriuretic peptide monitoring in heart failure was identified. From our review, one cost-effectiveness analysis from the United States was identified and presented to the GDG. In addition, we undertook our own economic analysis.

***US published evidence***

Morimoto et al. (2004)[137] developed a cost-utility analysis reporting cost per QALY gained. The assessment was based on the Troughton 2000 clinical study[132] and on an economic model for patients with heart failure developed by Delea in 1999[138]. A US Medicare perspective was taken and baseline results were presented at 9 months. The population considered was symptomatic CHF patients (NYHA class II-IV) aged 35-85 after hospital admission because of CHF with reduced LVEF. The study compared (1) outpatient BNP-guided heart failure management once every 3 months (BNP group) versus (2) no BNP measurement (clinical group). The analysis was developed using a Markov model proposed by Paul 1994[139] for outpatient follow-up after hospitalisation for CHF. The utility values used to calculate QALYs were obtained from data by Havranek 1999[140] (symptomatic CHF patients with reduced LVEF). The probabilities considered in the analysis, from Troughton 2000[132] and Delea 1999[138], were the difference between cohorts in hospitalisation rates (for CHF care and non-CHF care), CHF deaths, frequency of ambulatory care, doses of ACEI, and doses of diuretics. The costs were BNP measurement, drugs for CHF, dispensing fee, ambulatory care for CHF, inpatient care for CHF, and non-CHF related inpatient care. The sensitivity analysis varied all parameters**:** 95% CI for utility scores; ratios of increase in medication and ambulatory visits in the BNP group were varied between 1 and 2 (baseline probabilities of 1.5 for ambulatory care and 1.4 for doses of ACEI and diuretics); other parameters were varied within ±50%; and the follow-up period was varied from 6 to 18 months. Future costs and benefits were discounted at 3% per annum. Table 7.3 presents the quality and applicability assessment of this economic analysis.

**Table 7.3: Economic study assessment**

| Study | Study quality* | Study applicability** |
|---|---|---|
| Morimoto 2004[137] | Potentially serious limitations (a) | Partially applicable (b) |

*Very serious limitations / Potentially serious limitations / Minor limitations; ** Directly applicable / Partially applicable / Not applicable
(a) Analysis developed using limited clinical data; Short time horizon
(b) Analysis developed from the US perspective

***UK analysis developed for this Guideline***

In England and Wales, natriuretic peptide measurement is available, but its use as a monitoring tool is not widespread. National implementation might significantly affect resource use in the NHS. The published cost-effectiveness analysis assessing the management of medical treatment in chronic heart failure using BNP measurement compared to clinical assessment[137] was based on one RCT[132] and showed that BNP monitoring was cost-effective. However, this analysis was developed from a US perspective and the generalisation of these results to a UK context is questionable. Furthermore, there is now considerably more trial evidence. Therefore, we undertook an original cost-effectiveness analysis from a UK NHS and personal social services perspective (See Appendix H for details).

### *7.1.5 Health economic evidence statements*

***US published evidence***

In the base-case analysis, Morimoto et al. (2004)[137] (9 months) found that adding BNP monitoring to clinical assessment was more effective and less costly (dominant) than monitoring based on clinical assessment only (Table 7.4). When varying the follow-up time, the BNP group was dominant at 6, 9 and 12 months, and presented a favourable incremental cost-effectiveness ratio (ICER) at 15 months and 18 months. Results were sensitive to the degree of increase in ambulatory visits for the BNP group, the probability of first readmission for the clinical group, the costs of ambulatory visits, and the costs of inpatient care for CHF. However, the ICER stayed cost-effective in the majority of simulations. The BNP group ICER became not cost-effective (using a threshold of $50,000/QALY, ~£30,000/QALY) when the probability of first readmission for the clinical group and the cost of inpatient CHF care were decreased simultaneously.

This analysis was developed from a US perspective. The generalisation of these results in a UK context is questionable. Other limitations are that the analysis considered a time horizon only up to 18 months (a lifetime horizon is more appropriate for chronic diseases or when an intervention has an impact on mortality), and cost data were taken from published studies and not from national statistics, which might affect generalisability.

**Table 7.4: Results – Morimoto 2004 economic analysis***

| | 6 months | 9 months (base-case analysis) | 12 months | 15 months | 18 months |
|---|---|---|---|---|---|
| **BNP Group** | | | | | |
| **QALY** | **0.38** | **0.57** | **0.74** | **0.91** | **1.07** |
| **Cost** | **£3500** | **£6011** | **£8433** | **£10,767** | **£13,015** |
| **Clinical Group** | | | | | |
| **QALY** | **0.38** | **0.55** | **0.70** | **0.83** | **0.94** |
| **Cost** | **£3910** | **£6358** | **£8580** | **£10,582** | **£12,379** |
| **Result** | | | | | |
| **ICER** | **Dominant**** | **Dominant**** | **Dominant**** | **£2,191 per QALY** | **£4,887 per QALY** |

* Costs were converted in pound sterling using Purchasing Power Parities[81]
** Dominant means that the intervention was more effective and less costly

***UK analysis developed for this Guideline***

The objective of this economic analysis was to assess the cost-effectiveness of three alternative strategies:

- serial measurement in secondary care of circulating natriuretic peptide concentration for optimizing medical therapy
- clinical assessment in secondary care
- usual care in the community

These were strategies for patients in England and Wales with

1. chronic heart failure (CHF) , or
2. CHF and left ventricular systolic dysfunction (LVSD).

The economic analysis was based on four clinical trials identified from the systematic clinical review, above [Section 7.1.2], which assessed serial measurement of natriuretic peptide concentration for optimizing the medical therapy in CHF (Troughton 2000[132], Jourdain 2007[134], Pfisterer 2009[135], Lainchbury 2010[136]). Trougton 2000[132], Jourdain 2007[134], and Pfisterer 2009[135] compared serial measurement in secondary care of natriuretic peptide concentration and clinical assessment in secondary care. Lainchbury 2010[136] compared

natriuretic peptide measurement in secondary care, clinical assessment in secondary care, and usual care in the community.

The Trougton 2000[132], Jourdain 2007[134], and Pfisterer 2009[135] clinical trials were conducted in patients with CHF and LVSD. Lainchbury 2010 clinical trial[136] was conducted on patients with CHF of any causes. Hence, outcomes of the three clinical trials on patients with LVSD [132], [134], [135] were meta-analysed for use in this economic analysis, and outcomes from the Lainchbury clinical trial[136] were utilized independently. Furthermore, age subgroups were assessed in Pfisterer[135] (<75 years / ≥75 years) and Lainchbury[136] (≤75 years / >75 years), and cost-effectiveness analyses were therefore conducted for these subgroups.

The same mortality rate and yearly cost per patient were assumed for each intervention after the trial period. A lifetime horizon was used when the number of patients who were alive differed between the compared cohorts at the end of the trial follow-up. When the same number of patients were alive in each trial arm at the end of the trial, the trial period was used as the model time horizon. It was judged that the same number of patients were alive in the three compared cohorts at the end of Lainchbury main analysis, and between the clinical assessment and the usual care cohorts in Lainchbury age-subgroup analyses (≤75 years / >75 years)[136]. Therefore, cost-effectiveness assessments were conducted on these analyses on a three-year time horizon. In addition, for Lainchbury[136] age subgroups, cost-effectiveness assessments were conducted on a lifetime horizon as a higher proportion of patients were alive at the end of the trial in natriuretic peptide cohorts in comparison to clinical assessment or usual care. Cost-effectiveness assessments conducted on patients with CHF and LVSD were developed on a lifetime horizon.

Cost-effectiveness analyses were developed from an England and Wales NHS perspective. The health outcome considered was the Quality-Adjusted Life Year (QALY), and an annual discount rate of 3.5% was applied to both costs and health outcomes incurred after one year.

Quality-Adjusted Life Years (QALYs) are calculated by multiplying the patients' life expectancy (life years) by a utility score (a quality of life measure on a 0-1 scale). Within-trial mortality estimates were taken from the clinical trials themselves. Life years were calculated using survival curves when available (Lainchbury[136] and Pfisterer[135]), or risk ratios at the end of trials assuming deaths occurred evenly over the trial follow-up period. Patients' mortality post-trial was assumed to be the same for each of the compared cohorts in all the analyses.

The four clinical trials[132], [135], [134], [136] did not report utility scores. We used mean utility scores stratified by NYHA class for patients with CHF reported by Gohler 2009[141] to calculate a mean utility score from patients' baseline characteristics, as observed in the trials. We assumed that mean utility scores remained constant over time and were the same for each intervention.

Resource use was taken from the clinical trials and was combined with standard UK unit costs. Resource use components considered were hospitalisation, drug usage, outpatient visits, natriuretic peptide assessment, and biochemistry testing to assess renal function. For the post-trial period, the same yearly cost per patient was applied to compare cohorts.

Sensitivity analyses were performed to assess the robustness of the cost-effectiveness results to plausible variations in model parameters. First, for the cost-effectiveness assessment conducted on patients with CHF and LVSD, the Pfisterer[135] drug usage was used for the base case; drug usage from Jourdain[134] and Troughton[132] was applied in sensitivity analyses. Secondly, Jourdain[134] and Pfisterer[135] clinical trials were modelled independently in addition to the assessment combining outcomes from Pfisterer[135], Jourdain[134], and Troughton[132], because of some inconsistencies in outcomes. Troughton[132] was not modelled independently since it was small and did not report all-cause mortality. Furthermore, as discussed above, the cost-effectiveness assessment from Lainchbury[136] main analysis was conducted on a three-year time horizon, and cost-effectiveness

assessments from Lainchbury[136] age-subgroup analyses were conducted on both a three-year and a lifetime horizon. Cost-effectiveness assessments conducted on patients with CHF and LVSD were developed on a lifetime horizon in the base case analysis. They were based on trial follow-ups shorter than three years (18 months[135] and 15 months[134]). Considering that mortality ratios in natriuretic peptide and clinical assessment cohorts for all-age analyses might be the same at three years, as in Lainchbury[136] main analysis, we conducted additional analyses on patients with CHF and LVSD on a three-year time horizon. Finally, in the sensitivity analysis, we used a cost of £20 for natriuretic peptide testing in addition to the £27.71 used in the base case.

This economic analysis presents probabilistic results. A probabilistic analysis applies probability distributions to each model parameter and therefore allows us to calculate a distribution for the results of the cost-effectiveness analysis, equivalent to a confidence interval.

Table 7.5 presents the breakdown of resource use components, life years, and QALYs for the base-case cost-effectiveness analysis developed on patients with CHF and LVSD based on the Pfisterer[135], Jourdain[134], and Troughton[132] clinical trials. Table 7.6 presents cost-effectiveness results for the base-case analysis, subgroup analyses, and sensitivity analysis in this population.

Results show that serial measurement of natriuretic peptide concentration in secondary care is clearly cost-effective compared to clinical assessment in secondary care for the base-case population and both age subgroups (<75 years, ≥75 years). The probability of natriuretic peptide being cost-effective was high (98% for the base case, 99% for <75 years, and 68% for ≥75 years). The conclusion was the same in all the sensitivity analyses. In the sensitivity analysis based on Jourdain[134] with a three-year time horizon, the natriuretic peptide option was cost-saving compared to clinical assessment.

**Table 7.5: Cost and QALY results**

| Resource use | Natriuretic peptide | Clinical assessment | Difference NP-Clinic |
|---|---|---|---|
| Natriuretic peptide test | £136 | £0 | £136 |
| Drugs | £404 | £377 | £27 |
| Biochemistry test | £1.66 | £1.04 | £0.62 |
| Outpatient visit | £482 | £422 | £60 |
| Hospitalisation | £161 | £279 | -£118 |
| Post-trial cost | £8,337 | £7,698 | £639 |
| **Total cost** | **£9,521** | **£8,777** | **£744** |
| **Life years** | **7.23** | **6.74** | **0.49** |
| **QALYs** | **5.18** | **4.82** | **0.36** |

NP = Natriuretic Peptide; Clinic = Clinical assessment
* Discounting at 3.5% applied after one year

**Table 7.6: Cost effectiveness results (LVSD)**

| Analysis | Time horizon | Cost difference (NP-Clinic) | QALY difference (NP-Clinic) | INMB (20k/QALY) | Probability NP being cost-effective | ICER | ICER (Sensitivity analysis - NP measurement =£20) |
|---|---|---|---|---|---|---|---|
| **Base-case analysis** | | | | | | | |
| CHF and LVSD (Pfisterer drug usage) | Lifetime | £744 | 0.36 | £6,373 | 98.3% | £2,091 | £1,985 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Age subgroups** | | | | | | | |
| Pfisterer <75 years | Lifetime | £1,187 | 0.72 | £13,248 | 99.0% | £1,644 | £1,592 |
| Pfisterer ≥75 years | Lifetime | £321 | 0.09 | £1,383 | 67.6% | £3,766 | £3,323 |
| **Sensitivity analysis - Independent clinical trials** | | | | | | | |
| Pfisterer all ages | Lifetime | £646 | 0.35 | £6,264 | 98.4% | £1,870 | £1,761 |
| Jourdain | Lifetime | £157 | 0.21 | £3,970 | 89.8% | £762 | £579 |
| **Sensitivity analysis - Drug usage** | | | | | | | |
| CHF and LVSD (Jourdain drug usage) | Lifetime | £735 | 0.36 | £6,382 | 98.3% | £2,065 | £1,959 |
| CHF and LVSD (Troughton drug usage) | Lifetime | £767 | 0.36 | £6,350 | 98.2% | £2,155 | £2,048 |
| **Sensitivity analysis - Time horizon** | | | | | | | |
| Pfisterer all ages | 3 years | £359 | 0.17 | £3,124 | 99.4% | £2,060 | £1,843 |
| Jourdain | 3 years | -£83 | 0.05 | £1,148 | 92.1% | NP dominates* | NP dominates* |
| CHF and LVSD (Pfisterer drug usage) | 3 years | £327 | 0.10 | £1,690 | 97.9% | £3,240 | £2,865 |
| CHF and LVSD (Jourdain drug usage) | 3 years | £313 | 0.10 | £1,698 | 97.78% | £3,150 | £2,775 |
| CHF and LVSD (Troughton drug usage) | 3 years | £349 | 0.10 | £1,667 | 97.7% | £3,465 | £3,090 |

NP = Natriuretic Peptide; Clinic = Clinical assessment; INMB = Incremental Net Monetary Benefit; ICER = Incremental Cost-Effectiveness Ratio

* Natriuretic peptide is more effective and less costly than clinical assessment

**Table 7.7 presents a breakdown of cost components, life years, and QALYs for the base-case cost-effectiveness analysis developed from Lainchbury[136].**

Table 7.8: shows results of this cost-effectiveness analysis modelled on a three-year time horizon. Comparing an intervention with the next best alternative (Figure 7.1:), and applying a threshold of £20,000 per QALY gained, clinical assessment is cost-effective compared to usual care (ICER = £7,188/QALY) and natriuretic peptide is cost-effective compared to clinical assessment (ICER = £11,861/QALY). Serial measurement of natriuretic peptide is therefore the preferred option from a cost-effectiveness perspective.

For the age-subgroup cost-effectiveness assessment conducted on patients 75 years old and younger and developed on three-year and lifetime horizons, the diagram of the cost-effectiveness plane (Figure 7.2) shows that clinical assessment is ruled out due to 'extended dominance'. Extended dominance exists when an option is less effective and more costly

than a linear combination of two other strategies. The results show that serial measurement in secondary care of natriuretic peptide is highly cost-effective compared to usual care in the community for patients with CHF 75 years old and younger (

Table 7.8**:**).

For the age-subgroup cost-effectiveness assessment conducted on patients older than 75 years and developed on three-year and lifetime horizons, the natriuretic peptide option is dominated by usual care (usual care is more effective and less costly – Figure 7.2). However, clinical assessment is cost-effective compared to usual care (

Table 7.8**:**). Therefore, clinical assessment in secondary care is the preferred options for patients with CHF older than 75 years.

Finally, the results of all analyses stayed the same when using a cost of £20 for natriuretic peptide testing (instead of £27).

**Table 7.7: Cost and QALY results (CHF any cause)**

| Resource use | Natriuretic peptide | Clinical assessment | Usual care | Difference NP-Clinic | Difference Clinic-UC |
|---|---|---|---|---|---|
| Natriuretic peptide test | £270 | £0 | £0 | £270 | £0 |
| Drugs | £415 | £433 | £349 | -£18 | £84 |
| Biochemistry test | £1.65 | £1.03 | £0 | £0.62 | £1.03 |
| Outpatient visit | £951 | £894 | £461 | £57 | £433 |
| Hospitalisation | £638 | £699 | £588 | -£61 | £111 |
| **Total cost** | **£2,276** | **£2,027** | **£1,399** | **£249** | **£628** |
| **Life years** | **2.44** | **2.41** | **2.30** | **0.03** | **0.11** |
| **QALYs** | **1.84** | **1.82** | **1.73** | **0.02** | **0.09** |

NP = Natriuretic Peptide; Clinic = Clinical assessment; UC = Usual Care
* Discounting at 3.5% applied after one year

**Figure 7.1: Cost effectiveness results (CHF any cause; base case)**

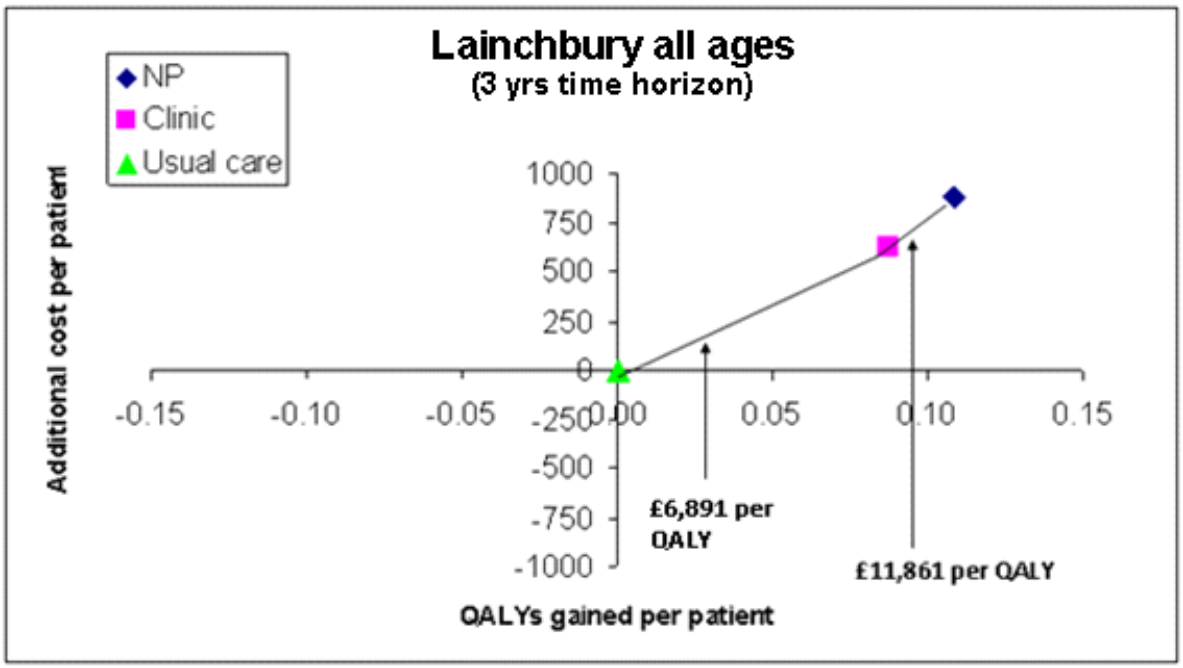
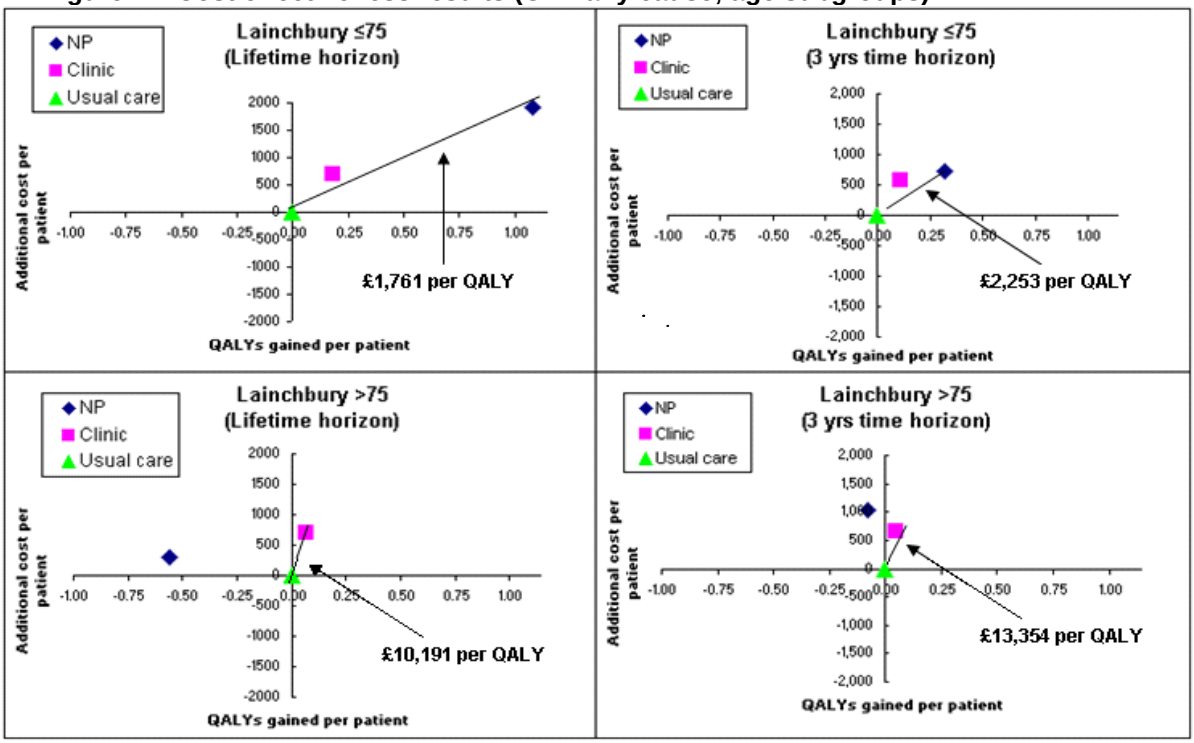


**Table 7.8: Cost effectiveness results (CHF any cause)**

| Time horizon | Compared interventions | Cost difference (Clinic-UC) (NP-Clinic) (NP-UC) | QALY difference (Clinic-UC) (NP-Clinic) (NP-UC) | INMB (20k/ QALY) | Probability NP/Clinic* being cost-effective | ICER | Sensitivity analysis - NP measurement £20 (ICER) |
|---|---|---|---|---|---|---|---|
| **Lainchbury all ages** | | | | | | | |
| 3 years | Clinic vs Usual care | £628 | 0.09 | £1,120 | 99.9% | £6,891 | £7,188 |
| 3 years | NP vs Clinic | £249 | 0.02 | £171 | 90.9% | £11,861 | £8,278 |
| **Lainchbury ≤75 years** | | | | | | | |
| Lifetime | NP vs Usual care | £1,905 | 1.08 | £19,734 | 97.9% | £1,761 | £1,692 |
| 3 years | NP vs Usual care | £720 | 0.32 | £5,671 | 100.0% | £2,253 | £2,018 |
| **Lainchbury >75 years** | | | | | | | |
| Lifetime | Clinic vs Usual care | £697 | 0.07 | £670 | 50.1% | £10,191 | N/A |
| 3 years | Clinic vs Usual care | £668 | 0.05 | £333 | 86.8% | £13,354 | N/A |

NP = Natriuretic Peptide; Clinic = Clinical assessment; UC = Usual Care; INMB = Incremental Net Monetary Benefit; ICER = Incremental Cost-Effectiveness Ratio
* Clinic for Clinic vs Usual care; NP for NP vs Clinic; NP for NP vs Usual care

**Figure 7.2 Cost effectiveness results (CHF any cause; age subgroups)**




We assessed the use of serial measurement of natriuretic peptide in secondary care for optimizing medical therapy in patients admitted to hospital because of chronic heart failure, compared to both clinical assessment in secondary care and usual care in the community:

- Clinical assessment was more costly than usual care
- Clinical assessment was more effective and cost-effective compared to usual care

- Natriuretic peptide monitoring was more costly than clinical assessment (with the exception of the analysis based on Jourdain[134] and the one based on Lainchbury[136] >75)
- Natriuretic peptide monitoring was more effective and cost-effective compared to clinical assessment (with the exception of the analysis based on Lainchbury[136] >75)
- Conclusions stayed consistent for age subgroups for patients with CHF and LVSD
- Clinical assessment was the preferred option in patients older than 75 years with CHF due to any cause
- Results were robust to sensitivity analyses

At the end of the Lainchbury trial[136], the same number of patients was alive in the three compared cohorts. In the base-case cost-effectiveness analysis based on Lainchbury[136] (patient with CHF due to any cause), the natriuretic peptide option being cost-effective relates to the calculation of life years using survival curves, which is more precise than using end-of-trial risk ratios. However, where we used survival curves to calculate life years, sampling error was not accounted for and uncertainty was underestimated. Nevertheless, for the analysis of patients with CHF and LVSD, which did not use this approach, the probability that natriuretic peptide monitoring is cost-effective was still convincingly high (98.3%).

Additional outpatient visits for up titrating medical therapy were reported by Troughton[132] only and were applied to all cost-effectiveness analyses for natriuretic peptide and clinical assessment cohorts. Troughton[132] was conducted before beta blockers were commonly used in heart failure and this may mean that we have under-estimated the additional outpatient visits associated with natriuretic peptide monitoring and therefore under-estimated the cost-effectiveness ratio.

In cost-effectiveness assessments of Lainchbury's age subgroups, using lifetime or three-year time horizons did not change conclusions. However, when comparing clinical assessment and usual care in patients older than 75 years, the probability of clinical assessment being cost-effective compared to usual care was 50% on a lifetime horizon and 87% on a three-year time horizon. As the same number of patients were alive at the end of Lainchbury trial[136] (3 years) in usual care and clinical assessment cohorts (in patients older than 75 years), the three-year time horizon results with the probability of cost-effectiveness of 87% are more relevant.

Results from cost-effectiveness assessments conducted on patients 75 years and older differed using outcomes from Lainchbury[136] (>75) or from Pfisterer[135] (≥75). The natriuretic peptide intervention improved survival in Pfisterer[135] and decreased it in Lainchbury[136] (compared to clinical assessment). It might be because patients with heart failure and preserved ejection fraction (HFPEF) were included in Lainchbury[136] and excluded in Pfisterer[135]. This possible explanation is based on the fact that pharmacological therapy in CHF were not shown to be as effective in HFPEF as they were in CHF with LVSD. The GDG also postulated that interventions in older CHF patients driven by raised natriuretic peptide could increase the risk of renal impairment, thus adding to the potential risk of the NP-guided strategy in this age group.

Results presented are related to this population of patients, and may not be applied to patients excluded from clinical trials on which we based our cost-effectiveness analysis. The use of natriuretic peptide intervention in general practice was not assessed in clinical trials and no conclusion regarding their use for monitoring in prmary care could be drawn. Considering the influence of the outpatient visit cost in the Lainchbury cost-effectiveness analyses, it might be advantageous to implement serial measurement of natriuretic peptide concentration for optimizing CHF medical therapy in general practice. Additional research is needed.

### 7.1.6 From evidence to recommendations

***Relative value placed on the outcomes considered***

The GDG reviewed the evidence of the use of serial measurements of the natriuretic peptides (NP) to monitor patients with heart failure and up-titrate or adjust their medical therapy; compared to standard clinical care.

Although one of five trials reviewed by the GDG was designed to uptitrate beta-blockers with NP guidance, the remaining trials had the majority of the patients on all the appropriate medication, with adjustment of the doses according to the NP level. The most commonly adjusted medication was diuretics.

The BATTLESCARRED trial [136] looked specifically at the difference between NP-guided therapy and usual care. In these circumstances the NP-guided therapy resulted in a significant reduction of all cause mortality at 1 year, but had no impact on 3 year mortality, or heart failure hospitalisation at 1 year and 3 years. .

The GDG noted the subgroup analysis that suggested less effect of the NP-guided therapy protocol in the elderly population (76 years and over). The patients in this subgroup are more likely to have heart failure with preserved left ventricular ejection fraction and this may have diluted any potential impact of NP-guided therapy since much pharmacological management for HFPEF remains of uncertain benefit. It was further speculated that increased use of diuretic therapy in the elderly population with associated adverse effects may have contributed to the lack of effect in this sub-group.

BATTLESCARRED [136] also provided the comparison with of BNP monitoring (and clinical monitoring) with usual care (where there is no clinical or NP parameter to trigger adjustment of therapy). Compared to usual care, NP-guided medical therapy was associated with a significant reduction in 1 year mortality for all ages, and with a significant reduction in 3 year mortality in patients 75 years or less. This was interpreted more as evidence that usual care in general practice can be sub-optimal rather than a justification for use of natriuretic peptide monitoring.

Another trial that was published after the formal review by the GDG (Berger et al. JACC 2010) showed that adding natriuretic peptide monitoring to multi-disciplinary intensive management by the specialist team was associated with reduced length of re-hospitalisation. Life expectancy was similar in those who were NP monitored and those who were intensively managed. NP monitoring was associated with higher use of pharmacotherapy.

***Quality of evidence***

The evidence of the comparison between strategies from the five RCTs was of moderate quality for the majority of outcomes.

The effects on mortality were only seen when NP-guided therapy was compared to a restricted form of ‘usual care’. The latter implied no formal monitoring was being made unless the patient deteriorated, which is sub-optimal care. This by itself does not justify the use of natriuretic peptide for monitoring, as mortality outcomes where NP-guided medical therapy were compared to clinically-guided medical therapy were less dramatic (and not statistically significant).

***Trade-off between clinical benefits and harms***

The trials reviewed showed no evidence of excess mortality or serious adverse events from the adoption of the natriuretic peptide-guided medical therapy.

Medication adjustment tended to occur more frequently in patients monitored by natriuretic peptide compared to the standard clinical strategies.

The strategy of NP-guided medical therapy was associated with some more favourable outcomes: significant reduction of heart failure hospitalisation rate at 18 months, compared

to clinically guided care, significant reduction of 1 year mortality in the BATTLESCARRED trial, in comparison with usual care, and significant reduction of 3 year mortality in those 75 years or less in the BATTLESCARRED trial, compared to usual care.

Part of the rationale for NP monitoring is the association of raised natriuretic peptide levels with poor prognosis.Kubanek ( 2009),Logeart (2004), Bettencourt (2004) and Bayes-Genis (2005) [40,142-144]

The GDG noted that RCT evidence that lowering natriuretic peptides would improve prognosis was lacking (since change in natriuretic peptide levels were (not surprisingly) not available in the control groups of the trials that the GDG considered.

The GDG noted that the impact of natriuretic peptide-guided medical therapy on the outcome was derived from intensifying medical therapy, and possibly avoiding admissions by intervening early at times of clinical deterioration associated with rising level of natriuretic peptides. Thus, it was not clear whether there were any distinct advantage to using NP-guided monitoring over other formal approaches to monitoring. Nevertheless, it was recognised that the use of natriuretic peptides to monitor the course of the patient with heart failure could be helpful in those in whom optimal uptitration had not been achieved.

The GDG considered that the use of measurement of natriuretic peptide levels as an early warning system ought to be considered as a research topic.

***Trade-off between net health benefits and resource use***

The economic analysis developed from a UK perspective for this Guideline found that the optimization of drug therapy in chronic heart failure using serial measurement in secondary care of natriuretic peptide concentration is cost-effective compared to clinical assessment in secondary care and to usual care in the community. The preferred option for patients older than 75 years might be clinical assessment in secondary care. The GDG accepted the conclusions of the economic analysis and agreed natriuretic peptide monitoring be available for specialist use in secondary care in selected patients. The GDG accepted that after a patient was admitted to hospital because of heart failure, the optimisation of heart failure medication with clinical assessment in secondary care is more cost-effective than usual care in general practice.

### *7.1.7 Recommendations*

- When a patient is admitted to hospital because of heart failure, seek advice on their management plan from a specialist in heart failure. **[new 2010]**
- Consider specialist monitoring of serum natriuretic peptides in some patients (for example, those in whom uptitration is problematic or those who have been admitted to hospital). **[new 2010]**.

## 7.2 Patient self-monitoring and remote monitoring

**What is the efficacy and safety of patient (self-monitoring) tele-monitoring in comparison to outpatient monitoring for adults with chronic heart failure?**

### *7.2.1 Clinical Introduction*

Heart failure patients have a high re-hospitalisation rate. Their treatment requires frequent review and adjustment to correct any congestion or weight gain that may herald clinical deterioration and hospitalisation. Some heart failure patients, with appropriate education, can monitor their own volume status by regular weighing and adjusting their diuretic therapy accordingly. This requires easy access to the heart failure team.

**Reason for review**

In the 2003 guideline, complex remote monitoring systems were mentioned, but experience at that time was limited. Tele-monitoring was in its infancy and it was not possible to make a clear recommendation. Since the 2003 guidelines evidence has been published on the use of tele-monitoring of patients with heart failure.

## *7.2.2 Clinical methodological introduction*

**What is the efficacy and safety of patient (self monitoring) telemonitoring in comparison to outpatient monitoring for adults with chronic heart failure?**

**Population:** all chronic heart, failure

**Intervention:** telemonitoring for:

- blood pressure
- weight
- swelling

**Comparison**: Outpatient monitoring

Low quality and non-randomised trials were excluded from the review. One prospective cohort study on older adults was included. One trial was excluded due to a significant interaction between the primary outcome and country of origin [145].

### a) All chronic heart failure

Eight RCTs on telemonitoring patients with chronic heart failure were reviewed [146; 147; 148; 149; 150; 151; 152]. Data were reported for the following outcomes:

- all cause mortality follow-up 8 to 12 months
- all cause mortality 450 days
- all cause hospitalisation (no. of patients) follow-up 3 to 12 months
- all cause hospitalisation (no. of patients) follow-up 450 days
- all cause hospitalisation (no of events) follow-up 90 to 120 days
- heart failure hospitalisation (no of patients) follow-up 6 to 12 months
- heart failure hospitalisation (no. of patients) follow-up 450 days
- quality of life (Minnesota Living with Heart Failure) follow-up 90 days

Table 7.9 below summarises the comparison and intervention for each study.

**Table 7.9: Study comparisons and interventions**

| Study | Comparison | Intervention |
|---|---|---|
| ANTONICELLI 2008 | Usual care<br>N=29<br>Standard care based on routinely scheduled clinic visits performed by a team specialised in CHF management. CHF outpatient clinic appointments were every four months with additional visits when required i.e. due to changes in condition | Telemonitoring<br>N=28<br>Managed by the same team as for comparison. Contacted by phone at least once a week to collect information on symptoms and adherence to prescribed treatment as well as blood pressure, heart rate, body weight and 24 hr urine output the previous day. A weekly ECG transmission was also required |
| CLELAND 2005 | Usual care<br>N=85<br>Individualised written management | Home telemonitoring<br>N=168<br>Usual care plus telephoned each month by |

| Study | Comparison | Intervention |
|---|---|---|
| | plan describing medication regimen sent to primary care physician. Patients assessed at research clinic every four months | a nurse specialist to assess symptoms and medication. The nurse could also be contacted by the patient. Plus the use of telemonitoring of weight, blood pressure and single lead ECG. Values outside of preset limits were automatically sent to the nurse |
| DANSKY 2008 | Usual care<br>N=110<br>Routine home visits. No further details provided, | Telemonitoring<br>N=126<br>Included education on HF and when to notify home care nurse or personal physician<br>One-way monitoring – patient took their own measurements which were then transmitted. This occurred typically once every day at predetermined time. |
| DAR 2009 | Usual care<br>N=91<br>This was provided by at least one cardiologist or a physician with a special interest in HF, and one specialist nurse. Regular clinical review and telephone support. Frequency of follow-up was at the discretion of the heart failure team | Home telemonitoring<br>N=91<br>Usual care plus telemonitoring including weighing scales, blood pressure, pulse oximeter and symptoms. Data outside of pre-determined triggered a phone call from the nurse |
| GIORDANO 2009 | Usual care<br>N=230<br>Referred to primary care physician. Structured follow-up with cardiologist at 12 months and an appointment with a primary care physician within 2 weeks from discharge.<br>Education on heart failure including advice on daily weights, daily self-management of blood pressure, dietary restrictions and signs and symptoms | Home-based tele-management (HBT)<br>N=230<br>This included two different procedures:<br>1) Telemonitoring Scheduled appointments every week or every 15 days for NYHA III-IV or II, respectively. Nurse performed a standardised interview. Patients questioned about the self-management of weight and blood pressure. Asked about drug regimen. ECG trace sent via portable device.<br>2) Tele-assistance: Occasional appointments were done when the patient, in the presence of symptoms or possible signs of decompensation were present.<br>Education as for comparison |
| SCHWARZ 2008 | Usual care N=51<br>No details provided | Telemonitoring N=51<br>Weight and symptoms monitored. Values outside range triggered call from nurse |
| WAKEFIELD 2008 | Usual care<br>N=49<br>No special discharge instructions. Follow-up appointments were scheduled in the usual manner. Patients contacted their primary care nurse case manager by telephone if needed. | Telemonitoring<br>N=47<br>Patients contacted three times during first week of discharge and then weekly for 11 weeks. Patients were given a symptom checklist and recorded daily weight, blood pressure and ankle circumference. The nurses also advised on diet and medication compliance<br>Telephone or videophone used for contact |

## b) **Women and non-Caucasian males**

One study specifically selected patients who were women or non-Caucasian males (primarily African Americans and Hispanics) with chronic heart failure [153].

Table 7.10 below summarises the comparison and intervention for this study

**Table 7.10: Comaprison and intervention for Soran study**

| Study | Comparison | Intervention |
|---|---|---|
| SORAN 2008 | Usual care<br>N=155<br>Included 1 to 1 education, availability of physician for education, an effort to use evidence-based optimal medical treatment and a commercially available digital home scale. Patients were instructed to weigh themselves daily and record symptoms | Telemonitoring<br>N=160<br>Usual care plus<br>Home-based disease management program to monitor and to detect early signs and symptoms of HF using telecommunication equipment. System included electronic scales and individual symptom response system linked to a database staffed by nurses. Data (weight and symptoms) was transmitted once daily |

### *7.2.3 Clinical evidence statements*

Telemonitoring compared with standard care in all chronic heart failure

Compared to standard care, telemonitoring resulted in a significant reduction of:

- all cause mortality follow-up 450 days [moderate quality]
- all cause hospitalisation (no. of patients) follow-up 8 to 12 months [low quality].

There was significant heterogeneity ($I^2$=76% and chi-square p=0.0008).

There was no significant difference between telemonitoring and standard care for the outcomes:

- all cause mortality follow-up 8 to 12 months [low quality]
- all cause hospitalisation follow-up 450 days [high quality] ($I^2$=73% and chi-square p=0.02).
- all cause hospitalisation (no. of events) follow-up 90 to 120 days [moderate quality]
- heart failure hospitalisation (no. of patients) follow-up 6 to 12 months [low quality]
- heart failure hospitalisation (no of patients) follow-up 450 days [moderate quality]
- quality of life (Minnesota Living with Heart Failure) follow-up 90 days [moderate quality]

Heterogeneity

For the two outcomes were heterogeneity was present in the meta-analysis the results are reported for each study separately in the GRADE table.

The evidence profile below summarises the quality of evidence and outcome data for the nine RCTs comparing telemonitoring with standard care in patients with chronic heart failure.

## Evidence profile: Telemonitoring vs standard care in patients with chronic heart failure

**Question:** Should telemonitoring vs standard care be used for chronic heart failure?
**Bibliography:**Antonicelli R, Testarmata P, Spazzafumo L et al. Impact of telemonitoring at home on the management of elderly patients with congestive heart failure. *Journal of Telemedicine & Telecare.* 2008; 14(6):300-305. Ref ID: 4531; Cleland JG, Louis AA, Rigby AS et al. Noninvasive home telemonitoring for patients with heart failure at high risk of recurrent admission and death: the Trans-European Network-Home-Care Management System (TEN-HMS) study. *Journal of the American College of Cardiology.* 2005; 45(10):1654-1664. Ref ID: 155; Dansky KH, Vasey J, Bowles K. Impact of telehealth on clinical outcomes in patients with heart failure. *Clinical Nursing Research.* 2008; 17(3):182-199. Ref ID: 4532; Dar O, Riley J, Chapman C et al. A randomized trial of home telemonitoring in a typical elderly heart failure population in North West London: results of the Home-HF study. *European Journal of Heart Failure.* 2009; 11(3):319-325. Ref ID: 4526; Giordano A, Scalvini S, Zanelli E et al. Multicenter randomised trial on home-based telemanagement to prevent hospital readmission of patients with chronic heart failure. *International Journal of Cardiology.* 2009; 131(2):192-199. Ref ID: 328; Schwarz KA, Mion LC, Hudock D et al. Telemonitoring of heart failure patients and their caregivers: a pilot randomized controlled trial. *Progress in Cardiovascular Nursing.* 2008; 23(1):18-26. Ref ID: 49; Wakefield BJ, Ward MM, Holman JE et al. Evaluation of home telehealth following hospitalization for heart failure: a randomized trial. *Telemedicine Journal & E-Health.* 2008; 14(8):753-761. Ref ID: 4530

| Quality assessment | | | | | | | Summary of findings | | | | | Hazard ratio |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality | |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | tele-monitoring | standard care | Relative (95% CI) | Absolute | | |
| **All cause mortality (follow-up 8 to 12 months)** | | | | | | | | | | | | |
| 5<br>Antonicelli<br>Cleland<br>Dansky<br>Giordano<br>Wakefield | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 72/515 (14%) | 14%<br>24% | RR 0.75 (0.56 to 1.01) | 35 fewer per 1000 (from 62 fewer to 1 more)<br>60 fewer per 1000 (from 106 fewer to 2 more) | ⊕⊕OO LOW | 0.91 (0.66 to 1.25) |
| **All cause mortality, 450 days (follow-up 450 days)** | | | | | | | | | | | | |
| 1<br>Cleland | randomised trials | no serious limitations | no serious inconsistency | no serious indirectness | serious[2] | none | 36/106 (34%) | 28/55 (50.9%) | RR 0.67 (0.46 to 0.97) | 168 fewer per 1000 (from 15 fewer to 275 fewer) | ⊕⊕⊕O MODERATE | |
| **Heart failure hospitalisation (no. of patients) DAR (follow-up 180 days)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious limitations | no serious inconsistency | no serious indirectness | serious[3] | none | 17/91 (18.7%) | 10/91 (11%) | RR 1.70 (0.82 to 3.51) | 77 more per 1000 (from 20 fewer to 276 more) | ⊕⊕⊕O MODERATE | 0.56 (0.34 to 0.94) |
| **Heart failure hospitalisation (no. of patients) CLELAND (follow-up 240 days)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | serious[4] | no serious inconsistency | no serious indirectness | serious[2] | none | 40/163 (24.5%) | 24/85 (28.2%) | RR 0.87 (0.56 to 1.34) | 37 fewer per 1000 (from 124 fewer to 96 more) | ⊕⊕OO LOW | |
| **Heart failure hospitalisation (no. of patients) GIORDANO (follow-up 12 months)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[4] | no serious inconsistency | no serious indirectness | serious[3] | none | 43/230 (18.7%) | 73/230 (31.7%) | RR 0.59 (0.42 to 0.82) | 130 fewer per 1000 (from 57 fewer to 184 fewer) | ⊕⊕OO LOW | |
| **Heart failure hospitalisation (no. of patients), 450 days (follow-up 450 days)** | | | | | | | | | | | | |
| 1 Cleland | randomised trials | no serious limitations | no serious inconsistency | no serious indirectness | serious[2] | none | 38/106 (35.8%) | 23/55 (41.8%) | RR 0.86 (0.57 to 1.28) | 59 fewer per 1000 (from 180 fewer to 117 more) | ⊕⊕⊕O MODERATE | |
| **All cause hospitalisation (no. of patient) ANTONICELLI (follow-up 12 months)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[4] | no serious inconsistency | no serious indirectness | serious[3] | none | 9/28 (32.1%) | 26/29 (89.7%) | RR 0.36 (0.21 to 0.62) | 574 fewer per 1000 (from 341 fewer to 708 fewer) | ⊕⊕OO LOW | |
| **All cause hospitalistion (no. of patients) CLELAND (follow-up 240 days; 2)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[4] | no serious inconsistency | no serious indirectness | serious[3] | none | 80/163 (49.1%) | 46/85 (54.1%) | RR 0.91 (0.71 to 1.17) | 49 fewer per 1000 (from 157 fewer to 92 more) | ⊕⊕OO LOW | |
| **All cause hospitalisation (no. of patients) DAR (follow-up 180 days)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious limitations | no serious inconsistency | no serious indirectness | very serious[5] | none | 33/91 (36.3%) | 23/91 (25.3%) | RR 1.43 (0.92 to 2.24) | 109 more per 1000 (from 20 fewer to 314 fewer) | ⊕⊕OO LOW | |
| **All cause hospitalisation (no. of patients) GIODANO (follow-up 12 months)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[4] | no serious inconsistency | no serious indirectness | serious[3] | none | 67/230 (29.1%) | 96/230 (41.7%) | RR 0.80 (0.69 to 0.94) | 83 fewer per 1000 (from 25 fewer to 129 fewer) | ⊕⊕OO LOW | |
| **All cause hospitalisation (no. of patients) SCHWARZ (follow-up 90 days)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious limitations | no serious inconsistency | no serious indirectness | very serious[5] | none | 12/44 (27.3%) | 13/40 (32.5%) | RR 0.84 (0.43 to 1.62) | 52 fewer per 1000 (from 185 fewer to 201 more) | ⊕⊕OO LOW | |
| **All cause hospitalisation (no. of patients) (follow-up 450 days)** | | | | | | | | | | | | |
| 1 | randomised | no serious | no serious | no serious | no serious | none | 75/106 | 40/55 | RR 0.97 (0.79 to | 22 fewer per 1000 (from 153 fewer to 138 | ⊕⊕⊕⊕ | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cleland | trials | limitations | inconsistency | indirectness | imprecision | | (70.8%) | (72.7%) | 1.19) | more) | HIGH | |
| **all cause hospitalisation (no. of events) (follow-up 90-120 days; Better indicated by lower values)** | | | | | | | | | | | | |
| 2<br>Dansky<br>Schwarz | randomised trials | no serious limitations | no serious inconsistency | no serious indirectness | no serious imprecision | none | 170 | 150 | - | MD -0.04 lower (-0.21 lower to 0.13 higher) | ⊕⊕⊕⊕ HIGH | |
| **Quality of life (follow-up 90 days; measured with: MLHF; range of scores: 0-105; Better indicated by lower values)** | | | | | | | | | | | | |
| 2<br>Schwarz<br>Wakefield | randomised trials | no serious limitations | no serious inconsistency | no serious indirectness | serious[6] | none | 91 | 89 | - | MD -3.98 lower (-10.87 lower to 2.9 higher) | ⊕⊕⊕O MODERATE | |

[1] 3/5 unclear allocation concealment (>50% total sample size); 5/5 unclear or no blinding (refers to outcome assessment)
[2] < 300 events and 95% confidence interval around the pooled estimate of effect includes both negligible effect and appreciable benefit or appreciable harm.
[3] 95% confidence interval around the pooled effect includes both negligible effect and appreciable benefit or appreciable harm.
[4] unclear allocation concealment and outcome assessment
[5] 95% confidence interval covers 'appreciable benefit' to 'very appreciable harm'
[6] The minimally important difference is 5 points

## Women and non-Caucasian males

There were no significant differences between patients receiving telemonitoring and standard care for:

- All cause mortality (follow-up mean 6 months) [low quality]
- All cause hospitalisation (follow-up mean 6 months) [low quality]

The evidence profile below summarises the quality of evidence and outcome data for the RCT comparing telemonitoring with standard care in women, older adults and non-Caucasian males with chronic heart failure.

### Evidence profile: Telemonitoring vs standard care in women, older adults and non-Caucasian males with chronic heart failure

**Question:** Should telemonitoring vs standard care be used for women and ethnic minorities with CHF?
**Bibliography:** Soran OZ, Pina IL, Lamas GA et al. A Randomized Clinical Trial of the Clinical Effects of Enhanced Heart Failure Monitoring Using a Computer-Based Telephonic Monitoring System in Older Minorities and Women. *J Card Fail.* 2008; 14(9):711-717. Ref ID: 453

| Quality assessment | | | | | | | Summary of findings | | | | | Hazard ratio |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No of patients | | Effect | | Quality | |
| No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | telemonitoring | standard care | Relative (95% CI) | Absolute | | |
| **all cause mortality (follow-up mean 6 months)** | | | | | | | | | | | | |
| 1 Soran 2008 | randomised trial | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 11/160 (6.9%) | 17/155 (11%) | RR 0.63 (0.30 to 1.29) | 41 fewer per 1000 (from 77 fewer to 32 more) | □□□□ LOW | 0.62 (0.30 to 1.31) |
| **all cause hospitalisation (follow-up mean 6 months)** | | | | | | | | | | | | |
| 1 Soran 2008 | randomised trial | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 68/160 (42.5%) | 73/155 (47.1%)<br>0% | RR 0.90 (0.71 to 1.15) | 47 fewer per 1000 (from 137 fewer to 71 more)<br>0 fewer per 1,000 | □□□□ LOW | |

[1] unclear method of allocation concealment; unclear blinding; drop-out rate reported and less than 20%; ITT analysis
[2] < 300 events and 95% confidence interval around the best estimate of effect includes both negligible effect and appreciable benefit or appreciable harm

## 7.2.4 Health economics methodological introduction

From the 2003 Guideline[22], no relevant economic evidence relating to tele-monitoring and self-monitoring was identified. From our review, two economic evaluations assessing tele-monitoring and self-monitoring in patients with chronic heart failure were identified. One was a cost analysis developed from a UK perspective. The other was a cost-consequence analysis developed from an Italian perspective, a country which we believe has a healthcare system reasonably comparable to the UK NHS.

***UK analysis***

Dar et al. (2009)[149] presented a cost-consequences analysis using data collected during the HOME-HF study. The HOME-HF study assessed the addition to usual care of home telemonitoring in patients with chronic heart failure. This study was conducted in three acute hospitals in West London. The follow-up period of the HOME-HF study was 6 months. The usual care group (n=91) was managed by a heart failure team providing regular clinical review and telephone support. In addition to usual care, patients in the intervention group (n=91) had self-monitoring equipments installed at home to monitor symptoms and signs indicative of worsening heart failure (electronic weighing scale, automated blood pressure cuff, and pulse oximeter). Patients assessed themselves every day and data were encrypted and transmitted via phone line to the hospital.Table 7.11 presents the quality and applicability assessment of this economic analysis.

***Italian analysis***

Scalvini et al. (2005)[154] developed a cost-consequence analysis based on a prospective cohort study. An Italian perspective was taken and the analysis was developed for a 1-year time horizon. The population considered was patients with stable chronic heart failure (n=426) with a mean age of 59 years (SD=9). Usual care (n=196) was compared to home-based telecardiology (n=230). Home-based telecardiology consisted of interactive teleconsultations with a nurse and ECG monitoring (an ECG portable device was given to patients, transferring data by phone). When necessary, tele-assistance and home visits by the paramedical and the medical team were available. The costs included were the cost of the home-based telecardiology (equipment, rental, personnel, and overhead) and hospitalisation cost. No sensitivity analysis was undertaken. Table 7.11 presents the quality and applicability assessment of this economic analysis.

**Table 7.11: Economic study assessment**

| Study | Study quality* | Study applicability** |
|---|---|---|
| Dar 2009[149] | Minor limitations (a) | Directly applicable |
| Scalvini 2005[154] | Very serious limitations (b) | Partially applicable (c) |

*Very serious limitations / Potentially serious limitations / Minor limitations; ** Directly applicable / Partially applicable / Not applicable

(a) Not a full cost-effectiveness analysis. However the cost and health outcomes presented are sufficient as one option clearly dominates the other

(b) Small cohort size. Outcomes were not measured as QALYs. The analysis did not include all relevant resource use components; No sensitivity analysis was conducted

(c) Analysis developed from the Italian perspective. Usual care intervention not described

## 7.2.5 Health economics evidence statements

***UK analysis***

Results of the HOME-HF study (Dar 2009)[149] are presented in Table 7.12. The cost analysis comparing home telemonitoring to usual care concluded that home telemonitoring is more costly than usual care. This was mainly due to additional costs related to the telemonitoring

intervention and to more hospital admissions in the telemonitoring cohort. The survival outcome from this study (reported as 'days alive and out of hospital') does not differ between cohorts. Finally, quality of life outcomes were not reported, but the author stated no difference between cohorts in the change in quality of life throughout the follow-up period using both the EuroQoL questionnaire and the Minnesota Living with Heart Failure questionnaire.

Looking at outcomes from the UK-based HOME-HF study, considering no difference between cohorts in mortality and quality of life and a higher cost related to the telemonitoring option compared to usual care, the telemonitoring option is not likely to be cost-effective.

**Table 7.12: Results – Dar 2009[149] economic analysis**

| | Usual care (n=91) | Home telemonitoring (n=91) | P-value |
|---|---|---|---|
| **Cost analysis** | | | |
| Mean direct NHS cost (SD) | £3,006 (£3,847) | £4,610 (£7,377) | Difference = £1,600 (p=0.2) |
| Median direct NHS cost (IQR) | £1,498 (£751-£4,053) | £1,688 (£878-£6,305) | |
| **Resource use estimates** | | | |
| All-cause hospitalization | | | |
| Patients hospitalized, n (%) | 23 (25) | 33 (36) | |
| Number of hospitalisations | 39 | 44 | |
| Duration of hospitalisation, median (IQR) | 13 (8-34) | 17 (6-25) | 0.99 |
| Heart failure hospitalisation | | | |
| Patients hospitalised, n (%) | 10 (11) | 17 (19) | |
| Number of hospitalisations | 16 | 22 | |
| Duration of hospitalisation, median (IQR) | 9 (7-33) | 17 (8-25) | 0.62 |
| Proportion of emergency heart failure hospitalization, n (%) | 13/16 (81) | 8/22 (36) | 0.01 |
| Number of secondary care outpatient visits | 733 | 622 | |
| Emergency room visits | 32 | 20 | |
| Primary care visits | 403 | 421 | |
| **Health outcomes** | | | |
| Days alive and out of hospital, median (IQR) | 180 (165-180) | 178 (90-180) | 0.3 |
| Quality of life change | | | |
| Euro-QoL | No significant difference between groups (not reported) | No significant difference between groups (not reported) | 0.5 |
| MLwHF* | No significant difference between groups (not reported) | No significant difference between groups (not reported) | 0.6 |

* Minnesota Living with Heart Failure questionnaire

***Italian analysis***

Cost and clinical outcomes from the Scalvini et al. (2005) analysis[154] are presented in Table 7.13. These results suggested that home-based telecardiology is more effective and less costly than usual care. The analysis presents potentially important limitations as it did not consider the effect of interventions on the use of some components of the resource use (drug treatment, outpatient visits, emergency visits). In addition, the analysis did not undertake a sensitivity analysis, was developed for a short time horizon (1 year), did not

integrate a quality of life measure, and considered a young population of patients (mean of 59 years) which restrict the generalisation of the results.

**Table 7.13: Results - Scalvini 2005 economic analysis***

| | Usual care (n=179) | Home-based telecardiology (n=230) | Relative risk (95% CI) |
|---|---|---|---|
| **One-year cost outcomes** | | | |
| Hospitalisation cost | £103,410 | £70,241 | N/A |
| Telecare service cost | N/A | £8666 | N/A |
| **Total cost** | **£103,410** | **£78,907** | N/A |
| **One-year clinical outcomes** | | | |
| Hospitalization, n (%) | 61 (34) | 56 (24) | 0.62 (0.43-0.81) |
| Patients with instability, n (%) | 74 (41) | 60 (26) | 0.50 (0.32-0.68) |
| Death, n (%) | 22 (12) | 6 (7) | 0.50 (0.20-0.80) |

* Costs were converted in pound sterling using Purchasing Power Parities[81]

## *7.2.6 From evidence to recommendations*

### *Relative value placed on the outcomes considered*

The GDG noted that the eight randomised controlled studies recruited patients with heart failure and randomised them to receive either standard care, where the patients are followed up routinely, or to the tele-monitoring arm that gave the specialist team access to data on the patients' vital parameters, including heart rate, blood pressure and body weight. Some also provided access to 24 hour urinary output. These parameters were accessed at variable set intervals. The detection of measurements beyond a pre-set level triggered a telephone call or a visit, if necessary, from the specialist heart failure team. Several studies were also designed to provide the patient with regular phone calls from the specialist team. Whilst the purpose of some of the calls may have been to gather the data, they also provided opportunities for the patients to access expert opinion, support and further educational encounters with the specialist team. The study by Cleland demonstrated the ability of some older patients to use the new technology and gain benefit. Some of the studies also provided the patient with easy access to the specialist heart failure team out-with the pre-defined calls initiated by the team.

Usual care generally comprised of regular outpatient appointments with a specialist in heart failure or cardiologist plus primary care visits.

The trials reviewed showed an improvement in all-cause mortality and all cause hospitalisation rates when tele-monitoring, with intensive reviews and contact with the specialist team, was compared to standard care [146, 147, 148, 149, 150, 145, 151, 152]. It was not clear as to the extent to which these effects were due to tele-monitoring per se or to the improvement in access to care by the patients assigned to tele-monitoring. Nevertheless, the studies demonstrated there is the potential for this technique to be used to extend specialist monitoring to a larger number of heart failure patients who currently have no access to such specialist care.

The trials found no evidence of harm from telemonitoring. In some studies there was an increase in the number of hospitalisations. These, however, were appropriate short admissions, probably due to early detection of deterioration.

### *Quality of evidence*

The only evidence of high quality was that of lack of difference in all cause hospitalisation.

The GDG noted that tele-monitoring was always associated with augmented opportunities for the patients to be contacted by the specialist heart failure team, and in some studies with further opportunities for the patients to contact the specialist team for advice and support.

This observation was central to several comments by some of the authors of the studies reviewed stating (as did the GDG) that it is not clear whether the differences in the outcomes were due to the application of tele-monitoring or due to the additional access to specialist opinion and care. The GDG believed that when the standard of care is high, allowing frequent contact between the patient and the specialist team, and the communication is good, the need for tele-monitoring is reduced.

***Trade-off between clinical benefits and harms***

Two questions were raised by GDG with regards to the way the adoption of tele-monitoring could impact on patients' care. These were:

- Whether tele-monitoring will result in more hospitalisations and more referrals to the cardiology services?
- Whether tele-monitoring will result in intensifying of medical therapy?

The GDG considered in particular two RCT's with regards to these questions:

The Giordano trial (2009) [150], which was the largest amongst the reviewed studies, found telemonitoring was associated with slightly more investigations. However, there were fewer interventions and referrals to the cardiologists in the home tele-monitoring arm, which was associated with less hospitalisation and lower costs at one year.

In the home tele-monitoring arm of the Cleland study (2005)[147] there was increased uptake of both the aldosterone antagonist spironolactone and beta-blockers. As with natriuretic peptide monitoring (see Section 7.1), the GDG was not convinced that telemonitoring per se was required to achieve this increased use of therapy.

Another role for remote monitoring relates to advanced pacing devices used in heart failure (usually within the cardiac re-synchronisation "CRT" devices). These send alarms when the patient develops increased congestion. The adoption of these devices into clinical practice will necessitate better communication between the pacing and the heart failure teams.

The GDG recommends further research into this topic.

***Trade-off between net health benefits and resource use***

The Italian study [154] was based on an observational cohort study and compared self-monitoring (ECG portable device) and telemonitoring (tele-consultations with a heart failure specialist nurse) to usual care. It was not clear if telephone support was offered to the usual care cohort. The study demonstrated that the intervention was more effective and less costly than usual care on a one-year time horizon. However, besides being partially applicable to the UK NHS, the study has important limitations. In addition to the short-time horizon, it did not consider possible important resource use and cost components that might be influenced by the intervention, and did not conduct a sensitivity analysis to test the conclusions.

The cost assessment presented by Dar (2009) [149] was conducted from a UK NHS perspective and for a 6-month time horizon. This study added self-monitoring with tele-consultations with a heart failure specialist nurse to usual care (including telephone support). The cost assessment concluded that telemonitoring is more costly than usual care. In addition, telemonitoring is not likely to be cost-effective according to reported health outcomes from the study. In this study, telephone support was offered to patients in both treatment arms and this might explain the similarity of the health outcomes between cohorts and lack of cost-effectiveness.

### *7.2.7 Recommendations*

Given the difficulties of interpretation of the evidence, the GDG did not make specific recommendations for home telemonitoring but agreed that a research recommendation should be made.

## 7.3 Recommendations for monitoring heart failure:

### Clinical Review

R62 All patients with chronic heart failure require monitoring. This monitoring should include:

- a clinical assessment of functional capacity, fluid status, cardiac rhythm (minimum of examining the pulse), cognitive status and nutritional status
- a review of medication, including need for changes and possible side effects
- serum urea, electrolytes, creatinine and eGFR[25]. **[2003, amended 2010] KPI**

R63 More detailed monitoring will be required if the patient has significant comorbidity or if their condition has deteriorated since the previous review. **[2003]**

R64 The frequency of monitoring should depend on the clinical status and stability of the patient. The monitoring interval should be short (days to 2 weeks) if the clinical condition or medication has changed, but is required at least 6-monthly for stable patients with proven heart failure. **[2003]**

R65 Patients who wish to be involved in monitoring of their condition should be provided with sufficient education and support from their healthcare professional to do this, with clear guidelines as to what to do in the event of deterioration. **[2003].**

R66 When a patient is admitted to hospital because of heart failure, seek advice on their management plan from a specialist in heart failure. **[new 2010].**

### Serum digoxin

R67 Routine monitoring of serum digoxin concentrations is not recommended. A digoxin concentration measured within 8-12 hours of the last dose may be useful to confirm a clinical impression of toxicity or non-adherence. **[2003]**

R68 The serum digoxin concentration should be interpreted in the clinical context as toxicity may occur even when the concentration is within the 'therapeutic range'. **[2003].**

### Serum natriuretic peptides

R69 Consider specialist monitoring of serum natriuretic peptides in some patients (for example, those in whom uptitration is problematic or those who have been admitted to hospital). **[new 2010].**

[25] This is a minimum. Patients with comorbidities or co-prescribed medications will require further monitoring. Monitoring serum potassium is particularly important if a patient is taking digoxin or an aldosterone antagonist.

# 8 Referral and approach to care

## 8.1 Introduction

This topic was not within the scope of the partial update (2010). For more information on the following aspects of care refer to Appendix M, the 2003 Guideline[22]:

- Referral (Chapter 12)
- Supporting patients and carers (Chapter13)
- Anxiety and depression (Chapter 14)
- End of Life (Chapter 15)
- Prevention (Chapter16)

## 8.2 Recommendations

### Referral for more specialist advice

Given the changes made to the diagnosis and therapeutic algorithms following the reviews undertaken of the relevant chapters and sections, some changes to the referrals to specialists have been made during the partial update of 2010.

R70 Refer patients to the specialist multidisciplinary heart failure team for:

- the initial diagnosis of heart failure and
- the management of:
  - severe heart failure (NYHA class IV)
  - heart failure that does not respond to treatment
  - heart failure that can no longer be managed effectively in the home setting. **[new 2010]**

### Discharge planning

R71 Patients with heart failure should generally be discharged from hospital only when their clinical condition is stable and the management plan is optimised. Timing of discharge should take into account patient and carer wishes, and the level of care and support that can be provided in the community. **[2003] KPI**

R72 The primary care team, patient and carer must be aware of the management plan. **[2003]**

R73 Clear instructions should be given as to how the patient/carer can access advice, particularly in the high-risk period immediately following discharge. **[2003]**

### Multidisciplinary team approach to heart failure management

R74 Heart failure care should be delivered by a multidisciplinary team with an integrated approach across the healthcare community. **[2003]**

### Non-NHS agencies

R75 Standard one of the 'National service framework for older people' states: 'social care services will not use age in their eligibility criteria or policies to restrict access to available services'. This applies to patients with heart failure. (See www.dh.gov.uk) **[2003]**

R76 Management plans for patients with heart failure should be discussed with non-NHS agencies where they are involved in or responsible for the care of a person with heart failure. **[2003]**

R77 The principles of pharmacological management for a patient cared for in a non-NHS institution should be similar to those for any other patient with heart failure. **[2003]**

R78 The education needs of non-NHS agency carers should be considered. **[2003]**

### Communication

For guidance on Medicines adherence refer to the NICE guideline:

- Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence. NICE clinical guideline 76 (2009). Available from www.nice.org.uk/guidance/CG76

R79 Good communication between healthcare professionals and patients and carers is essential for the best management of heart failure. **[2003]**

R80 Guidelines for good communication:

- Listen to patients and respect their views and beliefs
- Give patients the information they ask for or need about their condition, its treatment and prognosis, in a way they can understand including information about any serious side effects of drugs to be prescribed
- Provide the most important information first
- Explain how each item will affect patients personally
- Present information in separate categories
- Make advice specific, detailed and concrete
- Use words the patients will understand; confirm understanding by questions; define unfamiliar words; write down key words; draw diagrams and keep a copy in the medical notes
- Repeat the information using the same words each time
- Prepare material, written or taped, to back up handwritten notes
- Share information with patients' partners, close relatives or carers if they ask you to do so. When patients cannot indicate their consent for such sharing of information, it is advisable to share the information that those close to the patient need or want to know, except where you have reason to believe that the patient would object if able to do so.[**2003**]

R81 The content, style and timing of information provision should be tailored to the needs of the individual patient. **[2003]**

R82 Healthcare professionals should assess cognitive ability when sharing information. **[2003]**

R83 Carers and relatives of patients who are cognitively impaired should be made aware of treatment regimes for the patients they care for and be encouraged to identify any need for clinical support. **[2003]**

R84 Management of heart failure should be seen as a shared responsibility between patient and healthcare professional. **[2003]**

R85 Unless specifically excluded by the patient, carers and relatives should be involved in the management of the patient, particularly where the patient cannot look after him- or herself. **[2003]**

### Prognosis

R86 Prognosis should be discussed with patients and carers in a sensitive, open and honest manner. **[2003]**

### Support groups

R87 Healthcare professionals should be aware of local cardiac support networks and provide this information to patients and carers. **[2003]**

### Anxiety and depression

For guidance on managing depression refer to the NICE guidelines:

- Depression in adults with a chronic physical health problem: treatment and management. NICE clinical guideline 91 (2009). Available from www.nice.org.uk/guidance/CG91
- Depression: the treatment and management of depression in adults NICE clinical guideline 90 (2009). Available from: www.nice.org.uk/guidance/CG90

R88 The diagnosis of depression should be considered in all patients with heart failure. **[2003]**

R89 Where depression is likely to have been precipitated by heart failure symptoms then reassessment of psychological status should be undertaken once the physical condition has stabilised following treatment for heart failure. If the symptoms have improved no further specific treatment for depression is required. **[2003]**

R90 Where it is apparent that depression is co-existing with heart failure, then the patient should be treated for depression in line with 'Depression: the treatment and management of depression in adults', (NICE clinical guideline 90) and 'Depression in adults with a chronic health problem: treatment and management' (NICE clinical guideline 91.) **[2003]**

R91 For patients with heart failure, the potential risks and benefits of drug therapies for depression should be considered carefully. **[2003]**

R92 Patients with heart failure should consult a healthcare professional before using over-the-counter therapies for depression such as St John's wort (Hypericum perforatum). Healthcare professionals should be aware of the potential interaction with prescribed medication, and always ask about self-medication, including the use of herbal products. **[2003]**

### End of life

R93 Issues of sudden death and living with uncertainty are pertinent to all patients with heart failure. The opportunity to discuss these issues should be available at all stages of care. **[2003]**

R94 The palliative needs of patients and carers should be identified, assessed and managed at the earliest opportunity. **[2003]**

R95 Patients with heart failure and their carers should have access to professionals with palliative care skills within the heart failure team. **[2003]**

# 9 Research recommendations

Having reviewed the current evidence around several diagnostic and therapeutic questions, the Guideline Development Group identified areas where either there is no evidence at all, where the evidence present is inadequate to make a recommendation, or the evidence that exists is either applicable to only a small subsection of the community, or does not apply to certain subgroups. When obtaining further evidence is expected to bridge the gaps in our knowledge and potentially benefit significant sections of the population with heart failure then the GDG was able to recommend that particular topic to become a research recommendation. Such a position allows these topics to gain priority when being considered by the approving authorities and grant giving bodies.

The topics were identified during the evidence review. Subsequently the clinical questions were proposed formally into research recommendations, associated with a framework following the PICO model. For more information on the rationale for prioritising these topics please see Appendix K.

### Beta blockers and angiotensin-converting enzyme inhibitors for heart failure with preserved left ventricular ejection fraction

**Research recommendation/question:**

What is the effectiveness of angiotensin-converting enzyme (ACE) inhibitors and beta-blockers (given either alone or in combination) compared with placebo in patients with heart failure and preserved left ventricular ejection fraction?

| Population | Intervention | Comparison | Outcomes |
|---|---|---|---|
| Heart failure with preserved ejection fraction | Angiotensin converting enzyme and/or Beta- blocker | placebo | Mortality (all cause, heart failure)<br>Hospitalisation (heart failure, all cause)<br>Change in NYHA class<br>Quality of life<br>Adverse events |

**Why this is important:**

At least half of the people with heart failure in the community have preserved left ventricular ejection fraction. Research has focused on heart failure with left ventricular systolic dysfunction and found several agents to be beneficial (notably ACE inhibitors, beta-blockers and aldosterone antagonists). To date, studies of treatment in patients with preserved left ventricular ejection fraction have found no significant benefit. However there is limited evidence that suggests potential benefit of both beta-blockers and ACE inhibitors in this population. The equivocal evidence base for beta-blockers and ACE inhibitors needs to be explored in greater depth to establish whether there is definite benefit or not. This is particularly important because of the extent of heart failure with preserved left ventricular ejection fraction in the general population.

### Home telemonitoring, natriuretic peptide guided therapy and formal follow up by a heart failure team.

| **Research recommendation/question:** | | | |
|---|---|---|---|
| What is the effectiveness and cost effectiveness of home telemonitoring, monitoring of serum natriuretic peptides and formal follow-up by a heart failure team for patients with heart failure due to left ventricular systolic dysfunction? | | | |
| **Population** | **Intervention** | **Comparison** | **Outcomes** |
| Heart failure due to LVSD | Telemonitoring<br>Or BNP | Clinical care | Mortality (all cause, heart failure)<br>Hospitalisation (heart failure, all cause, planned, unplanned)<br>Change in NYHA class<br>Patient/carer acceptability<br>Quality of life<br>Adverse events |
| **Why this is important:** | | | |
| Heart failure is characterised by repeated hospitalisation. For people with systolic left ventricular dysfunction hospitalisation can be reduced by appropriate treatment and organised nursing care. Recent studies of ways to prevent hospitalisation have focused on telemonitoring (the patient's status is assessed in the patient's own home) and the use of serum natriuretic peptide levels (to guide uptitration of drugs) compared with "usual" care. The studies used various research methods and differing levels of “usual care”, which makes it difficult to compare the results. It has been suggested that, when care is delivered by an organised heart failure team under consultant supervision, then additional strategies such as telemonitoring and monitoring of serum natriuretic peptides may not confer advantage. Further research is important to ascertain whether monitoring and supervision techniques afford advantage over formal, organised care by a specialist multidisciplinary heart failure team. | | | |

### The role of natriuretlc peptides in the management and prognosis of heart failure.

| **Research recommendation/question:** | | | |
|---|---|---|---|
| What is the optimal use of natriuretic peptides in the management and prognostic stratification of patients with heart failure? | | | |
| **Population** | **Intervention** | **Comparison** | **Outcomes** |
| Heart failure | Natriuretic peptides | Clinical care | Mortality (all cause, heart failure)<br>Hospitalisation (heart failure, all cause, planned, unplanned)<br>Change in NYHA |

| | | | |
|---|---|---|---|
| | | | class<br>Quality of life |

**Why this is important**

Heart failure is characterised by repeated hospitalisation, high mortality in the period immediately following hospitalisation and an unpredictable course in the later stages. In people with heart failure natriuretic peptide levels have been shown to correlate with poor prognosis. Studies of the use of natriuretic peptides to guide drug titration have suggested a potential reduction in mortality in some groups, although the overall utility of this remains uncertain in the broader population with heart failure. Research is needed in three areas:

- Whether elevated natriuretic peptides despite maximum tolerated therapy could be used to predict prognosis and to guide an 'end-of-life' strategy for late-stage heart failure.
- Whether the level of natriuretic peptides at the time of discharge could be used to prioritise routine follow-up after discharge.
- Whether routine monitoring of natriuretic peptides in people with heart failure in the community might allow optimal use of community nursing resources.

## Aldosterone antagonists and angiotensin II receptor antagonists in heart failure

**Research recommendation/question:**

What is the comparative effectiveness of aldosterone antagonists and angiotensin II receptor antagonists (ARBs) in symptomatic patients with heart failure due to left ventricular systolic dysfunction who are:

A. on optimal therapy with a beta-blocker and an ACE Inhibitor, or

B. on a beta-blocker but are intolerant of ACE inhibitors?

| Population | Intervention | Comparison | Outcomes |
|---|---|---|---|
| Heart failure with LVSD who are symptomatic and:<br>A. on optimal therapy with BB and ACEI?<br>B. are intolerant to ACE inhibitor? | Spironolactone | Angiotensin receptor blocker | Mortality (all cause, heart failure)<br>Hospitalisation (heart failure, all cause)<br>Change in NYHA class<br>Quality of life<br>Adverse events |

**Why this is important:**

Inhibition of the renin-angiotensin-aldosterone system with an ACE inhibitor in combination with a beta-blocker is currently the cornerstone of the management of heart failure with left ventricular systolic dysfunction.

The first question is which antagonist of the renin-angiotensin-aldosterone system should be added if the patient remains symptomatic despite being on optimal therapy with a beta-blocker and an ACE inhibitor?

In trials, both aldosterone antagonists and ARBs have been used in addition to ACE inhibitors for patients with heart failure who remained symptomatic. However, there are no

trials comparing the effectiveness and safety of adding aldosterone antagonists or ARBs to otherwise optimal therapy.

The second question concerns the comparative effectiveness of aldosterone antagonists and ARBs in patients (at least 10%) who are intolerant of ACE inhibitors. An ARB may be less effective than an ACE inhibitor. Aldosterone antagonists have been shown to be beneficial in patients with heart failure due to left ventricular systolic dysfunction but most were taking an ACE inhibitor. It is important to know which is the most effective method for inhibition of the renin-angiotensin-aldosterone system when ACE inhibitors are not tolerated: an aldosterone antagonist in combination with a beta-blocker or an ARB in combination with a beta-blocker..

## Hydralazine in combination with nitrates for heart failure with preserved left ventricular ejection fraction

**Research recommendation/question:**

What is the comparative effectiveness of vasodilator therapy with nitrates and hydralazine in patients with heart failure and preserved ventricular ejection fraction?

| Population | Intervention | Comparison | Outcomes |
|---|---|---|---|
| Heart failure with preserved ventricular ejection fraction | Nitrate and hydralazine | Placebo | Mortality (all cause, heart failure)<br>Hospitalisation (heart failure, all cause)<br>Change in NYHA class<br>Quality of life<br>Adverse events |

**Why this is important:**

More than half of people with heart failure in the community have preserved left ventricular ejection fraction. To date, studies have not shown that ARBs, ACE inhibitors or beta-blockers afford significant prognostic benefit for this population. In patients with heart failure due to left ventricular systolic dysfunction, studies have indicated that the combination of nitrate and hydralazine improves prognosis.

The pathophysiology of heart failure with preserved left ventricular ejection fraction is not clearly understood. However, hypertension is common among these patients, arterial compliance may play a major part and increased preload is a potential problem contributing to this form of heart failure. Hydralazine is an arterial vasodilator, and nitrates may reduce preload. Research is needed to investigate whether these drugs in combination would benefit patients with heart failure and preserved left ventricular ejection fraction.

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