Full version of

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. 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. 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. 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. 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. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. 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. See related term 'Sensitivity' 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 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/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. Available from www.nice.org.uk/guidance/CG108/Guidance
NICE version:	Documents the recommendations without any supporting evidence. Available from www.nice.org.uk/guidance/CG108/NICEGuidance
"Quick reference guide":	An abridged version for healthcare professionals. Available from www.nice.org.uk/guidance/CG108/QuickRefGuide 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 Available from www.nice.org.uk/guidance/CG108/PublicInfo 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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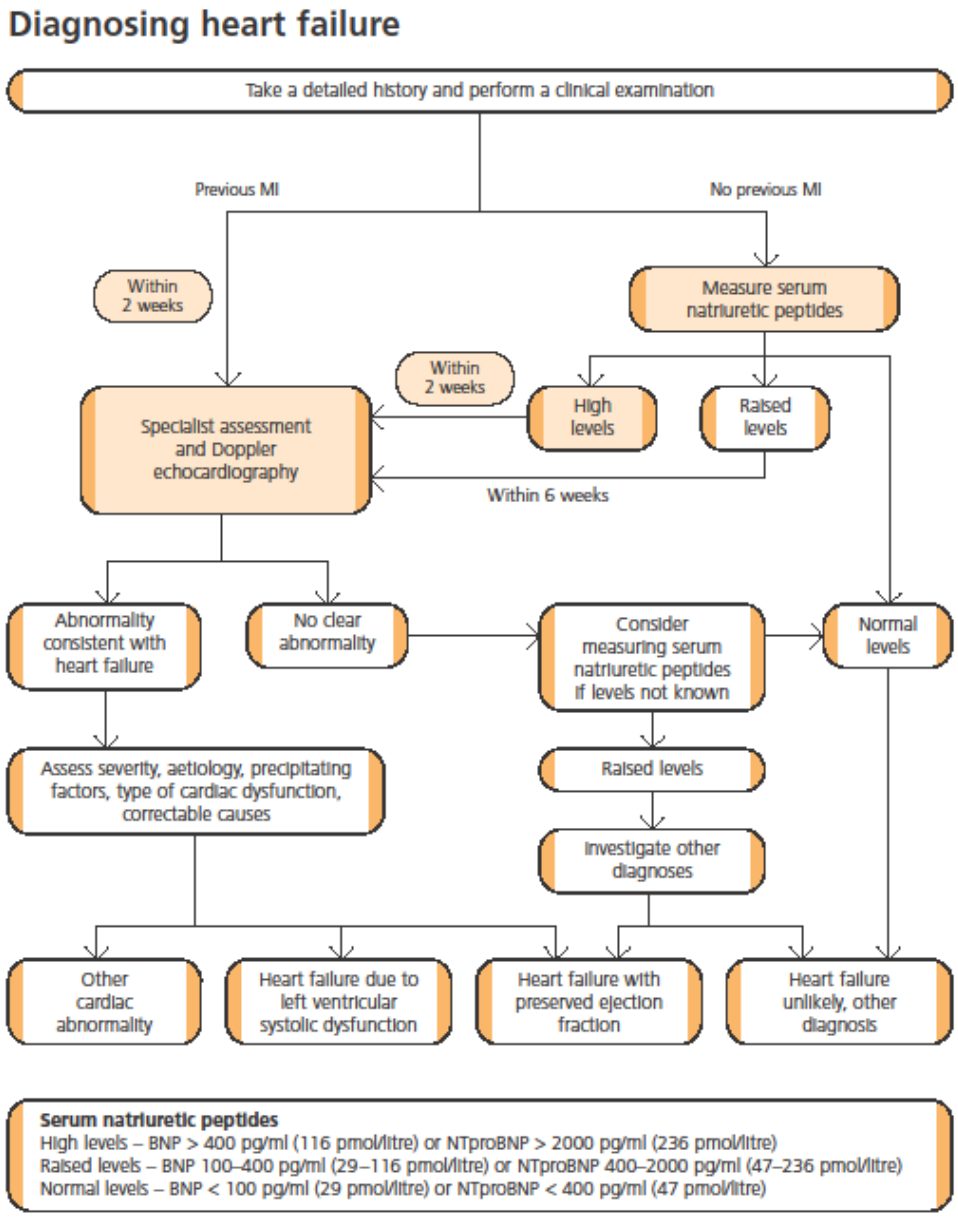
[2] Not all ARBs are licensed for use in heart failure in combination with ACE inhibitors

[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.

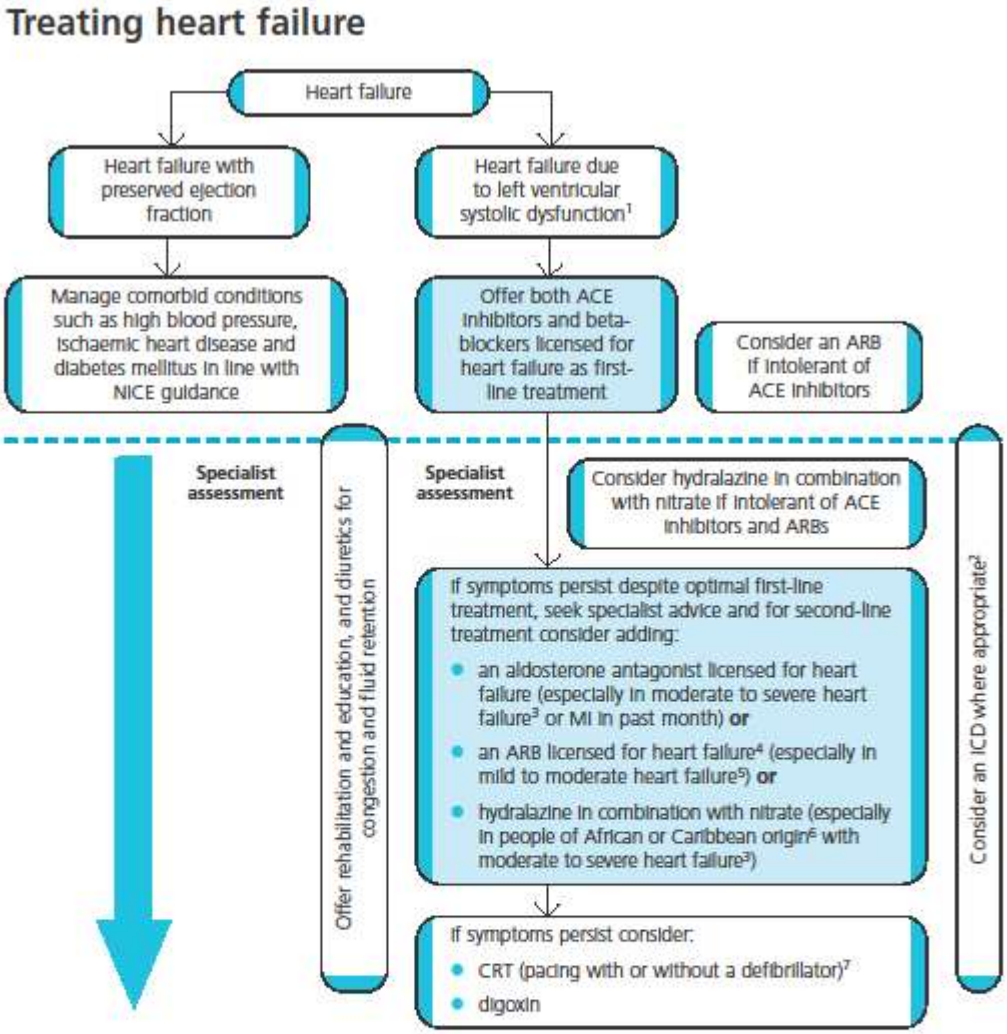
[5] This is a minimum. Patients with comorbidities or co-prescribed medications will require further monitoring. Monitoring serum potassium is particularly important if a patient is taking digoxin or an aldosterone antagonist.

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 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. Studies varied whether they included patients with previously diagnosed heart failure or not; both groups of studies were included in the review. in general practice (5 studies) N= 2,527 patients patients referred from primary to secondary care (5 studies)	Symptoms and signs: History of MI, Dyspnoea, Orthopnoea, Paroxysmal nocturnal dyspnoea, Oedema, Tachycardia, Elevated JVP, Cardiomegaly, Added heart sounds, Lung crepitation, Hepatomegaly	Adequate reference standards were prospective planned evaluation of: a) a clinical diagnosis including all information, for example using ESC (European Society of Cardiology) criteria. b) echocardiographic criteria for left ventricular systolic dysfunction (LVSD) (such as

		N=1,249 patients in acute care (5 studies) N= 1,890 patients		assessment of left ventricular ejection fraction or global assessment of ventricular function) c) echocardiographic criteria for heart failure with preserved left ventricular ejection fraction.
MADHOK 2008 N= 24 studies 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. 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 N= 22 studies 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. 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 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 **NT-proBNP**	**Echocardiogram** E/Ea ratio ≤15 diastolic function was normal; E/Ea >15 diastolic function was defined as abnormal.	When the echo measures: - Ea <8 cm/s - E/Ea >15 the diastolic function was defined as abnormal.
Hettwer 2007 **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: 1) dyspnoea of cardiac origin 2) clinical signs of heart failure with normal left ventricular systolic function 3) longstanding arterial hypertension	**NT-proBNP**	**Echocardiogram** Myocardial relaxation velocity 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): 1. impaired relaxation pattern. 2. pseudomormal pattern 3. restrictive pattern (- figures provided)

	Aim of trial	Population	Type of test	Comparison	Diagnosis of diastolic dysfunction
Tschope 2005 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 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%). (- 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 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) 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) 31% diastolic dysfunction with preserved left ventricular function 31% healthy controls 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 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: 1. those with LVEF ≥55% 2. those with LVEF <55% Compared with healthy controls (n=43)	NT-proBNP	Echocardiogram 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 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 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. (no figures provided)
Lubien 2002 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 Echo Doppler velocity (E, A velocities, IVRT, DT)	Classified in 3 categories: 1. impaired relaxation 2. pseudonormal 3. restrictive like According to echo measures (E/A ratio, IVRT, DT, PVd/PVs) (- figures provided)
Wei 2005 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 Measures: Doppler echo of transmitral flow, E and A peaks, diastolic time and the isovolumic relaxation time.	Based on 3 criteria: 1.) the presence of signs or symptoms of congestive heart failure, 2.) the echo measured LVEF >50% 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 NT-proBNP 489pg/mL Normal vs reduced LVEF	81.6	85.2	75.5	89.3
DONG 2006 NT-proBNP 150pg/mL E/Em ≥ 8 NT-proBNP 550pg/mL E/Em > 15	74 100	71 100	NR	NR
ABHAYARATNA 2006 Men 60 to 86 yrs NT-proBNP 240pg/mL Moderate diastolic dysfunction[1] Women 60 to 86 yrs NT-proBNP 270pg/mL Moderate diastolic dysfunction	83 89	85 86	NR	NR
LUBIEN 2002 BNP 17.5pg/mL Diastolic dysfunction[1] BNP 62pg/mL Diastolic dysfunction BNP 92pg/mL Diastolic dysfunction BNP 130pg/mL Diastolic dysfunction	 97 (92 to 99) 85 (77 to 90) 74 (65 to 81) 62 (53 to 71)	 45 (37 to 52) 83 (77 to 88) 98 (94 to 99) 98 (94 to 99)	 54 (47 to 81) 78 (70 to 84) 96 (89 to 98) 95 (87 to 98)	 95 (88 to 98) 89 (83 to 93) 85 (79 to 89) 79 (73 to 84)
WEI 2005 42[2] BNP 40pg/mL 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**]

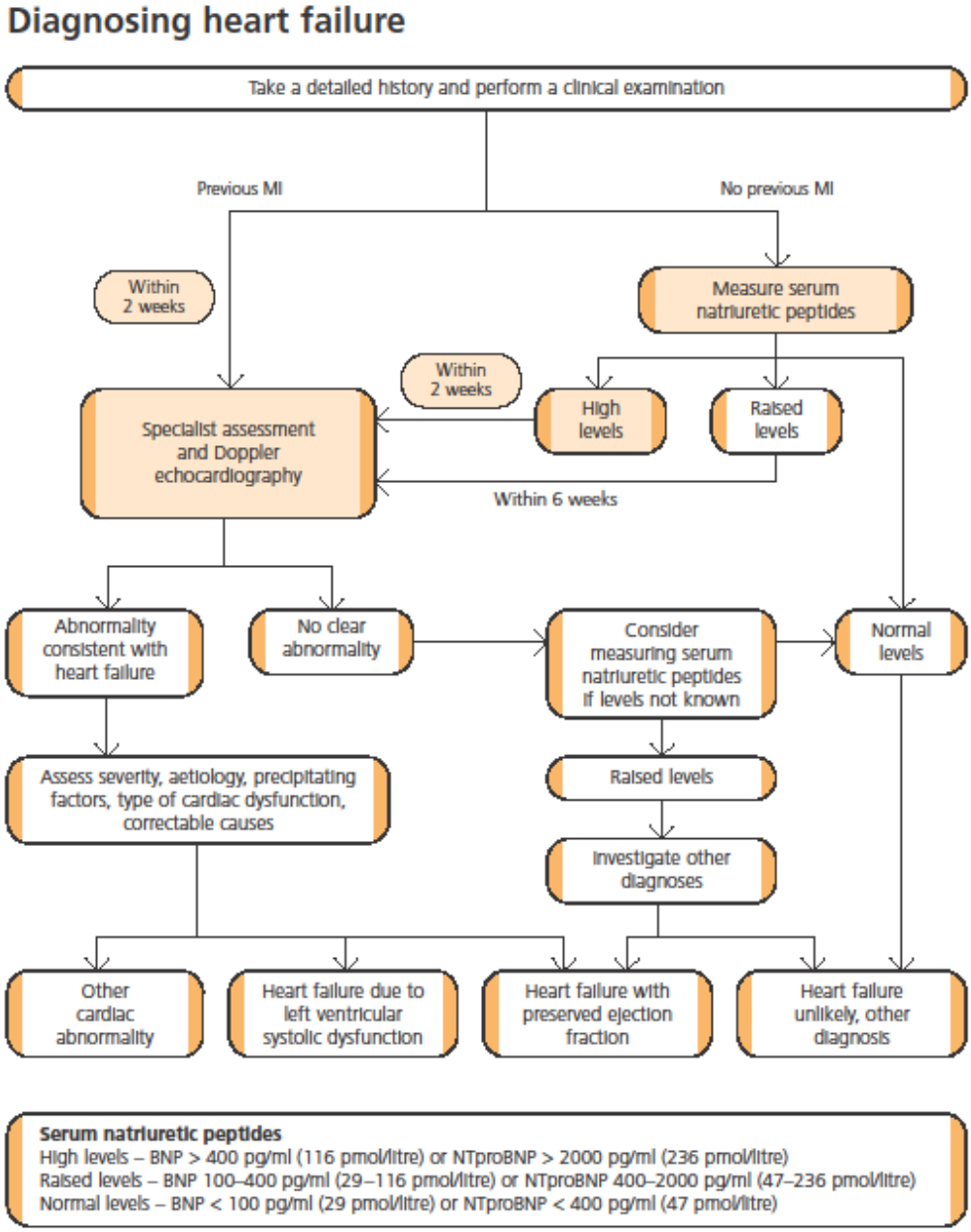
R15 When a diagnosis of heart failure has been made, assess severity, aetiology, precipitating factors, type of cardiac dysfunction and correctable causes. **[new 2010]**

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)	⊕⊕⊕○ 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)	⊕⊕⊕○ 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%) 19%	RR 0.91 (0.49 to 1.71)	0 fewer per 1,000 17 fewer per 1,000	⊕⊕⊕○ 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%) 0%	RR 1.06 (0.73 to 1.53)	2 more per 1000 (from 10 fewer to 20 more) 0 more per 1,000	⊕⊕⊕○ 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)	⊕⊕⊕○ 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	⊕⊕⊕○	0.96 (0.62 to 1.50)

									1.47)	11 fewer to 13 more)	MODERATE	
								0%		0 fewer per 1,000		
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)	⊕⊕⊕◯ 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%)	RR 0.89 (0.65 to 1.21)	6 fewer per 1000 (from 18 fewer to 11 more)	⊕⊕⊕◯ MODERATE	
								0%		0 fewer per 1,000		
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)	⊕⊕⊕◯ 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)	⊕⊕⊕◯ 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%)	RR 1.28 (0.97 to 1.69)	11 more per 1,000	⊕⊕⊕◯ MODERATE	
								28%		78 more per 1,000		

[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).

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[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 N=1982	Patients ≥ 65 yrs with EF ≤ 30% and NYHA II to IV	Metroprolol CR/XL 25 mg NYHA II 12.5 mg NYHA III and IV Dose doubled at each 2-week period until target dose of 200 mg or highest tolerated
EDES N=260	Patients with chronic heart failure aged more than 65 yrs 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 Titration period of 8 weeks. 1.25 mg double every 14 days until highest tolerated or maximum of 10 mg/day
ERDMANN N=539 Sub-group analysis	Patients ≥ 71 yrs with chronic heart failure Inclusion criteria: NYHA II, IV EF ≤35% Concomitant medication diuretics and ACEI	Bisoprolol 1.25 mg to a maximum of 10 mg/day
FLATHER 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 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 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 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 N=51	Patients with typical symptoms of heart failure and reduced LV ejection fraction (0.45 or lower)	Metoprolol Four week titration period increasing the dose from 3.125 to 25 mg twice daily at weekly intervals	Carvedilol Titration as for intervention. Dose titrated from 6.25 to 50 mg twice daily.
POOLE-WILSON N=3029	Adults with symptomatic chronic heart failure (NYHA II	Metroprolol 5 mg bd	Carvedilol 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 N=1010	Adults of 65 yrs or older with mild to moderate CHF (NYHA II or III) and LVEF ≤ 35%. Inclusion criteria: clinically stable, without clinically relevant fluid retention or diuretic adjustment in the 7 days before randomisation	ß blocker first Bisoprolol 1.25 mg QD Progressively titrated at two week intervals (or slower if intolerant) Target dose 10 mg QD Maintenance period 16 weeks if drug used first 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 Combination therapy: Addition of enalapril and up titration as for monotherapy phase	ACEI first Enalapril 2.5 mg BID Progressively titrated at two week intervals (or slower if intolerant) Target dose 10 mg BID Maintenance period 22 weeks if drug used first Procedure as for ß blocker 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%) 25%	RR 0.78 (0.67 to 0.90)	13 fewer per 1,000 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%) 51%	RR 0.95 (0.88 to 1.03)	17 fewer per 1,000 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)	⊕⊕⊕○ 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)	⊕⊕⊕○ 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)	⊕⊕⊕○ 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)	⊕⊕⊕○ 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			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Selective BB	non-selective BB	Relative (95% CI)	Absolute	Quality	
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%) 0%	RR 1.17 (1.06 to 1.28)	58 more per 1000 (from 20 more to 95 more) 0 more per 1,000	⊕⊕⊕○ 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)	⊕⊕⊕○ 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)	⊕⊕⊕○ 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)	⊕⊕⊕○ 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)	⊕⊕⊕○ 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: (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; (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)	⊕⊕⊕○ 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)	⊕⊕⊕○ 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)	⊕⊕⊕○ 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)	⊕⊕⊕◯ 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)	⊕⊕⊕◯ 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)	⊕⊕⊕◯ 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)	⊕⊕⊕○ 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)	⊕⊕⊕○ 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)	⊕⊕○○ 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 AGOSTONI (2005) 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)	⊕⊕◯◯ LOW	
hyperkalaemia >5.5mmol/l (follow-up 2 months)												
1 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)	⊕⊕◯◯ LOW	
raised creatinine >300umol/L (follow-up 8 weeks)												
1 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)	⊕⊕◯◯ LOW	
creatinine mean change (follow-up 6 months; measured with: mg/dl; range of scores: -; Better indicated by less)												
1 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)	⊕⊕◯◯ 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 - 15% Reduction in mortality: £2,180 per LYG - 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 - One-way sensitivity analysis – additional outpatient visits required to initiate medication for spironolactone group (1, 2, 4): from £291/LYG to £710/LYG - 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 VHEFT I: N=642 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:** - prazosin 5mgX4/day OR - combination of (hydralazine 75mg + isosorbide dinitrate 40mg)X4/ day. **VHEFT II:** - combination of (hydralazine 75mg	**VHEFT I:** - placebo **VHEFT II:** **-** 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. NYHA class VHEFT I II-III 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 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 Evidence of left ventricular ejection fraction (LVEF) within the six months preceding	Diuretic 90% ACEI 70% ARB 17% Beta-blocker 74% Carvedilol 56% Digoxin 60% Spironolactone 39%	Fixed-dose combination of isosorbide dinitrate plus hydralazine N=518 37.5 mg hydralazine hydrochloride + 20 mg isosorbide dinitrate three times daily Dose increased to two tables three time daily, total dose 225 mg hydralazine and 120 mg isosorbide Increase in dose was dependent on the absence of drug-induced side effects	Placebo 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 N=459	Men between the ages of 18 to 75 yrs with chronic heart failure Inclusion criteria: evidence of cardiac dysfunction (cardiothoracic ratio $\geq$ 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 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 **Run-in period**: 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)	⊕⊕⊕○ 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)	⊕⊕⊕○ 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)	⊕⊕⊕○ 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)	⊕⊕⊕○ 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)	⊕⊕⊕◯ 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)	⊕⊕⊕○ 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)	⊕⊕⊕○ 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)	⊕⊕⊕◯ 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)	⊕⊕⊕◯ 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					Hazard ratio
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	isosorbide + hydralazine	placebo	Relative (95% CI)	Absolute		
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)	⊕⊕◯◯ 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%) 0%	RR 0.91 (0.52 to 1.59)	17 fewer per 1000 (from 91 fewer to 112 more) 0 fewer per 1,000	⊕⊕◯◯ 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): **Date:** 2009-03-11 **Question:** Should isosorbide dinitrate + hydralazine vs ACE I be used for chronic heart failure in different ages? **Settings:** **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 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)	⊕⊕◯◯ LOW	1.14 (0.84 to 1.55)
all cause mortality at 2 years >60 yrs (follow-up 2 years)												
1 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)	⊕⊕◯◯ 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%) 30%	RR 0.90 (0.79 to 1.04)	0 fewer per 1,000 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%) 28%	RR 0.71 (0.61 to 0.83)	34 fewer per 1,000 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%) 3%	(1.42 to 3.22)	1,000 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%) 1.3%	RR 4.06 (2.15 to 7.64)	0 more per 1,000 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%) 21%	RR 1.00 (0.91 to 1.10)	0 fewer per 1,000 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%) 15%	RR 1.02 (0.9 to 1.14)	2 more per 1,000 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%) 18%	RR 0.92 (0.83 to 1.02)	12 fewer per 1,000 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%) 24%	RR 0.94 (0.86 to 1.03)	12 fewer per 1,000 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%) 0.5%	RR 1.88 (1.07 to 3.33)	3 more per 1,000 4 more per 1,000	⊕⊕⊕◯ 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)	⊕⊕⊕◯ MODERATE	

Mean increase in creatinine (follow-up mean 49.5 months; measured with: mg/dl; range of scores: -; Better indicated by less)												
1 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)	⊕⊕⊕⊕ HIGH	
Hypotension (follow-up 24-49 months)												
2 I-PRESERVE, CHARM PRESERVED	randomised trial	no serious limitations	serious[3]	no serious indirectness	serious[1]	none	97/3581 (2.7%)	79/3570 (1%) 3%	RR 1.22 (0.91 to 1.64)	2 more per 1,000 6 more per 1,000	⊕⊕◯◯ 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 Val-Heft (subgroup Krum et al) 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%) 25.4% 38.7%	RR 0.95 (0.85 to 1.05)	13 fewer per 1000 (from 40 fewer to 13 more) 12 fewer per 1,000 19 fewer per 1,000	⊕⊕⊕◯ MODERATE	0.93 (0.83 to 1.05)
First hospitalisation (follow-up mean 23 months)												
1 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)	⊕⊕◯◯ LOW	
Hyperkalaemia (follow-up 41 months)												
1 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 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)	⊕⊕◯◯ LOW	

Quality of Life (MLHQ) (follow-up mean 23 months; measured with: umol/L; range of scores: -; Better indicated by less)												
1 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)	⊕⊕⊕◯ 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)	⊕⊕⊕○ 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)	⊕⊕⊕○ 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)	⊕⊕⊕○ MODERATE	

added Val-Heft Cocco 2002								25%		115 more per 1000 (from 18 more to 250 more)		
Hyperkalaemia (follow-up median 41 months)												
1 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 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 Cocco 2002 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)	⊕⊕◯◯ LOW	
Unchanged NYHA class (follow-up 8 weeks)												
1 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)	⊕⊕◯◯ LOW	
Worsened NYHA class (follow-up 6 wks and 23 months)												
2 Cocco 2002 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)	⊕⊕◯◯ 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	834/4885 (17.1%)	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)	⊕⊕⊕○ 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]**

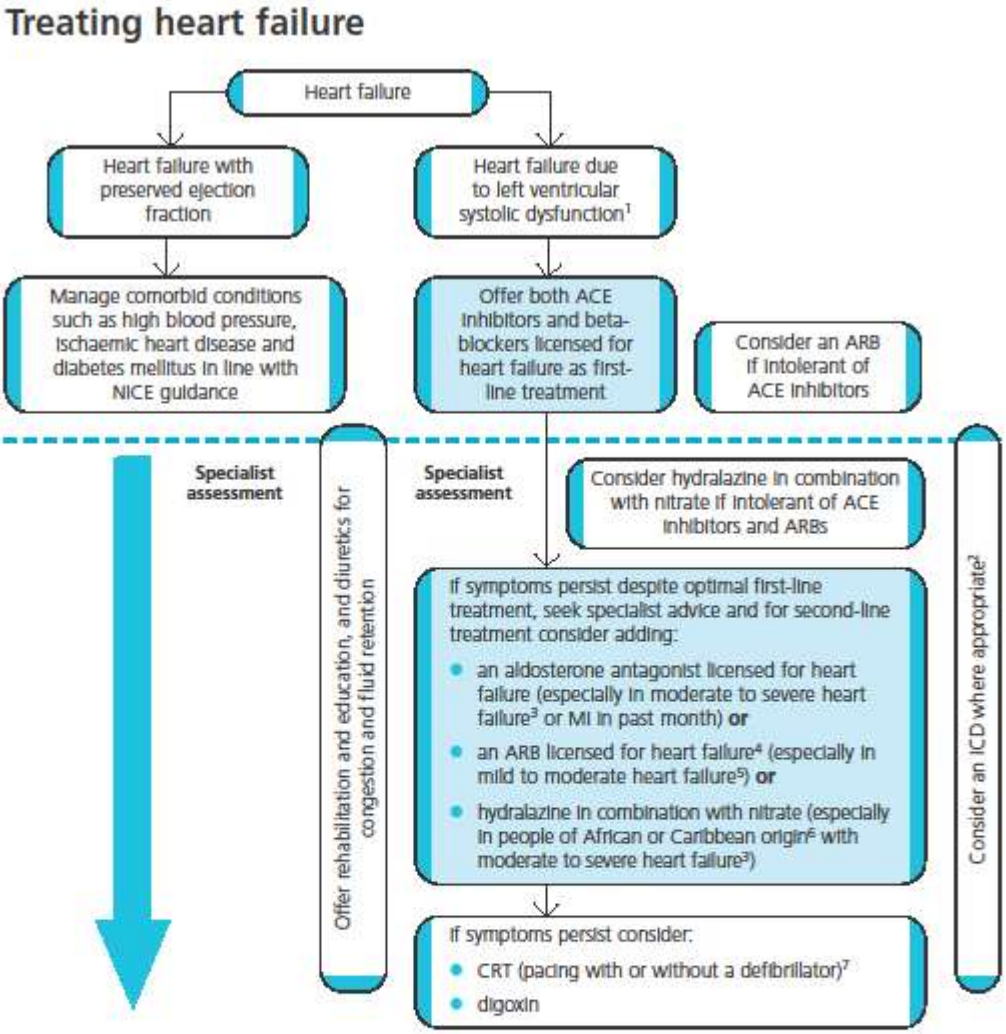
Cardiac resynchronisation therapy

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% - NYHA class II-IV - median age 59 years - N=2331	- Structured supervised group exercise phase: 3 sessions/week of walking, treadmill or stationary cycling - Home exercise phase after 36 sessions (3 months): cycling or treadmill 5 times/week - telephone follow-up	- usual care: no formal exercise programme, given educational leaflet which included information about exercise. - telephone calls to give comparable level of attention as per the exercise group - 8% of patients were doing their own continuous exercise	- all cause death - CV death - all cause hospitalisation - median 6MWT (12 months follow-up) - change in NYHA class Median 30 months
COVERA 2004	- LVEF ≤40% - NYHA class II-IV - mean age 61.3-63.8 years - N=79	- Home walking exercise 1/day for 5 days/week - pedometer use - nurse home visits and reviews	- control group: maintained normal exercise and measured with pedometer - nurse home visits and reviews	- all cause death - all cause hospitalisation - mean 6MWT (12 week follow up)
NILSSON 2008	- LVEF <40% or ≥40% with clinical symptoms of HF - NYHA class II-IIIB - mean age 69-72 - 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 - 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 - mean 6MWT (4 month follow up)
NILSSON 2008 (follow up)	AS ABOVE	AS ABOVE	AS ABOVE	- mean Qol score - mean 6MWT (12 month follow up)
AUSTIN 2005	- LVEF ≤40% - NYHA class II-III - mean age 72 - N=200	- standard care plus 8 week cardiac rehabilitation programme by a nurse specialist 2/week for 2.5 hrs - 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. - advice and treatment self monitoring information	- all cause death - all cause hospitalisation - mean Qol score - mean 6MWT - NYHA class (follow up: 24 weeks)

STUDY	POPULATION	INTERVENTION	COMPARISON	OUTCOMES
		and low resistance/ highly repetitive muscular strength work - exercise at home encouraged 3/week - weekly education sessions - optional counselling from dietician, psychotherapist and occupational therapist.		
AUSTIN 2008 (follow up)	AS ABOVE 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 - all cause hospitalisation - mean Qol score - mean 6MWT - NYHA class (follow up: 5 years)
CIDER 2003	- LVEF <45% - NYHA class II-III - mean age 70-75 years - N=25	- Hydrotherapy: 45 min sessions in pool, 3/week over 8 weeks. - Exercise used muscles required for activities of daily living. - Improving aerobic capacity, peripheral muscle strength and endurance. - Heart rate monitors used.	- control group: instructed to live life as normal and not increase physical activity during the 8 weeks	- mean Qol score - mean 6MWT (follow up: 8 weeks)
COLLINS 2004	- LVEF <40% - NYHA class II-III - mean age 62-66 years - N=31	- Rehabilitation programme: supervised moderate aerobic exercise programme - Included polestriding and treadmill walking: 3/week with duration increasing to 45-50 mins by week 12. - 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 Qol score (follow up: 12 weeks)
SARULLO 2006	- LVEF <40% - NYHA class II-III - mean age 53 years	- Supervised physical training programme: bicycle ergometer 30 mins 3/week	- control group: no change to physical activity	- mean Qol score - NYHA class (follow up: 3 months)

STUDY	POPULATION	INTERVENTION	COMPARISON	OUTCOMES
	- N=60			
DRACUP 2007	- LVEF ≤40% - NYHA class II-IV - mean age 53-54 years - N=173	- Low level aerobic and resistive/strength training programme. - walking 4/week, increasing to 45 mins at 12 weeks - Resistance programme 3/week on days they did not walk.	- control group: no change to physical activity	- all cause death - all cause hospitalisation (follow up: 1 year) - mean QoL score - mean 6MWT (follow up: 6 months)
WITHAM 2005	- LVEF: not reported (just those with LVSD) - NYHA class II-III - mean age 80-81 - N=82	- Physiotherapist delivered exercise - supervised phase (0-3 months): outpatients of small groups 2/week mainly aerobic and weights (resistance/strength) - 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% - NYHA class not reported - mean age 53-56 years - N=99	- 2 phases of supervised exercise training - phase 1: 3/week for 8 weeks: sessions were 1 hr including 40 mins on cycle ergometer - phase 2: 12 months maintenance programme 2 sessions/week	- Control group: no exercise.	- CV death - HF hospitalisation - Mean QoL 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]

<u>Change in NYHA class</u>

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 AUSTIN 2005 CORVERA 2004 DRACUP 2007 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)	⊕⊕⊕○ MODERATE	0.98 (0.81 to 1.19)
All cause mortality (follow-up 5 years)												
1 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)	⊕⊕⊕○ MODERATE	0.78 (0.48 to 1.25)
CV mortality up (follow-up mean 30 months-4.4 years)												
2 BELARDINELLI 1999 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)	⊕○○○ VERY LOW	0.86 (0.69 to 1.08)
All cause hospitalisation (follow-up 3-30 months)												
4 AUSTIN 2005 CORVERA 2004 DRACUP 2007 O'CONNOR 2009	randomised trial	serious[1]	serious[7]	no serious indirectness	serious[6]	none	778/1373 (56.7%)	834/1389 (60%) 11% 65%	RR 0.77 (0.53 to 1.12)	138 fewer per 1000 (from 282 fewer to 72 more) 25 fewer per 1,000 149 fewer per 1,000	⊕○○○ VERY LOW	

HF hospitalisation (follow-up mean 4.4 years)												
1 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)	⊕⊕⊕◯ 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 CIDER 2003 DRACUP 2007 NILSSON 2008 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)	⊕⊕⊕◯ 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 AUSTIN 2008 BELARDINELLI 1999 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)	⊕⊕◯◯ 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 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)	⊕⊕◯◯ LOW	
Mean 6MWT (follow-up 2-6 months; measured with: 6 minute walking test (metres); range of scores: -; Better indicated by more)												
5 CIDER 2003 CORVERA 2004 DRACUP 2007 NILSSON 2008 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)	⊕⊕⊕◯ MODERATE	
Mean 6MWT up (follow-up 12 months; measured with: 6 minute walking test (metres); range of scores: -; Better indicated by more)												
1 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 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)	⊕⊕⊕◯ 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					Importance
							No of patients		Effect		Quality	
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%) 0%	RR 0.79 (0.44 to 1.42)	50 fewer per 1000 (from 133 fewer to 100 more) 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%) 0%	RR 0.99 (0.45 to 2.15)	1 fewer per 1000 (from 72 fewer to 151 more) 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: (1) Patient-level cost removed: £258 per LYG; (2) Within-trial survival rates varied: £5400 to £660 per LYG; (3) Post-trial survival rates varied: £1108 to £1211 per LYG; (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 BATTLESCARRED	▪ Included patients with persevered LVEF mean 40% ▪ Symptomatic HF. 75% NYHA II or III ▪ Inclusion criteria included NT-proBNP > 50 pmol/L ▪ Age (median) 76 yrs ▪ 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 ▪ Symptomatic HF (New York Heart Association class II- IV) for at least 3 months or previous hospital admission due to HF ▪ Age (mean) : 65 yrs ▪ < 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) ▪ Established symptomatic HF (NYHA class II-IV) ▪ Age (range): 35- 85 yrs ▪ <50% females	-NT-proBNP guided treatment -The treatment target was NT-proBNP below 200pmol/l -If the targets were not achieved drug treatment was intensified according to a strict and predetermined stepwise protocol	-Treatment guided by standardised clinical assessment -The treatment target was clinically compensated heart failure according to an objective score
Jourdain, 2007 STARS-BNP	▪ Symptomatic (New York Heart Association functional class II to III) systolic heart failure defined by left ventricular ejection fraction (LVEF) <45% ▪ Age (mean): 65 yrs ▪ <50% females	-Medical therapy was increased with the aim of lowering plasma BNP levels (target <100 pg/ml) - 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 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. -Medical therapy to reduce BNP level to 2	- Symptom guided medical therapy. -Medical therapy to reduce symptoms to

	year ▪ Age (mean): 76 yrs ▪ <50% females ▪ 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% ▪ Symptomatic HF. 75% NYHA II or III ▪ Inclusion criteria included NT-proBNP > 50 pmol/L ▪ Age (median) 76 yrs ▪ 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* 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 BATTLESCARRED 2010 STARS-BNP 2007 TIME-CHF 2007	randomised trial	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[2]	none	58/482 (12%)	77/479 (10%) 22%	RR 0.75 (0.55 to 1.02)	25 fewer per 1,000 54 fewer per 1,000	⊕⊕⊕O MODERATE	0.73 (0.52 to 1.03)
Mortality (all cause) (follow-up 3 years)												
1 BATTLESCARRED 2010	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	40/121 (33.1%)	40/121 (33.1%) 0%	RR 1.00 (0.70 to 1.43)	0 fewer per 1000 (from 99 fewer to 142 more) 0 fewer per 1,000	⊕⊕⊕O MODERATE	1.00 (0.65 to 1.55)
Mortality (HF) (follow-up 3 to 15 months)												
2 Beck-de-Silva 2005 STARS-BNP	randomised trial	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	4/131 (3.1%)	11/130 (8%) 10%	RR 0.36 (0.12 to 1.10)	51 fewer per 1,000 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 STARS-BNP 2007 Beck-de-Silva 2005	randomised trial	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	54/131 (41.2%)	64/130 (20%) 55%	RR 0.84 (0.65 to 1.09)	32 fewer per 1,000 88 fewer per 1,000	⊕⊕OO LOW	
Hospitalisation (heart failure) (no. of patients) (follow-up 9.5-15 months)												

4 BATTLESCARRED 2010 TIME-CHF 2009 STARS-BNP 2007 Troughton 2000	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[5]	none	86/515 (16.7%)	131/515 (12%) 24%	RR 0.66 (0.52 to 0.84)	40 fewer per 1,000 81 fewer per 1,000	⊕⊕⊕O MODERATE	
Hospitalisation (heart failure) (no. of patients) (follow-up 3 years)												
1 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 BATTLESCARRED 2010 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 BATTLESCARRED 2010 TIME-CHF 2009	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	None	64/206 (31.1%)	60/212 (25%) 35%	RR 1.10 (0.82 to 1.47)	25 more per 1,000 35 more per 1,000	⊕⊕⊕○ 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 BATTLESCARRED 2010 TIME-CHF 2009	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	None	11/108 (10.2%)	11/102 (20%) 31%	RR 0.49 (0.30 to 0.79)	50 fewer per 1,000 158 fewer per 1,000	⊕⊕⊕○ 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 BATTLESCARRED 2010 TIME-CHF 2009	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	None	53/206 (25.7%)	56/212 (20%) 41%	RR 0.98 (0.72 to 1.34)	3 fewer per 1,000 8 fewer per 1,000	⊕⊕⊕○ MODERATE	
75 yrs or less - Hospitalisatioj (HF) - 18 mths to 3 yrs (follow-up 1.5-3 years)												
2 BATTLESCARRED 2010 TIME-CHF 2009	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	None	26/166 (15.7%)	38/157 (16%) 40%	RR 0.65 (0.42 to 1.00)	56 fewer per 1,000 140 fewer per 1,000	⊕⊕⊕○ 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%) 0%	RR 1.01 (0.7 to 1.44)	3 more per 1000 (from 98 fewer to 144 more) 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%) 0%	RR 1.08 (0.77 to 1.53)	27 more per 1000 (from 77 fewer to 178 more) 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)	⊕⊕⊕○ 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)	⊕⊕⊕○ 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)	⊕⊕⊕○ 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)	⊕⊕⊕○ 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)	⊕⊕⊕○ 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)	⊕⊕⊕○ 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)

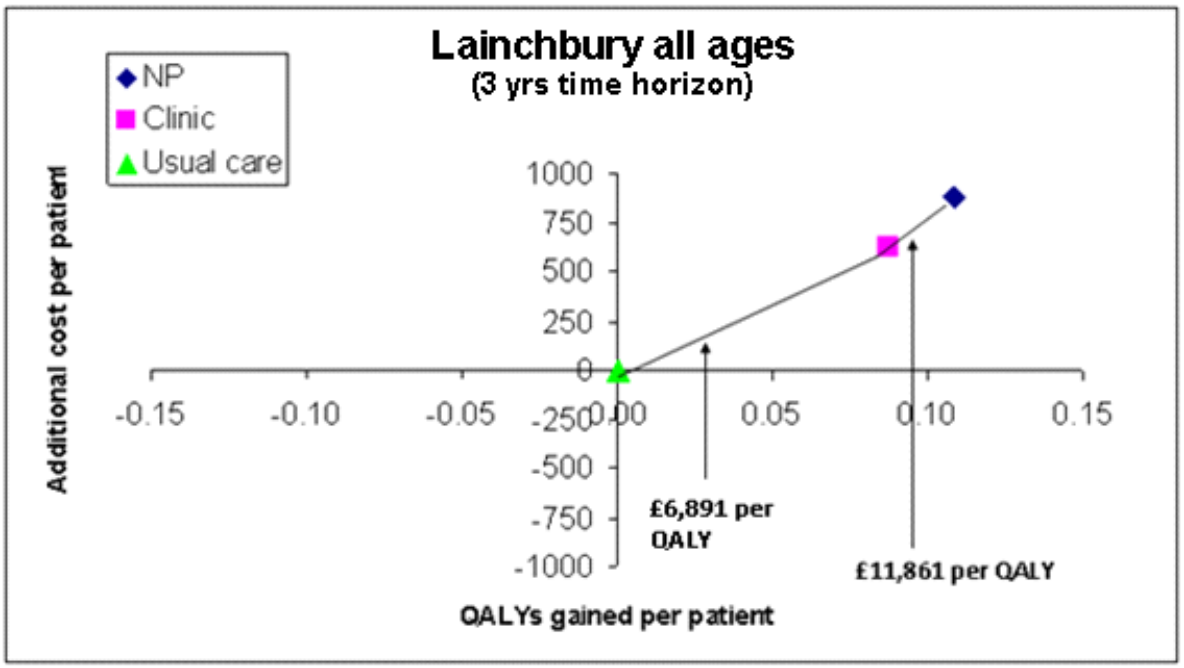
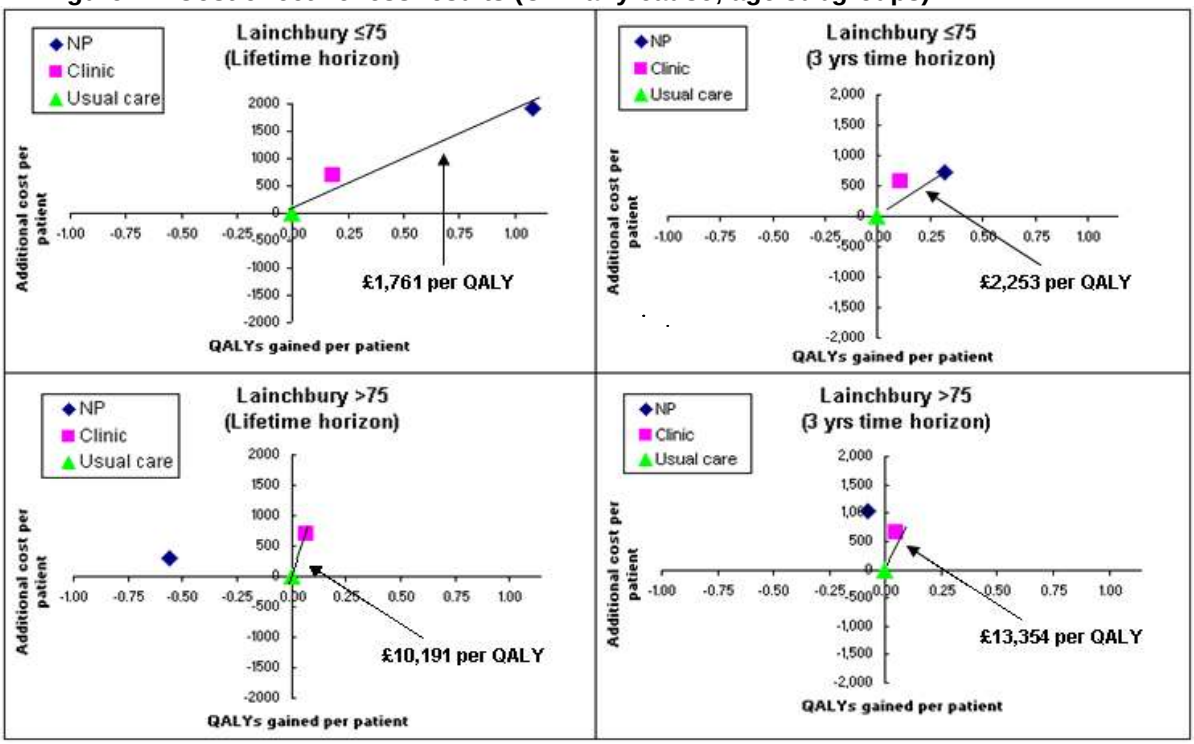


Table 7.8: Cost effectiveness results (CHF any cause)

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 N=29 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 N=28 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 N=85 Individualised written management	Home telemonitoring N=168 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 N=110 Routine home visits. No further details provided,	Telemonitoring N=126 Included education on HF and when to notify home care nurse or personal physician 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 N=91 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 N=91 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 N=230 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. 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) N=230 This included two different procedures: 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. 2) Tele-assistance: Occasional appointments were done when the patient, in the presence of symptoms or possible signs of decompensation were present. Education as for comparison
SCHWARZ 2008	Usual care N=51 No details provided	Telemonitoring N=51 Weight and symptoms monitored. Values outside range triggered call from nurse
WAKEFIELD 2008	Usual care N=49 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 N=47 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 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 N=155 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 N=160 Usual care plus 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 Antonicelli Cleland Dansky Giordano Wakefield	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	72/515 (14%)	14% 24%	RR 0.75 (0.56 to 1.01)	35 fewer per 1000 (from 62 fewer to 1 more) 60 fewer per 1000 (from 106 fewer to 2 more)	⊕⊕◯◯ LOW	0.91 (0.66 to 1.25)
All cause mortality, 450 days (follow-up 450 days)												
1 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)	⊕⊕⊕◯ 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)	⊕⊕⊕◯ 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)	⊕⊕◯◯ 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)	⊕⊕◯◯ 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)	⊕⊕⊕◯ 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)	⊕⊕◯◯ 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)	⊕⊕◯◯ 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)	⊕⊕◯◯ 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)	⊕⊕◯◯ 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)	⊕⊕◯◯ 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 Dansky 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 Schwarz 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)	⊕⊕⊕◯ 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%) 0%	RR 0.90 (0.71 to 1.15)	47 fewer per 1000 (from 137 fewer to 71 more) 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) Hospitalisation (heart failure, all cause) Change in NYHA class Quality of life 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 Or BNP	Clinical care	Mortality (all cause, heart failure) Hospitalisation (heart failure, all cause, planned, unplanned) Change in NYHA class Patient/carer acceptability Quality of life 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) Hospitalisation (heart failure, all cause, planned, unplanned) Change in NYHA

			class 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: A. on optimal therapy with BB and ACEI? B. are intolerant to ACE inhibitor?	Spironolactone	Angiotensin receptor blocker	Mortality (all cause, heart failure) Hospitalisation (heart failure, all cause) Change in NYHA class Quality of life 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) Hospitalisation (heart failure, all cause) Change in NYHA class Quality of life 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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Full version of
NICE Clinical guideline 108

CHRONIC HEART FAILURE

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

Appendices
(except E, F, G, M)

August 2010

Royal College of Physicians
Setting higher medical standards

Chronic heart failure update: Appendices

Appendix A - Scope of partial update

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

SCOPE

1 Guideline title

Chronic heart failure: the management of adults with chronic heart failure in primary and secondary care (partial update)

1.1 Short title

Chronic heart failure (partial update)

2 Background

a) The National Institute for Health and Clinical Excellence ('NICE' or 'the Institute') has commissioned the National Collaborating Centre for Chronic Conditions to partially update the existing guideline 'Chronic heart failure: management of chronic heart failure in adults in primary and secondary care' (NICE clinical guideline 5, 2003) for use in the NHS in England and Wales. The partial update will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.

b) NICE clinical guidelines support the implementation of National Service Frameworks (NSFs) in those aspects of care for which a Framework has been published. The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisals published by NICE after an NSF has been issued have the effect of updating the Framework.

c) NICE clinical guidelines support the role of healthcare professionals in providing care in partnership with patients, taking account of their individual needs and preferences, and ensuring that patients (and their carers and families, if appropriate) can make informed decisions about their care and treatment.

3 Clinical need for the guideline

a) Much progress has been made in the management of chronic heart failure since the publication of NICE clinical guideline 5 (2003) and new initiatives such as the introduction of the General Practice Quality and Outcomes Framework (QOF) have facilitated the delivery of evidence-based care. Heart failure is a clinical syndrome caused by a reduction in the heart's ability to pump blood around the body. The majority of the estimated 900,000 cases of heart failure in the UK are due to coronary heart disease (CHD), often with coexisting hypertension, diabetes and atrial fibrillation. It is most commonly caused by left ventricular dysfunction, but it can also result from several other diseases of the heart, such as abnormalities of the valves. In its advanced stages heart failure impairs the function of many other body systems, particularly the kidneys.

b) 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 in to account the new evidence available.

4 The guideline

a) The guideline development process is described in detail in two publications that are available from the NICE website (see 'Further information'). 'How NICE clinical guidelines are developed: an overview for stakeholders' the public and the NHS' describes how

organisations can become involved in the development of a guideline. 'The guidelines manual' provides advice on the technical aspects of guideline development.

b) This scope defines what this guideline update will (and will not) examine, and what the guideline developers will consider. This scope should be read along with the original scope for NICE clinical guideline 5 (2003), which is reproduced in the appendix.

c) The areas that will be addressed by the partial guideline update are described in the following sections.

d) Clinical and economic evidence published since September 2002, and conforming to the criteria for consideration in the existing guideline, will be considered.

e) Original health economic modelling may be carried out once the evidence base has been assessed.

4.1 Population

4.1.1 Groups that will be covered

a) Adults with symptoms or a diagnosis of chronic heart failure (including diastolic dysfunction).

4.1.2 Groups that will not be covered

a) Patients with right heart failure as a consequence of respiratory disease.

b) Pregnant women.

4.2 Healthcare setting

a) Care given by primary and secondary healthcare professionals who have direct contact with patients with chronic heart failure and make decisions concerning their care.

4.3 Clinical management

4.3.1 Topics that will be updated

a) Diagnosing heart failure:

- symptoms and signs
- use of B-type natriuretic peptides (BNP and NT-proBNP)
- echocardiography.

b) Pharmacological treatment of heart failure, for example:

- aldosterone antagonists
- angiotensin II receptor antagonists.

c) Invasive procedures:

- cardiac resynchronisation therapy (incorporating relevant recommendations from NICE technology appraisal guidance 120 – see section 4.4.1)
- implantable cardioverter defibrillators (incorporating relevant recommendations from NICE technology appraisal guidance 95 – see section 4.4.1).

d) Disease monitoring in chronic heart failure:

- serial measurement of circulating natriuretic peptide concentration
- monitoring at home.

e) Cardiac rehabilitation for heart failure.

f) Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform their decisions for individual patients.

g) The Guideline Development Group will take reasonable steps to identify ineffective interventions and approaches to care. If robust and credible recommendations for re-positioning the intervention for optimal use, or changing the approach to care to make more efficient use of resources, can be made, they will be clearly stated. If the resources released are substantial, consideration will be given to listing such recommendations in the 'Key priorities for implementation' section of the guideline.

h) Where there is evidence, the guideline will consider any subgroups (for example, ethnic groups) in whom the management of chronic heart failure may differ from the general population.

4.3.2 Topics that will not be updated

The following topics will not be updated.

a) Lifestyle (section 7.1 of full guideline with the exception of the section on rehabilitation, which will be updated).

b) Pharmacological treatments to modify cardiovascular risk.

c) Comorbidities.

d) Drugs to be avoided or used with caution in heart failure.

e) Invasive procedures (with the exception of those specifically mentioned within the scope above).

f) Oxygen therapy and continuous positive airways pressure treatment.

g) Review of management plans.

h) Serial cardiac imaging.

i) Referral and approach to care (section 9).

j) Supporting patients and carers.

k) Anxiety and depression.

l) End of life.

m) Prevention.

4.4 Status

4.4.1 Scope

This is the final scope.

The guideline will partially update the following NICE guidance.

- Chronic heart failure: management of chronic heart failure in adults in primary and secondary care. NICE clinical guideline 5 (2003). Available from www.nice.org.uk/CG5

The guideline will incorporate aspects of the following NICE guidance which are relevant to heart failure.

- Implantable cardioverter defibrillators for arrhythmias. NICE technology appraisal guidance 95 (2006). Available from www.nice.org.uk/TA95
- Cardiac resynchronisation therapy for the treatment of heart failure. NICE technology appraisal guidance 120 (2007). Available from www.nice.org.uk/TA120

4.4.2 Guideline

The development of the guideline update will begin in October 2008.

5 Related NICE guidance

Published

1. 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/CG67

2. Type 2 diabetes: the management of type 2 diabetes. NICE clinical guideline 66 (2008). Available from www.nice.org.uk/CG66
3. 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/CG48
4. Atrial fibrillation: the management of atrial fibrillation. NICE clinical guideline 36 (2006). Available from www.nice.org.uk/CG36
5. Hypertension: management of hypertension in adults in primary care. NICE clinical guideline 34 (2006). Available from www.nice.org.uk/CG34
6. 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/IPG177

6 Further information

The guideline development process is described in:

- 'How NICE clinical guidelines are developed: an overview for stakeholders' the public and the NHS'
- 'The guidelines manual'.

These are available from the NICE website (www.nice.org.uk/guidelinesmanual).

Information on the progress of the guideline will also be available from the NICE website.

Appendix: Scope for NICE clinical guideline

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

Scope for the development of a clinical guideline on the management of heart failure

1 Objective

1.1 The National Institute for Clinical Excellence has commissioned a clinical guideline for patients and clinicians on the management of heart failure. The guideline will provide advice on effective care using evidence from clinical trials and economic analyses.

1.2 The commission received from the Department of Health and the National Assembly for Wales is in Figure 1.

1.3 The Institute's clinical guidelines will support the implementation of National Service Frameworks (NSF) in those aspects of care where a framework has been published. The statements in each NSF reflect the evidence that was used at the time the framework was prepared. The clinical guidelines and technology appraisals published by the Institute after a NSF has been issued will have the effect of updating the framework.

2 Title

The diagnosis and management of chronic heart failure in primary and secondary care.

Clinical Need and Practice[a]

2.1 Heart failure is a clinical syndrome caused by a reduction in the heart's ability to pump blood around the body. Most cases of heart failure in the UK are due to CHD and about a third result from hypertensive heart disease. It is most commonly caused by ventricular dysfunction usually from coronary heart disease and or hypertension, but it can also result from several other diseases of the heart such as abnormalities of the valves. In its advanced stages heart failure impairs the function of many other body systems especially the kidneys.

2.2 The incidence of heart failure is about one new case per 1000 population per year and is rising at about 10% per year. This increases with age and is over 10 cases per 1000 in people age 85 years and over.

2.3 Prognosis is poor with survival rates worse than those for breast or prostate cancer. Annual mortality for those with heart failure ranges from 10% to over 50% depending on severity. There are thought to be about 6,000 deaths a year due to heart failure due to coronary heart disease.

2.4 Heart failure imposes a considerable disease burden in both primary and secondary care, consuming substantial resources. Heart failure accounts for about 5% of all medical admissions to hospital and is associated with very high readmission rates – estimated to be as high as 50% over three months in severe cases.

[a] Based upon the National Service Framework for Coronary Heart Disease.

Figure 1 – Commission from the Department of Health and National Assembly for Wales

We would want the following to have been considered in drawing up the guidelines:

Appropriate means of diagnosis (including consideration of possible role of new developments in diagnosis e.g. BNP)

Optimum symptom control using established treatments but also including relatively new evidence around drugs such as spironolactone, A II blockers (e.g. losartan), beta blockers (and if appropriate how and where to manage treatment with beta blockers)

Appropriate make-up of medical team treating (evidence for MD approach)

Evidence on exercise tolerance and the possible beneficial effects of exercise on quality of life (limited evidence available but traditional advice to rest may not be appropriate in all cases)

Role of supportive care – the potential of the 'palliative care approach', when to consider supportive care and when the use of specialist palliative care services may be appropriate

The role of primary care and community services – may these have an effect on frequent acute re-admissions?

Role of lifestyle advice

- Role of surgical interventions to treat or relieve symptoms

Population

2.5 The guideline should offer best practice advice on the care of adult patients (≥18 years) who have symptoms or a diagnosis of chronic heart failure.

2.6 The guideline will not address the screening or diagnosis of people who are asymptomatic. Screening programmes will be addressed by the screening committee.

2.7 The guideline will not address the management of patients with right heart failure as a consequence of respiratory disease.

Health care setting

2.8 The guideline will cover the care received from primary and secondary health care professionals who have direct contact with and make decisions concerning the care of patients with heart failure.

2.9 The guideline will address the interface between primary and secondary care including in what circumstances patients should be referred or admitted to secondary care.

2.10 Where evidence is available, the circumstances under which referral for invasive procedures including pacing, implantable cardiac defibrillators (using NICE recommendations), coronary artery bypass grafting, angioplasty, valve surgery and transplantation surgery will be considered.

2.11 Where evidence is available, the circumstances under which a referral to supportive and palliative care should be made will be considered.

2.12 The guideline will also be relevant to the work but will not cover the practice of social services, the voluntary sector and those working in post transplant care.

2.13 The guidelines will not address models of care nor the roles or composition of primary or secondary care health care teams

2.14 Neither will it address competencies, skill mix or training requirements which are the remit of the Modernisation Agency.

Interventions and treatment

The guideline will define the most effective combination of symptoms, signs and investigations required to establish the cause of heart failure and which will influence therapy or provide important prognostic information.

The goals of treatment will be defined in terms of symptom reduction, functional ability, hospitalisation and mortality.

The guidelines will consider

2.15 Diagnosis

2.15.1 Systolic and diastolic dysfunction, valve disease and the other causes of heart failure.

2.15.2 Diagnostic techniques: the value of a range of diagnostic techniques including ECG, chest x-ray, biochemical markers (e.g. BNP) and imaging techniques (e.g. echo/MRI).

2.16 Pharmacological treatments:

2.16.1 Type – where evidence is available the guideline will consider diuretics, digoxin, ACE inhibitors, beta blockers, angiotensin receptor blockers, spironolactone, nitrates, other vasodilators and newer therapies.

2.16.2 The guideline will review dose, initiation, frequency, monitoring, combined treatments and sequencing.

2.16.3 Advice on treatment options will be based on the best evidence available to the development group. When referring to pharmacological treatments, the guideline will normally recommend within the license indications. Exceptionally, and only where the evidence clearly supports it, recommendations for the guideline may recommend use outside the license indications.

2.16.4 The guideline assumes that prescribers will use the Summary of Product Characteristics to inform their prescribing decisions for individual patients

2.17 Non-pharmacological treatment including, where evidence is available:

2.17.1 exercise programmes

2.17.2 lifestyle advice on diet, physical activity, weight reduction and smoking cessation

2.17.3 management of depression and/or anxiety as it pertains directly to patients with heart failure and is outside the scope of the 'Management of Depression' guideline which is under development.

Presentation

The guideline will be available in three forms:

2.18 The full guideline containing the evidence base used by the developers.

2.19 A short form version, using a standard template, which will form the Institute's guidance to the NHS including a clinical practice algorithm.

2.20 A version, prepared specifically for patients and their carers, will interpret the recommendations made in the Institute's short form version and will be designed to help patients to make informed choices about their care.

Status

2.21 This scoping statement is subjected to a four week period of consultation with stakeholders. The scope is then re-drafted and submitted to the Guidelines Advisory Committee and subsequently the Institute's Guidance Executive, for approval. Once approved, it is posted on the Institute's website, together with details of the Commissioning Brief and the name of the Collaborating Centre through which the guideline is being commissioned. The development of the guideline will begin in the autumn of 2001.

2.22 Information on the guidelines development process, stakeholder involvement and the progress of this guideline is available on the website http://www.nice.org.uk/.

Appendix B – Clinical Questions

DIAG: symptoms and signs vs gold standard

What is the diagnostic accuracy of a collection of symptoms and signs, including any scoring systems vs gold standard in the diagnosis of heart failure?

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 accuracy of echocardiography *vs* natriuretic peptides in the diagnosis of diastolic dysfunction?

BNP3: natriuretic peptide monitoring (guided therapy) vs standard care

Does serial BNP monitoring (guided therapy) improve outcome compared to standard care in adults with chronic heart failure?

ACE: Angiotensin converting enzyme inhibitors

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

ALDO: Aldosterone antagonists + optimal medical management vs placebo + optimal medical management

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?

ARB1: angiotensin II receptor antagonists vs placebo

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

ARB2: a) angiotensin-II receptor antagonists + angiotensin converting enzyme inhibitor vs placebo + angiotensin converting enzyme inhibitor;

b) angiotensin-II receptor antagonists + angiotensin converting enzyme inhibitor + beta blocker vs placebo + angiotensin converting enzyme inhibitor + beta blocker

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

BB: beta blockers vs placebo, optimal medical management or other beta blockers

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?

ISO: isosorbide/hydralazine vs placebo or ACE or placebo+optimal medical treatment

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

MONIT: patient telemonitoring vs out patient monitoring

What is the efficacy and safety of patient telemonitoring in comparison to outpatient monitoring for adults with chronic heart failure?

REHAB: exercise based cardiac rehabilitation

What is the safety and efficacy of exercise based cardiac rehabilitation in adults with chronic heart failure?

Appendix C – Review protocols

DIAG: Diagnostic accuracy of symptoms and signs

<table>
<tr><td colspan="5">REVIEW PROTOCOL GDG2</td></tr>
<tr><td colspan="5">A: REVIEW QUESTION: DIAG
What is the diagnostic accuracy of a collection of symptoms and signs, including any scoring systems vs gold standard in the diagnosis of heart failure?
B: OBJECTIVES:
To estimate the diagnostic accuracy of signs and symptoms or any scoring systems in heart failure.</td></tr>
<tr><td colspan="5">C: SEARCH CRITERIA AND PICO</td></tr>
<tr><td>Population

✓ All Chronic Heart failure

☐ Other

Exclusions: right heart failure due to
Respiratory disease</td><td>Demographics

☐ All
✓ Adults only
Age:
☐ Children only
Age range:

Sex:
Ethnic group:</td><td>Study types

✓ SRs
☐ RCTs
☐ C/C Studies
☐ Obs Studies
☐ Cases
☐ Diagnostic studies
☐ Prognostic studies</td><td>Limits
Dates:

✓ All years
☐ 1966-
☐ 1980-
☐ 1995-
☐2002-

Language:
✓English</td><td>Databases

✓ M/E/Coch
✓ CINAHL
☐ BNI
☐ PsycInfo
☐ AMED
☐ HMIC
☐ Other</td></tr>
<tr><td colspan="3">Intervention (OR diagnostic procedure or prognostic factors)
Symptoms and signs, namely:

Breathlessness *
fatigue *
Effort intolerance
Raised JVP (jugular venous pressure)
Third heart sound
Apex beat
Murmurs
Fluid retention /ankle oedema *

* also if reported individually</td><td colspan="2">Comparison
Cardiologists diagnosis+ combination of investigations

Outcomes
1. sensitivity
2. specificity</td></tr>
</table>

Chronic heart failure update appendices (except E,F,G,M)

D: REVIEW STRATEGY

Gold standard defined as cardiologist diagnosis in conjunction with signs/symptoms +/- echo.

Restricting to systematic reviews

May be updating existing meta-analysis.

Subgroups:

Populations to be identified:

Patients with LVSD

Patients with PLVEF

E. EQUALITIES ISSUES

Possible subgroups may be:

Different age groups; Different ethnicities; male/female

BNP1: Diagnostic accuracy of natriuretic peptides vs gold standard

<table>
<tr><td colspan="5">REVIEW PROTOCOL GDG1</td></tr>
<tr><td colspan="5">A: REVIEW QUESTION: BNP1
What is the accuracy of natriuretic peptides v gold standard in the diagnosis of heart failure?
B: OBJECTIVES:
To assess when in the diagnostic pathway BNP should be performed e.g. before or after echo.</td></tr>
<tr><td colspan="5">C: SEARCH CRITERIA AND PICO</td></tr>
<tr><td>Population

✓ All Chronic Heart failure

☐ Other

Exclusions: right heart failure due to
Respiratory disease</td><td>Demographics

☐ All
✓ Adults only
Age:
☐ Children only
Age range:

Sex:
Ethnic group:</td><td>Study types

✓ SRs
✓ RCTs
✓ C/C Studies
✓ Obs Studies
☐ Cases
✓ Diagnostic studies
☐ Prognostic studies</td><td>Limits
Dates:

☐ All years
☐ 1966-
☐ 1980-
☐ 1995-
✓ 2002-

Language:
✓English</td><td>Databases

✓ M/E/Coch
✓ CINAHL
☐ BNI
☐ PsycInfo
☐ AMED
☐ HMIC
☐ Other</td></tr>
<tr><td colspan="3">Intervention (OR diagnostic procedure or prognostic factors)

BNP
NT-pro BNP
Natriuretic peptides

+ Symptoms and signs + echo</td><td colspan="2">Comparison
Symptoms and signs + echo

Outcomes
1. sensitivity
2. specificity
3.
4.
5.</td></tr>
</table>

Chronic heart failure update appendices (except E,F,G,M)

D: REVIEW STRATEGY

Gold standard defined as cardiologist diagnosis in conjunction with signs/symptoms +/- echo.

May be updating existing meta-analysis.

Subgroups:

Populations to be identified:

Patients with LVSD

Patients with PLVEF

E. EQUALITIES ISSUES

Possible subgroups may be:

Different age-groups ; Different ethnicities; male/female

BNP2: Diagnostic accuracy of natriuretic peptides vs echocardiography

<table>
<tr><td colspan="5">REVIEW PROTOCOL GDG1</td></tr>
<tr><td colspan="5">A: REVIEW QUESTION: BNP2
W hat is the accuracy of echocardiography v natriuretic peptides in the diagnosis of diastolic dysfunction?
B: OBJECTIVES:
To assess when in the diagnostic pathway BNP should be performed e.g. before or after echo in people with suspected diastolic dysfunction.</td></tr>
<tr><td colspan="5">C: SEARCH CRITERIA AND PICO</td></tr>
<tr><td>Population

☐All Chronic Heart failure
☐ LVSD
✓ Diastolic dysfunction - suspected
☐ Other
Exclusions: right heart failure due to
Respiratory disease</td><td>Demographics

☐ All
✓ Adults only
Age:
☐ Children only
Age range:

Sex: 🚹 🚺
Ethnic group:</td><td>Study types

✓ SRs
✓ RCTs
✓ C/C Studies
✓ Obs Studies
☐ Cases
✓ Diagnostic studies
☐ Prognostic studies</td><td>Limits
Dates:

☐ All years
☐ 1966-
☐ 1980-
☐ 1995-
✓ 2002-

Language:
✓English</td><td>Databases

✓ M/E/Coch
✓ CINAHL
☐ BNI
☐ PsycInfo
☐ AMED
☐ HMIC
☐ Other</td></tr>
<tr><td colspan="3">Intervention (OR diagnostic procedure or prognostic factors)

echocardiogram</td><td colspan="2">Comparison

BNP
NT-pro BNP
Natriuretic peptides</td></tr>
<tr><td colspan="3"></td><td colspan="2">Outcomes
1. sensitivity
2. specificity
3.
4.
5.</td></tr>
</table>

Chronic heart failure update appendices (except E,F,G,M)

D: REVIEW STRATEGY

Limit to symptomatic patients

E. EQUALITIES ISSUES

Possible subgroups may be:

Different age-groups; different ethnicities; male/female

BNP3: Natriuretic peptide guided therapy

<table>
<tr><td colspan="5">REVIEW PROTOCOL GDG6</td></tr>
<tr><td colspan="5">A: REVIEW QUESTION: BNP 3
Does serial BNP monitoring (guided therapy) improve outcome compared to standard care in adults with chronic heart failure?
B: OBJECTIVES:
To assess the role of serial measurement of circulating natriuretic peptide concentration in adults with chronic heart failure</td></tr>
<tr><td colspan="5">C: SEARCH CRITERIA AND PICO</td></tr>
<tr><td>Population

✓ All Chronic Heart failure

☐other

Exclusions: right heart failure due to
Respiratory disease</td><td>Demographics

☐ All
✓ Adults only
Age:
☐ Children only
Age range:

Sex:
Ethnic group:</td><td>Study types

✓ SRs
✓ RCTs
✓ C/C Studies
✓ Obs Studies
☐ Cases
☐Diagnostic studies
☐ Prognostic studies</td><td>Limits
Dates:

☐ All years
☐ 1966-
☐1986-
☐ 1995-
☐2002-
✓Post 2000

Language:
✓English</td><td>Databases

✓ M/E/Coch
✓ CINAHL
☐ BNI
☐ PsycInfo
☐ AMED
☐ HMIC
☐ Other</td></tr>
<tr><td colspan="3">Intervention (OR diagnostic procedure or prognostic factors)

serial measurement of circulating natriuretic peptide concentration
BNP levels monitoring</td><td colspan="2">Standard care

1.all cause death up to 5 yrs
2. all cause hospitalization
3.Qol
4. HF hospitalization</td></tr>
<tr><td colspan="5">D: REVIEW STRATEGY
Subgroups:
Populations to be identified: different age groups; people with renal failure

E. EQUALITIES ISSUES
Possible subgroups may be:
Different age groups; Different ethnicities; male/female</td></tr>
</table>

ACE: Efficacy and safety of Angiotensin converting enzyme inhibitors

<table>
<tr><td colspan="5">REVIEW PROTOCOL GDG5</td></tr>
<tr><td colspan="5">A: REVIEW QUESTION: ACE
What is the efficacy and safety of ACE inhibitors in people with heart failure and preserved left ventricular ejection fraction?
B: OBJECTIVES:
To assess the role of ACE Inhibitors in people with heart failure and PLVEF especially in the older population</td></tr>
<tr><td colspan="5">C: SEARCH CRITERIA AND PICO</td></tr>
<tr><td>Population

☐ All Chronic Heart failure

✓HF with PLVEF

Exclusions: right heart failure due to
Respiratory disease</td><td>Demographics

☐ All
✓ Adults only
Age:
☐ Children only
Age range:

Sex:
Ethnic group:</td><td>Study types

✓ SRs
✓ RCTs
✓ C/C Studies
☐ Obs Studies
☐ Cases
☐Diagnostic studies
☐ Prognostic studies</td><td>Limits
Dates:

☐ All years
☐ 1966-
✓ 1986-
☐ 1995-
☐2002-

Language:
✓English</td><td>Databases

✓ M/E/Coch
✓ CINAHL
☐ BNI
☐ PsycInfo
☐ AMED
☐ HMIC
☐ Other</td></tr>
<tr><td colspan="3">Intervention (OR diagnostic procedure or prognostic factors)

Angiotensin-converting enzyme inhibitors/ inhibition
ACE inhibitors/ACEI
Captopril cilazipril enalipril fosinopril imidapril lisinopril moexipril perindopril quinapril ramipril trandolapril</td><td colspan="2">placebo

1.all cause mortality up to 5 yrs
2.Unplanned hospitalization
3.Qol
4.Side effects/adverse events
5. NYHA class</td></tr>
</table>

Chronic heart failure update appendices (except E,F,G,M)

D: REVIEW STRATEGY

Subgroups:

Populations to be identified:

Older people

E. EQUALITIES ISSUES

Possible subgroups may be:

Different age groups; Different ethnicities; male/female

ALDO: Efficacy and safety of Aldosterone antagonists

<table>
<tr><td colspan="5">REVIEW PROTOCOL GDG3</td></tr>
<tr><td colspan="5">A: REVIEW QUESTION: ALDO

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?

B: OBJECTIVES:

To assess whether the use of aldosterone antagonists adds any extra benefit to the management of adults with heart failure, and in the sub-group of patients with renal impairment</td></tr>
<tr><td colspan="5">C: SEARCH CRITERIA AND PICO</td></tr>
<tr><td>Population

✓ All Chronic Heart failure

☐ Other

Exclusions: right heart failure due to
Respiratory disease</td><td>Demographics

☐ All
✓ Adults only
Age:
☐ Children only
Age range:

Sex:
Ethnic group:</td><td>Study types

✓ SRs
✓ RCTs
✓ C/C Studies
☐ Obs Studies
☐Cases
☐ Diagnostic studies
☐ Prognostic studies</td><td>Limits
Dates:

☐ All years
☐ 1966-
✓ 1986-
☐ 1995-
☐ 2002-

Language:
✓English</td><td>Databases

✓ M/E/Coch
✓ CINAHL
☐ BNI
☐ PsycInfo
☐ AMED
☐ HMIC
☐ Other</td></tr>
<tr><td colspan="3">Intervention (OR diagnostic procedure or prognostic factors)

Aldosterone receptor antagonists
Eplerenone
Spironolactone

+ optimal medical management (= ACE, ARB, diuretic, BB +/- digoxin)</td><td colspan="2">Comparison
Placebo + optimal medical management (= ACE, ARB, diuretic, BB +/- digoxin)

Outcomes
1. all cause death
2. hospitalization
3. sudden cardiac death
4. renal failure
5. hyperkalaemia
6. QoL</td></tr>
</table>

Chronic heart failure update appendices (except E,F,G,M)

D: REVIEW STRATEGY subgroups
Chronic heart failure (include post MI)
Renal impairment
E. EQUALITIES ISSUES
Possible subgroups may be: different age groups; Different ethnicities; male/female

ARB1: Efficacy and safety of angiotensin II receptor antagonists

<table>
<tr><td colspan="5">REVIEW PROTOCOL GDG4</td></tr>
<tr><td colspan="5">A: REVIEW QUESTION: ARB1
W hat is the efficacy and safety of angiotensin-II receptor antagonists (ARBS) in comparison to placebo in the medical management of adults with heart failure?
B: OBJECTIVES:
To evaluate the use of these agents in adults with heart failure. To identify new evidence since previous guideline.</td></tr>
<tr><td colspan="5">C: SEARCH CRITERIA AND PICO</td></tr>
<tr><td>Population

✓ All Chronic Heart failure

☐ Other

Exclusions: right heart failure due to
Respiratory disease</td><td>Demographics

☐ All
✓ Adults only
Age:
☐ Children only
Age range:

Sex:
Ethnic group:</td><td>Study types

✓ SRs
✓ RCTs
☐ C/C Studies
☐ Obs Studies
☐ Cases
☐Diagnostic studies
☐ Prognostic studies</td><td>Limits
Dates:

☐ All years
☐ 1966-
✓ 1986-
☐ 1995-

Language:
✓English</td><td>Databases

✓ M/E/Coch
✓ CINAHL
☐ BNI
☐ PsycInfo
☐ AMED
☐ HMIC
☐ Other</td></tr>
<tr><td colspan="3">Intervention (OR diagnostic procedure or prognostic factors)

Angiotensin-II receptor antagonists/blockers
ARBs
Candesartan valsartan losartan irbesartan eprosartan olmesartan telmisartan</td><td colspan="2">Comparison
placebo

Outcomes
1. composite score (death and hospitalization) up to 5 yrs
2. hypotension
3. renal failure
4. hyperkalaemia
5. qol
6. NYHA class</td></tr>
</table>

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Chronic heart failure update appendices (except E,F,G,M)

D: REVIEW STRATEGY

Note: Papers included in ARB2 will not be included here

Subgroups: Populations to be identified:

patients with PLVEF (preserved left ventricular ejection fraction)

E. EQUALITIES ISSUES

Possible subgroups may be:

Different ethnicities; male/female; Different age groups

ARB2: Efficacy and safety of ARBs + ACEI

<table>
<tr><td colspan="5">REVIEW PROTOCOL GDG4</td></tr>
<tr><td colspan="5">A: REVIEW QUESTION: ARB2

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

B: OBJECTIVES:

To evaluate the use of these agents in adults with heart failure already taking an ACE inhibitor</td></tr>
<tr><td colspan="5">C: SEARCH CRITERIA AND PICO</td></tr>
<tr><td>Population

✓ All Chronic Heart failure

☐ Other

Exclusions: right heart failure due to

Respiratory disease</td><td>Demographics

☐ All
✓ Adults only
Age:
☐ Children only
Age range:

Sex:
Ethnic group:</td><td>Study types

✓ SRs
✓ RCTs
☐ C/C Studies
☐ Obs Studies
☐ Cases
☐Diagnostic studies
☐ Prognostic studies</td><td>Limits
Dates:

☐ All years
☐ 1966-
✓ 1986-
☐ 1995-

Language:
✓English</td><td>Databases

✓ M/E/Coch
✓ CINAHL
☐ BNI
☐ PsycInfo
☐ AMED
☐ HMIC
☐ Other</td></tr>
<tr><td colspan="3">Intervention (OR diagnostic procedure or prognostic factors)

Angiotensin-II receptor antagonists/blockers

ARB

Candesartan valsartan losartan irbesartan eprosartan olmesartan telmisartan

+ ACE I</td><td colspan="2">Comparison

a)ACE I + placebo

b)Placebo + ACEI + BB

Outcomes

1. composite score (death and hospitalization up to 5 yrs)

2. renal failure

3. qol

4. NYHA class</td></tr>
</table>

Formatted: German (Germany)

D: REVIEW STRATEGY

Subgroups:

Populations to be identified:

Patients with LVSD

E. EQUALITIES ISSUES

Possible subgroups may be:

Different age groups; Different ethnicities; male/female

BB: Efficacy and safety of beta blockers

<table>
<tr><td colspan="5">REVIEW PROTOCOL GDG3</td></tr>
<tr><td colspan="5">A: REVIEW QUESTION: BB
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?
B: OBJECTIVES:
To assess the role of beta blockers in people with heart failure especially in the following two sub-populations; elderly people; non LVSD population</td></tr>
<tr><td colspan="5">C: SEARCH CRITERIA AND PICO</td></tr>
<tr><td>Population

✓ All Chronic Heart failure

☐ Other

Exclusions: right heart failure due to
Respiratory disease</td><td>Demographics

☐ All
✓ Adults only
Age:
☐ Children only
Age range:

Sex:
Ethnic group:</td><td>Study types

✓ SRs
✓ RCTs
✓ C/C Studies
☐ Obs Studies
☐ Cases
☐Diagnostic studies
☐ Prognostic studies</td><td>Limits
Dates:

☐ All years
☐ 1966-
✓ 1986-
☐ 1995-
☐2002-

Language:
✓English</td><td>Databases

✓ M/E/Coch
✓ CINAHL
☐ BNI
☐ PsycInfo
☐ AMED
☐ HMIC
☐ Other</td></tr>
<tr><td colspan="3">Intervention (OR diagnostic procedure or prognostic factors)

beta blockers /b-adrenoceptor antagonists
Metoprolol
Carvedilol
Bisoprolol
Nebivolol</td><td colspan="2">Comparison
Placebo
Optimal medical management
Selective vs non-selective BBs
BBs then ACEI vs ACEI then BB
(but also see sub-groups below)</td></tr>
<tr><td colspan="3"></td><td colspan="2">Outcomes
1. all cause death up to 5 yrs
2. all cause hospitalization
3. sudden death
4. QoL
5. Adverse event</td></tr>
</table>

D: REVIEW STRATEGY

Subgroups:

Populations to be identified:

The elderly (BB v placebo)

Non LVSD (BB v placebo)

- all heart failure (selective v non selective BBs, BB then ACEI vs ACEI vs BB)

E. EQUALITIES ISSUES

Possible subgroups may be:

Different age groups; Different ethnicities; male/female

ISO: Efficacy and safety of isosorbide/hydralazine

<table>
<tr><td colspan="5">REVIEW PROTOCOL GDG2</td></tr>
<tr><td colspan="5">A: REVIEW QUESTION: ISO

What is the efficacy and safety of isosorbide /hydralazine in comparison to a) placebo b) ACE inhibitor, c) placebo + optimal medical management in the medical management of adults with heart failure?

B: OBJECTIVES:

To estimate the usefulness of isosorbide/hydralazine as a therapy in HF especially in people with renal failure and in the black population</td></tr>
<tr><td colspan="5">C: SEARCH CRITERIA AND PICO</td></tr>
<tr><td>Population

✓ All Chronic Heart failure

☐ Other

Exclusions: right heart failure due to
Respiratory disease</td><td>Demographics

☐ All
✓ Adults only
Age:
☐ Children only
Age range:

Sex:
Ethnic group:</td><td>Study types

✓ SRs
✓ RCTs
☐ C/C Studies
☐ Obs Studies
☐ Cases
☐ Diagnostic studies
☐ Prognostic studies</td><td>Limits
Dates:

✓All years
☐ 1966-
☐ 1980-
☐1995-
☐ 2002-

Language:
✓English</td><td>Databases

✓ M/E/Coch
✓ CINAHL
☐ BNI
☐ PsycInfo
☐ AMED
☐ HMIC
☐ Other</td></tr>
<tr><td colspan="3">Intervention (OR diagnostic procedure or prognostic factors)

Isosorbide dinitrate
Hydralazine
Combination isosorbide/hydralazine</td><td colspan="2">Comparison
Placebo
ACE I
Placebo +optimal</td></tr>
</table>

	Outcomes 1. cardiovascular death at 1 yr 2. cardiovascular death at 5 yrs 3 all cause death at 1 yr 4. all cause death at 5 yrs 5. unplanned admission 6. qol a) disease specific b) general 7. exercise tolerance 8. hospitalization for HF
D: REVIEW STRATEGY Restrict to RCT, SRs May need to perform original meta-analysis Subgroups: Black population, patients with renal failure E. EQUALITIES ISSUES Possible subgroups may be: Different age groups; Different ethnicities (see review strategy) ; male/female	

MONIT: Efficacy and safety of telemonitoring

<table>
<tr><td colspan="5">REVIEW PROTOCOL GDG</td></tr>
<tr><td colspan="5">A: REVIEW QUESTION: MONIT
What is the efficacy and safety of patient telemonitoring in comparison to outpatient monitoring for adults with chronic heart failure?
B: OBJECTIVES:
To assess the role of different types of patient monitoring</td></tr>
<tr><td colspan="5">C: SEARCH CRITERIA AND PICO</td></tr>
<tr><td>Population

✓ All Chronic Heart failure

☐ Other

Exclusions: right heart failure due to
Respiratory disease</td><td>Demographics

☐ All
✓ Adults only
Age:
☐ Children only
Age range:

Sex:
Ethnic group:</td><td>Study types

✓ SRs
✓ RCTs
✓ C/C Studies
✓ Obs Studies
☐ Cases
☐Diagnostic studies
☐ Prognostic studies</td><td>Limits
Dates:

☐ All years
☐ 1966-
✓ 1986-
☐ 1995-
☐2002-

Language:
✓English</td><td>Databases

✓ M/E/Coch
✓ CINAHL
☐ BNI
☐ PsycInfo
☐ AMED
☐ HMIC
☐ Other</td></tr>
<tr><td colspan="3">Intervention (OR diagnostic procedure or prognostic factors)

telemonitoring
for:
blood pressure
weight
swelling</td><td colspan="2">Comparison
Outpatient monitoring

Outcomes
1. all cause death up to 5 yrs
2. planned hospitalization
3. unplanned hospitalization
4. qol</td></tr>
</table>

D: REVIEW STRATEGY

Subgroups:

Populations to be identified: appropriateness/ language barrier issues

Subgroup according to intervention given

E. EQUALITIES ISSUES

Possible subgroups may be:

Different age groups; Different ethnicities; male/female

REHAB: Efficacy and safety of exercise based cardiac rehabilitation

<table>
<tr><td colspan="5">REVIEW PROTOCOL GDG5</td></tr>
<tr><td colspan="5">A: REVIEW QUESTION: REHAB
What is the safety and efficacy of exercise based cardiac rehabilitation in adults with chronic heart failure?
B: OBJECTIVES:
To assess the role of exercise based cardiac rehabilitation in adults with chronic heart failure</td></tr>
<tr><td colspan="5">C: SEARCH CRITERIA AND PICO</td></tr>
<tr><td>Population

✓ All Chronic Heart failure

☐ Other

Exclusions: right heart failure due to
Respiratory disease</td><td>Demographics

☐ All
✓ Adults only
Age:
☐ Children only
Age range:

Sex:
Ethnic group:</td><td>Study types

✓ SRs
✓ RCTs
✓ C/C Studies
✓ Obs Studies
☐ Cases
☐Diagnostic studies
☐ Prognostic studies</td><td>Limits
Dates:

☐ All years
☐ 1966-
☐ 1986-
☐ 1995-
✓2002-

Language:
✓English</td><td>Databases

✓ M/E/Coch
✓ CINAHL
☐ BNI
☐ PsycInfo
☐ AMED
☐ HMIC
☐ Other</td></tr>
<tr><td colspan="3">Intervention (OR diagnostic procedure or prognostic factors)

Exercise programmes
Cardiac rehabilitation programmes
Exercise based rehabilitation</td><td colspan="2">Comparison
Standard care

Outcomes
1. all cause death up to 5 yrs
2. all cause hospitalization
3. qol (MLWHFQ)
4. improvement in exercise tolerance (6 min walking test)
5. improvement in NYHA functional class</td></tr>
</table>

D: REVIEW STRATEGY

Subgroups:

Populations to be identified: All chronic heart failure

E. EQUALITIES ISSUES

Possible subgroups may be :

Different age groups; different ethnicities; male/female

Appendix D Search strategies

Search strategies used for the Chronic Heart Failure Guideline partial update are outlined below.

Searches were run in Medline, Embase (OVID), the Cochrane Library and Cinahl (EBSCO) according to the NICE Guidelines Manual 2007 http://www.nice.org.uk/media/FA1/59/GuidelinesManualChapters2007.pdf and 2009 http://www.nice.org.uk/media/5F2/44/The_guidelines_manual_2009_-_All_chapters.pdf .

Searches were constructed using the PICO format.

Population AND Intervention AND Comparison (if there was one) AND study type search filters (if used)

Outcomes were not used in the search strategy. Whilst correct at the time of writing strategies may need editing for future use in light of changes in terminology and index headings.

The cut off date for searches for this partial update was **9 October 2009**

Chronic Heart Failure Population Search strategies

Medline search terms

1. Heart Failure/
2. Cardiomyopathy, Dilated/
3. Shock, Cardiogenic/
4. exp Ventricular Dysfunction/
5. Cardiac Output, Low/
6. ((heart or cardiac or myocardial) adj2 (failure or decompensation)).ti.
7. ((congestive or chronic) adj2 " heart failure").ti,ab.
8. ((dilated or congestive) adj2 cardiomyopath$).ti.
9. "cardiogenic shock".ti.
10. ((ventricular or ventricle$) adj2 (failure or insufficien$ or dysfunction$)).ti.
11. (("left ventricular" or "left ventricle") adj2 (failure or insufficien$ or dysfunction$))ti,ab.
12. lvsd.ti,ab.
13. or/1-12
14. letter.pt.
15. letter/
16. letter$/
17. editorial.pt.
18. historical article.pt.
19. anecdote.pt.

20 commentary.pt.
21. note.pt.
22. case report/
23. case report$.pt.
24. case study/
25. case study.pt.
26. exp animal/ not human/
27. nonhuman/
28. exp Animal Studies/
29. Animals, Laboratory/
30. exp experimental animal/
31. exp animal experiment/
32. exp animal model/
33. exp Rodentia/
34. exp rodents/
35. or/14-34
36. 13 not 35
37. limit 36 to English language

Embase search terms

1. *heart failure/ or *acute heart failure/ or *cardiogenic shock/ or *diastolic dysfunction/ or *forward heart failure/ or *high output heart failure/ or *systolic dysfunction/
2. *Congestive Cardiomyopathy/ or exp *Congestive Heart Failure/
3. exp *Heart Ventricle Failure/
4. ((heart or cardiac or myocardial) adj2 (failure or decompensation)).ti.
5. ((congestive or chronic) adj2 " heart failure").ti,ab.
6. ((dilated or congestive) adj2 cardiomyopath$).ti.
7. "cardiogenic shock".ti.
8. ((ventricular or ventricle$) adj2 (failure or insufficien$ or dysfunction$)).ti.
9. (("left ventricular" or "left ventricle") adj2 (failure or insufficien$ or dysfunction$)).ti,ab.
10. lvsd.ti,ab.
11. or/1-10
12. letter.pt.
13. letter/
14. letter$/
15. editorial.pt.
16. historical article.pt.
17. anecdote.pt.

Chronic heart failure update appendices (except E,F,G,M)

18. commentary.pt.
19. note.pt.
20. case report/
21. case report$.pt.
22. case study/)
23. case study.pt. (0)
24. exp animal/ not human/
25. nonhuman/
26. exp Animal Studies/
27. Animals, Laboratory/
28. exp experimental animal/
29. exp animal experiment/
30. exp animal model/
31. exp Rodentia/
32. exp rodents/
33. or/12-32
34. 11 not 33
35. limit 34 to english language

Cinahl search terms

S1	(MH "Heart Failure, Congestive+") or (MH "Shock, Cardiogenic") or MH "Ventricular Dysfunction+")
S2	TI heart N2 failure or TI heart N2 decompensation or TI cardiac N2 failure or TI cardiac N2 decompensation or TI myocardial N2 decompensation or TI myocardial N2 failure or TX congestive N2 "heart failure" or TX chronic N2 "heart failure" or TI dilated N2 cardiomyopath* or TI congestive N2 cardiomyopath* or TI cardiogenic N2 shock or TX LVSD
S3	TX ventricular N2 failure or TX ventricular N2 dysfunction or TX ventricular N2 insufficiency or TX ventricle N2 failure or TX ventricle N2 dysfunction or TX ventricle N2 insufficiency
S4	S1 or S2 or S3 or S4
S5	(MH "Case Studies") or (MH "Mammals+") or PT case study or PT commentary or PT anecdote or PT editorial or PT letter or (MH "Rodents+") or (MH "Animals+") or (MH "Animals, Laboratory") or (MH "Animal Studies") or (MH "Models, Biological")
S6	S4 NOT S5 LIMIT English language

Cochrane search terms

1. MeSH descriptor Heart Failure explode all trees
2. MeSH descriptor Cardiomyopathy, Dilated, this term only
3. MeSH descriptor Shock, Cardiogenic, this term only
4. MeSH descriptor Ventricular Dysfunction explode all trees
5. MeSH descriptor Cardiac Output, Low, this term only
6. ((heart or cardiac or myocardial) NEXT (failure or decompensation)):ti
7. ((congestive or chronic) NEXT ("heart failure")):ti,ab

8. ((dilated or congestive) NEXT cardiomyopath*):ti
9. ("cardiogenic shock"):ti
10. ((ventricular or ventricle) NEXT (failure or insufficienc* or dysfunction*)):ti
11. lvsd:ti,ab
12. (("left ventricular" or "left ventricle") NEXT (failure or insufficienc* or dysfunction*)):ti,ab
13. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)

Generic study type search filters

Medline and Embase systematic reviews search terms

1. "review"/ or review.pt. or review.ti.
2. (systematic or evidence$ or methodol$ or quantitativ$) ti,ab.
3. 1 and 2
4. meta-analysis.pt.
5. Meta-Analysis/
6. exp Meta-Analysis as Topic/
7. "systematic review"/
8. (meta-analy$ or metanaly$ or metaanaly$ or meta analy$).ti,ab.
9. ((systematic$ or evidence$ or methodol$ or quantitativ$) adj3 (review$ or survey$ or overview$)).ti,ab.
10. ((pool$ or combined or combining) adj2 (data or trials or studies or results)).ti,ab.
11. or/3-10

Medline randomised controlled trials search terms

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. double-blind method/ or random allocation/ or single-blind method/
4. exp Clinical Trial/
5. exp Clinical Trials as Topic/
6. clinical trial.pt.
7. random$.ti,ab.
8. ((clinical$ or control$) adj3 (trial$ or study or studies)).ti,ab
9. ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).ti,ab.
10. Placebos/ or placebo$.ti,ab.
11. (volunteer$ or "control group" or controls). ti,ab.
12. Cross-Over Studies/
13. ((crossover or cross-over or cross over) adj2 (design$ or stud$ or procedure$ or trial$)).ti,ab.

14. or/1-13

Medline observational studies search terms

1. Research Design/ or Comparative Studies/ or nonexperimental studies/
2. exp Evaluation Studies/ or evaluation studies as topic/ or follow-up studies/ or exp prospective studies/ or retrospective studies/
3. exp Cohort studies/ or cohort analysis/ or longitudinal studies/
4. exp Case-Control Studies/ or control group/
5. exp Cross-Sectional Studies/
6. (case-control or case control).ti,ab
7. (observ$ or cohort$ or follow-up or follow up or longitudinal or prospective or retrospective or comparative) adj1 (stud$ or research or analys$).ti,ab
8. or/1-7

Medline diagnostic studies search terms

1. exp Heart Failure/di [Diagnosis]
2. diagnosis/ or diagnosis, differential/ or "diagnostic techniques and procedures"/ or diagnostic techniques, cardiovascular/ or early diagnosis/
3. "Sensitivity and Specificity"/
4. detection.ti,ab.
5 specificity.ti,ab.
6. diagnos$.ti,ab.
7 or/1-6

Medline prognostic studies search terms

1. exp prognosis/
2. (prognos$ or predict$).ti,ab
3. 1 or 2

Embase randomised controlled trials search terms

1. controlled study/ or randomized controlled trial/
2. Clinical Trial/
3. clinical study/ or major clinical study/ or clinical trial/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/
4. Placebo/
5. "Double Blind Procedure"/
6. ((clinical$ or control$) adj3 (trial$ or study or studies)).ti,ab
7. "Clinical Article"/
8. Randomization/

9. placebo.ti,ab.
10. randomi$.ti,ab.
11. ((singl* or double$ or triple$ or treble$) adj5 (blind$ or mask$)).ti,ab.
12. (volunteer$ or "control group" or controls). ti,ab.
13. crossover procedure/
14. ((crossover or cross-over or cross over) adj2 (design$ or stud$ or procedure$ or trial$)).ti,ab.
15. or/1-14

Embase observational studies search terms

1. Cohort Analysis/
2. Longitudinal Study/
3. Prospective Study/ or retrospective study/
4. Comparative study/ or observational study/
5. (cross-sectional or cross sectional).ti,ab
6. (observ$ or cohort$ or follow-up or follow up or longitudinal or prospective or retrospective or comparative) adj1 (stud$ or research or analys$).ti,ab
7. Case Control Study/ or control group/
8. ("case control" or case-control).ti,ab
9. or/1-8

Embase diagnostic studies search terms

1. exp Heart Failure/di [Diagnosis]
2. diagnosis/ or diagnosis, differential/ or "diagnostic techniques and procedures"/ or diagnostic techniques, cardiovascular/ or early diagnosis/
3. "Sensitivity and Specificity"/
4. (detection or diagnos$).ti,ab.
5. specificity.ti,ab.
6. or/1-5

Embase prognostic studies search terms

1. prognosis/
2. (prognos$ or predict$).ti,ab

3.1 or 2

Cinahl and Cochrane generic study type search filters

None used **except** in Question DIAG

Cinahl diagnostic studies search terms (DIAG only)

Chronic heart failure update appendices (except E,F,G,M)

S1 diagnos* or specificity

S2 (MH "Sensitivity and Specificity")

S3 (MH "Diagnostic Tests, Routine") or (MH "Clinical Assessment Tools")

S4 (MH "Diagnosis") or (MH "Diagnosis, Cardiovascular") or (MH "Diagnosis, Differential")

S5 S1 or S2 or S3 or S4

Cochrane diagnostic studies search terms (DIAG only)

1. MeSH descriptor Heart Failure explode all trees with qualifier: DI
2. MeSH descriptor Diagnosis, this term only
3. MeSH descriptor Diagnosis, Differential, this term only
4. MeSH descriptor Early Diagnosis, this term only
5. MeSH descriptor Diagnostic Techniques and Procedures, this term only
6. MeSH descriptor Diagnostic Techniques, Cardiovascular, this term only
7. MeSH descriptor Sensitivity and Specificity, this term only
8. (diagnos* or specificity):ti,ab
9. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)

Clinical Questions and intervention search strategies

DIAG: What is the diagnostic accuracy of a collection of symptoms and signs,including any scoring systems vs gold standard in the diagnosis of heart failure?

Population	Intervention	Comparison	Filters used	Date parameters
Chronic Heart failure	Symptoms/ signs scoring systems		SR	All years

Intervention search strategies

Medline search terms

1. ((framingham or boston or duke or killip or MICE or clinical) adj2 (criteria or scor$ or class or system$)).ti,ab.
2. ((scor$ or diagnost$) adj2 (system$ or tool$ or criteria)).ti,ab.
3. (symptom$ adj5 sign$).ti,ab.
4. (jugular adj3 (pressure or pulse)).ti,ab.
5. JVP.ti,ab.
6. ((venous or vein) adj2 distension).ti,ab.
7. exp Heart Sounds/

8. (heart adj2 sound$).ti,ab.
9. (gallop or oscillation$ or tachypnea or murmur$ or rale$ or crackle$ or crepitation$).ti,ab.
10. exp Cardiomegaly/
11. cardiomegal$.ti,ab.
12. ((displaced or beat) adj2 apex).ti,ab.
13. (apical adj2 impulse).ti,ab.
14. exp Edema/
15. (fluid adj2 retention).ti,ab.
16. exp Fatigue/
17. (edema or oedema or fatigue or asthenia or malaise or tired$ or dyspnea or dyspnoea or SOB or breathless$ or orthopnoea or orthopnea).ti,ab.
18. exp Dyspnea/
19. (venous adj2 insufficicien$).ti,ab.
20. ((swelling or swollen) adj2 (leg$ or ankle$ or limb$ or extremit$)).ti,ab.
21. Physical Examination/
22. ((physical or clinical) adj2 examination).ti,ab.
23. Exercise Test/ or Exercise Tolerance/
24. (effort adj2 intolerance).ti,ab.
25. or/1-24

Embase search terms

1. ((framingham or boston or duke or killip or MICE or clinical) adj2 (criteria or scor$ or class or system$)).ti,ab.)
2. ((scor$ or diagnost$) adj2 (system$ or tool$ or criteria)).ti,ab.
3. (symptom$ adj5 sign$).ti,ab.
4. (jugular adj3 (pressure or pulse)).ti,ab
5. JVP.ti,ab
6. ((venous or vein) adj2 distension).ti,ab.
7. exp Heart Sounds/
8. (heart adj2 sound$).ti,ab.
9. (gallop or oscillation$ or tachypnea or murmur$ or rale$ or crackle$ or crepitation$).ti,ab.
10. exp Cardiomegaly/
11. cardiomegal$.ti,ab.
12. ((displaced or beat) adj2 apex).ti,ab.
13. (apical adj2 impulse).ti,ab.
14. exp Edema/
15. (fluid adj2 retention).ti,ab.)

16. exp Fatigue/
17. (edema or oedema or fatigue or asthenia or malaise or tired$ or dyspnea or dyspnoea or SOB or breathless$ or orthopnoea or orthopnea).ti,ab.
18. exp Dyspnea/
19. (venous adj2 insufficicien$).ti,ab.
20. ((swelling or swollen) adj2 (leg$ or ankle$ or limb$ or extremit$)).ti,ab.
21. Physical Examination/
22. ((physical or clinical) adj2 examination).ti,ab.
23. Exercise Test/ or Exercise Tolerance/
24. (effort adj2 intolerance).ti,ab
25. or/1-24

Cinahl search terms

S1 (MH "Dyspnea+")

S2 duke or boston or framingham or killip or MICE or diagnos* N2 criteria or diagnos* N2 tool* or scor* N2 tool* or scor* N2 criteria

S3 heart N2 sound* or venous N2 distension or vein N2 distension or jugular N3 pressure or jugular N3 pulse or symptom* N5 sign* or scor* N2 system*

S4 apical N2 impulse or displaced N2 apex or apex N2 beat or swelling N2 ankle* or swollen N2 ankle* or swelling N2 limb* or swollen N2 limb*

S5 (JVP or gallop or oscillation* or tachypnea or murmur* or rale* or crackle* or crepitation* or cardiomegal* or edema or oedema or fatigue or asthenia or malaise or tired* or dyspnea or dyspnoea or SOD or breathless* or orthopnoea or orthopnea) or venous N2 insufficienc* or fluid N2 retention or effort N2 intolerance or exercise N2 tolerance or physical N2 examination or clinical N2 examination

S6 (MH "Heart Hypertrophy+") or (MH "Physical Examination") or (MH "Exercise Tolerance") or (MH "Heart Sounds") or (MH "Fatigue+") or (MH "Edema")

S7 S1 or S2 or S3 or S4 or S5 or S6

Cochrane search terms

1. MeSH descriptor Heart Sounds, this term only
2. MeSH descriptor Cardiomegaly explode all trees
3. MeSH descriptor Edema explode all trees
4. MeSH descriptor Fatigue explode all trees
5. MeSH descriptor Dyspnea explode all trees
6. MeSH descriptor Physical Examination, this term only
7. MeSH descriptor Exercise Tolerance explode all trees
8. ((effort or exercise) NEXT (intolerance or tolerance)):ti,ab
9. ((physical or clinical) NEXT examination):ti,ab
10. ((swelling or swollen) NEXT (leg* or ankle* or limb* or extremit*)):ti,ab
11. (venous NEXT insufficiency):ti,ab
12. (cardiomegal* or edema or oedema or fatigue or asthenia or malaise or tired* or dyspnea or dyspnoea or SOB or breathless* or orthopnea or orthopnoea or JVP or gallop or oscillation* or tachypnea or murmur* or rale* or crackle* or crepitation*):ti,ab

Chronic heart failure update appendices (except E,F,G,M)

13. (fluid NEXT retention):ti,ab
14. (apical NEXT impulse):ti,ab
15. ((displaced or beat) NEXT apex):ti,ab
16. (heart NEXT sound*):ti,ab
17. ((venous or vein) NEXT distension):ti,ab
18. (jugular NEXT (pressure or pulse)):ti,ab
19. (symptom* NEAR sign*):ti,ab
20. ((scor* or diagnost*) NEXT (criteria or tool* or system*)):ti,ab
21. ((framingham or boston or duke or killip or MICE or clinical) NEXT (criteria or scor* or class* or system*)):ti,ab
22. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21)

BNP1: What is the accuracy of natriuretic peptides vs gold standard in the diagnosis of heart failure?

BNP2: What is the accuracy of echocardiography vs natriuretic peptides in the diagnosis of diastolic dysfunction?

BNP3: Does serial BNP monitoring (guided therapy) improve outcome compared to standard care in adults with chronic heart failure?

Questions BNP 1, 2 and 3 were run as one search

Population	Intervention	Comparison	Filters used	Date parameters
Chronic heart failure	Natriuretic peptides		SR, RCT, observational, diagnostic, prognostic	2002-2009 (2000-2009 for BNP3)

<u>Intervention search strategies</u>

Medline search terms

1. exp Natriuretic Peptide, Brain/
2. (natriuretic adj2 peptide$).ti,ab.
3. (BNP or NT-proBNP or NT-pro BNP or NT-BNP).ti,ab.
4. (nesiritide or natrecor).ti,ab.
5. (natriuretic adj2 factor$).ti,ab.
6. *Natriuretic Peptides/

7. 1 or 2 or 3 or 4 or 5 or 6

Embase search terms

1. *natriuretic factor/ or *amino terminal pro brain natriuretic peptide/ or *brain natriuretic peptide/ or *nesiritide/
2. (BNP or NT-proBNP or NT-pro BNP or NT-BNP).ti,ab.
3. (nesiritide or natrecor).ti,ab.
4. (natriuretic adj2 peptide$).ti,ab.
5. 1 or 2 or 3 or 4

Cinahl search terms

S1 ((MH "Natriuretic Peptides") or (MH "Natriuretic Peptide, Brain")) or TX BNP or TX probnp or TX nesiritide or TX natrecor or TX natriuretic N2 peptide*

Cochrane search terms

1. MeSH descriptor Natriuretic Peptide, Brain, this term only
2. MeSH descriptor Natriuretic Peptides, this term only
3. (BNP or NT-proBNP or NT-pro BNP or NT-BNP):ti,ab
4. (natriuretic NEAR/4 peptide*):ti,ab
5. (nesiritide or natrecor):ti,ab
6. (#1 OR #2 OR #3 OR #4 OR #5)

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

Population	Intervention	Comparison	Filters used	Date parameters
Chronic heart failure	ACE Inhibitors		SR, RCT	1986-2009

<u>Intervention search strategies</u>

Medline search terms

1 exp *Angiotensin-Converting Enzyme Inhibitors/
2. (("angiotensin-converting enzyme" or ACE) adj2 (inhibitor$ or antagonist$)).ti.)
3. (captopril or capoten or cilazapril or vascace or enalapril or innovace or fosinopril or staril or imidapril or tanatril or lisinopril or carace or zestril or perdix or moexipril or perindopril or coversyl or quinapril or tritace or triapin or trandolapril or gopten).ti.

4. or/1-3

Embase search terms

1. (("angiotensin-converting enzyme" or ACE) adj2 (inhibitor$ or antagonist$)).ti.
2. (captopril or capoten or cilazapril or vascace or enalapril or innovace or fosinopril or staril or imidapril or tanatril or lisinopril or carace or zestril or perdix or moexipril or perindopril or coversyl or quinapril or tritace or triapin or trandolapril or gopten).ti.
3. exp *Dipeptidyl Carboxypeptidase Inhibitor/
4. or/1-3

Cinahl search terms

S1 (MM "Angiotensin-Converting Enzyme Inhibitors+")

S2 TI angiotensin-converting enzyme N2 inhibitor* or TI angiotensin-converting enzyme N2 antagonist* or TI ACE N2 inhibitor*

S3 TI captopril or cilazapril or enalapril or fosinopril or imidapril or lisinopril or moexipril or perindopril or coversyl or quinapril or ramipril or trandolapril

S4 S1 or S2 or S3

Cochrane search terms

1. MeSH descriptor Angiotensin-Converting Enzyme Inhibitors explode all trees with qualifiers: TH,DE,DT,AD,AE,TU,CO,CT,TO
2. (captopril or capoten or cilazapril or vascace or enalapril or innovace or fosinopril or staril or imidapril or tanatril or lisinopril or carace or zestril or moexipril or perdix or perindopril or coversyl or quinapril or accupro or ramipril or tritace or triapin or trandolapril or gopten):ti
3. ("angiotensin-converting enzyme" or ACE) NEXT (inhibitor* or antagonist*):ti
4. (#1 or #2 or #3)

ALDO: 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?

Population	Intervention	Comparison	Filters used	Date parameters
Chronic heart failure	Aldosterone antagonists		SR, RCT	1986-2009

Intervention search strategies

Medline search terms

1. exp Aldosterone Antagonists/
2. eplerenone.ti,ab.

3. spironolactone.ti,ab.
4. (inspra or aldactone).ti,ab.
5. (aldosterone adj2 antagonist$).ti,ab.
6. (ALDO or ALDOs).ti,ab.
7. or/1-6

Embase search terms

1. exp *Aldosterone Antagonist/
2. (aldosterone adj2 antagonist$).ti,ab.
3. spironolactone.ti,ab.
4. (eplerenone or aldactone or inspra).ti,ab.
5. (ALDO or ALDOs).ti,ab.
6. or/1-5

Cinahl search strategy

S1 (MH "Aldosterone Antagonists+") or aldosterone N3 antagonist* or
(spironolactone or aldactone or eplerenone or aldactone or ALDO or ALDOs or inspra)

Cochrane search terms

1. MeSH descriptor Aldosterone Antagonists explode all trees
2. (aldosterone NEXT antagonist*):ti,ab
3. (spironolactone or eplerenone or aldactone or inspa):ti,ab
4. (ALDO or ALDOs):ti,ab
5. (#1 or #2 or #3 or #4)

ARB1: What is the efficacy and safety of angiotensin-II receptor antagonists (ARBs) in comparison to placebo in the medical management of adults with heart failure?

ARB2: What is the efficacy and safety of a)ARB plus ACE I in comparison to ACE I plus placebo b) ARB and ACEI and BB vs placebo and ACEI and BB in the medical management of adults with heart failure?

Questions ARB1 and ARB2 were run as one search

Population	Intervention	Comparison	Filters used	Date parameters
Chronic heart failure	ARBS		SR,RCT	1986-2009

Chronic heart failure update appendices (except E,F,G,M)

Intervention search strategies

Medline search terms

1. exp Angiotensin II Type 1 Receptor Blockers/
2. exp Receptors, Angiotensin/ai [Antagonists & Inhibitors]
3. (candesartan or valsartan).ti,ab.
4. (angiotensin adj3 receptor adj3 (antagonist$ or blocker$)).ti,ab.
5. (ARB or ARBs).ti,ab.
6. amias.ti,ab.
7. (teveten or aprovel or cozaar or cozaar-comp or diovan or co-diovan or micardis or olmetec or coaprovel or losartan or eprosartan or irbesartan or olmesartan or telmisartan or saralasin).ti.
8. or/1-7

Embase search terms

1. exp *Angiotensin Receptor Antagonist/
2. candesartan/ or valsartan/)
3. (candesartan or valsartan).ti,ab.
4. (ARB or ARBs or amias).ti,ab.
5. (angiotensin adj3 receptor adj3 (antagonist$ or blocker$)).ti,ab.
6. (teveten or aprovel or cozaar or cozaar-comp or diovan or co-diovan or micardis or olmetec or coaprovel or losartan or eprosartan or irbesartan or olmesartan or telmisartan or saralasin).ti.
7. or/1-6

Cinahl search terms

S1 (MH "Angiotensin II Type I Receptor Blockers+") or (MH "Angiotensins+/AI")

S2 TI losartan or eprosartan or irbesartan or olmesartan or telmisartan or angiotensin N2 receptor N2 antagonist* or angiotensin N2 receptor N2 blocker* or candesartan or valsartan or amias or ARB or ARBs

S3 S1 or S2

Cochrane search terms

1. MeSH descriptor Angiotensin II Type 1 Receptor Blockers explode all trees
2. MeSH descriptor Receptors, Angiotensin explode all trees with qualifier: AI
3. (ARB or ARBs or amias or candesartan or valsartan or diovan):ti,ab
4. ((angiotensin NEAR/2 receptor) NEAR/2 (antagonist* or blocker*)):ti,ab
5. (losartan or eprosartan or irbesartan or olmesartan or telmisartan or saralasin):ti
6. (#1 or #2 or #3 or #4 or #5)

BB: 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?

Population	Intervention	Comparison	Filters used	Date parameters
Chronic heart failure	Beta-blockers		SR,RCT	1986-2009

Intervention search strategies

Medline search terms

1. *adrenergic beta-antagonists/ or exp bisoprolol/ or exp metoprolol/
2. (carvedilol or metoprolol or bisoprolol or nebivolol).ti,ab.
3. ((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) adj3 (blockade or blocker$ or blocking or antagonist$)).ti.
4. (beta adj2 (blocker$ or blockade)).ti.
5. or/1-4

Embase search terms

1. *beta adrenergic receptor blocking agent/ or *bisoprolol/ or *bisoprolol fumarate/ or *bisoprolol fumarate plus hydrochlorothiazide/ or *carvedilol/ or *metoprolol/ or *metoprolol fumarate/ or *metoprolol succinate/ or *metoprolol tartrate/ or *nebivolol/
2. (carvedilol or metoprolol or bisoprolol or nebivolol).ti,ab.
3. (beta adj2 (blocker$ or blockade)).ti.
4. ((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) adj3 (blockade or blocker$ or blocking or antagonist$)).ti.
5. or/1-4

Cinahl search terms

S1 ((MH "Adrenergic Beta-Antagonist") or (MH "Carvedilol") or (MH "Metoprolol")) or (carvedilol or metoprolol or bisoprolol or nebivolol) or TI beta N2 block* or TI beta-adrenoceptor N2 block* or TI beta-adrenoceptor N2 antagonist* or TI b-adrenoceptor N2 block* or TI b-adrenoceptor N2 antagonist* or TI beta-adrenergic N2 block* or TI beta-adrenergic N2 antagonist*

Cochrane search terms

1. MeSH descriptor Adrenergic beta-Antagonists, this term only with qualifiers: AD,AE,DE,DT,TU,TH
2. MeSH descriptor Bisoprolol, this term only
3. MeSH descriptor Metoprolol, this term only
4. (metoprolol or bisoprolol or nebivolol or carvedilol):ti,ab
5. (beta NEXT (blocker$ or blockade)):ti

6. ((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) NEXT (block* or antagonist*)):ti
7. (#1 or #2 or #3 or #4 or #5 or #6)

ISO: What is the efficacy and safety of isosorbide/hydralazine combination in comparison to a) placebo b) ACE I c) placebo and optimal medical management in the medical management of adults with heart failure?

Population	Intervention	Comparison	Filters used	Date parameters
Chronic heart failure	Isosorbide/ hydralazine combination		SR,RCT	All years

Intervention search strategies

Medline search terms

1. exp Hydralazine/ or exp Isosorbide/
2. (hydralazine$ or isosorbide$).ti,ab.
3. (depressan or dihydralazine or dihydrallazine or dihydrazinophthalazin or hydrallazin or hydrazinophthalazine or angitak or cedocard or retard-20 or apressin or nepresol or apressoline or apresoline).ti,ab.
4. (dianhydrosorbitol or dilatrate or iso-bid or iso bid or isobid or isodinit or isoket or sorbonit or isomak or isordil or isotrate or nitrosorbide or cardonit or sorbitrate).ti,ab.
5. bidil.ti,ab.
6. or/1-5

Embase search terms

1. *isosorbide/ or *isosorbide derivative/ or *isosorbide dinitrate/
2. *hydralazine plus isosorbide dinitrate/
3. *Hydralazine/
4. isosorbide$.ti,ab.
5. (depressan or dihydralazine or cedocard or retard-20 or angitak or dihydrallazine or dihydrazinophthalazin or hydrallazin or hydrazinophthalazine or apressin or nepresol or apressoline or apresoline).ti,ab.
6. (bidil or disorlon).ti,ab.
7. hydralazine$.ti,ab.
8. (dilatrate or iso bid or iso-bid or isobid or dianhydrosorbitol or isodinit or isoket or sorbonit or isomak or isordil or isotrate or nitrosorbide or sorbitrate or cardonit).ti,ab.

9. or/1-8

Cinahl search terms

S1 (MH "Hydralazine") or (MH "Isosorbide Dinitrate") or (hydralazine* or isosorbide*) or (bidil or disorlon or depressen or dihydralazine or dihydrallazine or dihydrazinophthalazin or hydrallazin or apressin or nepresol or apressoline or apresoline or dilatrate or dianhydrosorbitol or iso bid or iso-bid or isobid or isodinit or isomak or sorbonit or isordil or isotrate or nitrosorbide or sorbitrate or cardonit)

Cochrane search terms

1. MeSH descriptor Isosorbide explode all trees
2. MeSH descriptor Hydralazine explode all trees
3. (isosorbide* or hydralazine* or disorlon or bidil or depressen or dihydralazine or dihydrallazine or hydrallazin or apressin or nepresol or apressoline or apresoline or dihydrazinophthalazin or hydrazonophthalizine):ti,ab
4. (dilatrate or dianhydrosorbitol or iso-bid or iso bid or isobid or isodinit or isoket or sorbonit or isomak or isordil or isotrate or nitrosorbide or sorbitrate or cardonit):ti,ab
5. (#1 or #2 or #3 or #4)

MONIT: What is the efficacy and safety of patient telemonitoring in comparison to outpatient monitoring for adults with chronic heart failure?

Population	Intervention	Comparison	Filters used	Date parameters
Chronic heart failure	telemonitoring		SR, RCT, observational	1986-2009

Intervention search strategies

Medline search terms

1. Self Care/
2. ("telemanag$" or tele-manag$ or self-manag$ or "self manag$" or selfmonitor$ or "self monitor$" or self-monitor$ or "self care" or self-care or tele-monitor$ or "tele monitor$" or telemonitor$).ti,ab.
3. (remote adj2 monit$).ti,ab.
4. Telemedicine/
5. *home care services/ and (telemetry/ or monitor$.ti,ab.))
6. or/1-5

Embase search terms

1. (self-manag$ or "self manag$" or selfmonit$ or "self monitor$" or self-monitor$ or "self care" or self-care or tele-monitor$ or "tele monitor$" or telemonitor$ or telemanag$ or tele-manag$).ti,ab.
2. home monitoring/ or self monitoring/ or telemonitoring/

3. self care/ or telehealth/ or telemedicine/ or telecardiology/
4. (remote adj2 monitor$).ti,ab.
5. *home care/ and (exp telemetry/ or monitor$.ti,ab.)
6. or/1-6

Cinahl search terms

S1 MH ("Telemedicine") or (MH "Telehealth") or (MH "Self Care")

S2 (MH "Home Health Care") and monit*

S3 (MH "Home Health Care") and (MH "telemetry")

S4 remote N1 monit* or self N1 monit* or self N1 manag* or self N1 care or telemonitor* or tele N1 monitor* or telemanag* or tele N1 manag* or selfmonitor* or selfcare

S5 S1 or S2 or S3 or S4

Cochrane search terms

1. MeSH descriptor Self Care, this term only
2. MeSH descriptor Telemedicine, this term only
3. ("self manag*" or self-manag* or "self monitor*" or self-monitor* or selfmonitor* or telemanag* or tele-manag* or "self care" or self-care or selfcare or telemanag* or tele-manag* or telemonitor* or "tele monitor*" or tele-monitor*):ti,ab
4. (remote NEXT monitor*):ti,ab
5. (#1 or #2 or #3 or #4)

REHAB: What is the efficacy and safety of exercise based cardiac rehabilitation in adults with chronic heart failure?

Population	Intervention	Comparison	Filters used	Date parameters
chronic heart failure	Rehabilitation programmes		SR,RCT, observational	2002-2009

<u>Intervention search strategies</u>

Medline search terms

1. rehabilitation/ or exp exercise therapy/
2. heart rehabilitation/
3. community based rehabilitation/
4. *"Physical Education and Training"/
5. exp *exercise/ or *physical exertion/ or *muscle training/
6. *Physical Fitness/

7. (*Exercise Test/ or *exercise tolerance/) and rehab$.ti,ab.
8. exp heart failure/rh
9. (exp *Sports/ or *community care/ or *health program/) and (exercise$ or rehab$).ti,ab.
10. rehabilitation.ti.
11. ((cardiac or heart or coronary or exercise) adj2 rehabilitation).ti,ab.
12. (rehabilitation adj2 (program$ or class$ or team$)).ti,ab.
13. exercise$.ti.
14. (exercise adj2 (therap$ or training or program$ or class$ or session$)).ti,ab.
15. (physical adj2 (fitness or education or training or activit$)).ti,ab.
16. ((aerobic or muscle or resistive) adj2 (exercise$ or training)).ti,ab.
17. Rehabilitation Nursing/
18. or/1-17

Embase search terms

1. rehabilitation/ or exp exercise therapy/ or treadmill exercise/
2. heart rehabilitation/
3. community based rehabilitation/
4. *"Physical Education and Training"/
5. exp *exercise/ or *physical exertion/ or *muscle training/
6. *Physical Fitness/
7. (*Exercise Test/ or *exercise tolerance/) and rehab$.ti,ab.
8. exp heart failure/rh
9. (exp *Sports/ or *community care/ or *health program/) and (exercise$ or rehab$).ti,ab.
10. rehabilitation.ti.
11. ((cardiac or heart or coronary or exercise) adj2 rehabilitation).ti,ab.
12. (rehabilitation adj2 (program$ or class$ or team$)).ti,ab.
13. exercise$.ti.
14. (exercise adj2 (therap$ or training or program$ or class$ or session$)).ti,ab.
15. (physical adj2 (fitness or education or training or activit$)).ti,ab.
16. ((aerobic or muscle or resistive) adj2 (exercise$ or training)).ti,ab.
17. Rehabilitation Nursing/
18. home rehabilitation/ or geriatric rehabilitation/ or rehabilitation patient/
19. or/1-18

Cinahl search strategy

S1 (MH "Physical Activity") or (MH "Physical Fitness") or (MH "Rehabilitation Nursing") or (MH "Rehabilitation, Geriatric")

S2 ((MH "Exercise Tolerance") or (MH "Exercise Test") or (MH "Exercise Test, Cardiopulmonary")) and rehab*

Chronic heart failure update appendices (except E,F,G,M)

S3 ((MM "Sports+") or (MH "Community Health Nursing") or (MH "Community Health Services") or (MH "Community Programs")) and (exercise* or rehab*)

S4 TI (rehabilitation or exercise*) or cardiac N2 rehabilitation or heart N2 rehabilitation or exercise N2 rehabilitation or rehabilitation N2 program* or exercise N2 therap* or exercise N2 training or exercise N2 therap* or physical N2 training or aerobic N2 exercise* or resistive N2 exercise or resistive N2 training

S5 S1 or S2 or S3 or S4

Cochrane search terms

1. ((cardiac or heart or coronary or exercise) NEAR/2 rehabilitat*):ti,ab
2. (exercise NEAR/2 (therap* or training or program* or class* or session*)):ti,ab
3. MeSH descriptor Rehabilitation, this term only
4. MeSH descriptor Exercise Therapy explode all trees
5. MeSH descriptor Physical Education and Training, this term only
6. MeSH descriptor Exercise explode all trees
7. MeSH descriptor Physical Exertion explode all trees
8. MeSH descriptor Physical Fitness, this term only
9. MeSH descriptor Heart Failure explode all trees with qualifier: RH
10. (rehabilitation or exercise):ti
11. (rehabilitation NEAR/2 (program* or class*)):ti,ab
12. MeSH descriptor Rehabilitation Nursing, this term only
13. (physical NEXT (fitness or education or training or activit*)):ti,ab
14. ((aerobic or resistant or resistive or muscle) NEXT (exercise* or training)):ti,ab
15. MeSH descriptor Exercise Test explode all trees
16. MeSH descriptor Exercise Tolerance explode all trees
17. MeSH descriptor Sports explode all trees
18. MeSH descriptor Community Health Services, this term only
19. exercise*:ti,ab
20. rehab*:ti,ab
21. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20)

Economics Search

Economic searches were conducted in Medline, Embase and Cochrane Library EED and HTA databases

Population	Intervention	Comparison	Filters used	Date parameters
Chronic heart failure			Economic (Medline and Embase only	2002-2009

Chronic heart failure update appendices (except E,F,G,M)

Medline economic filter search terms

1. exp "costs and cost analysis"/
2. economics/
3. (economic$ or pharmacoeconomic$).ti,ab.
4. (cost or costs or costed or costly or costing$ or price or prices or pricing).ti.
5. (expenditure or budget$).ti,ab.
6. cost-effective$.ti,ab.
7. (cost adj2 (effectiv$ or reduc$ or saving$)).ti,ab.
8. (value adj2 money).ti,ab.
9. quality-adjusted life years/
10. QALY$.ti,ab.
11. or/1-10
12. ((metabolic or energy or oxygen) adj2 (expenditure or cost$)).ti,ab.
13. 11 not 12

Embase economic filter search terms

1. exp economic aspect/
2. (economic$ or pharmacoeconomic$).ti,ab.
3. (cost or costs or costed or costly or costing$ or price or prices or pricing).ti.
4. (expenditure or budget$).ti,ab.
5. cost-effective$.ti,ab.
6. (cost adj2 (effectiv$ or reduc$ or saving$)).ti,ab.
7. (value adj2 money).ti,ab.
8. quality-adjusted life years/
9. QALY$.ti,ab.
10. or/1-9
11. ((metabolic or energy or oxygen) adj2 (expenditure or cost$)).ti,ab.
12. 10 not 11

Appendix E – Clinical Evidence tables

DIAG: symptoms and signs vs gold standard

What is the diagnostic accuracy of a collection of symptoms and signs, including any scoring systems vs gold standard in the diagnosis of heart failure?

Reference	Study type	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity and specificity Positive and Negative predictive value	Source of funding
Mant J, Doust JA, Roalfe AK et al. ***Systematic Review and Individual Patient Data meta-Analysis of Diagnosis of Heart Failure, with Modelling of Implications of Different Diagnostic strategies in***	SR Search until July 2006 Studies assessed using the QUADAS tool by two reviewers. If disagreement, by a third reviewer The studies were of variable quality, although most of the quality criteria were	**N=15 studies** **in general practice** n=5 N= 2,527 patients **patients referred from primary to secondary care** n=5 N=1,249 patients	Prevalence of clinically defined heart failure: range 2%-49%	Inclusion criteria: studies that estimated the diagnostic accuracy or reliability of symptoms or signs for detecting heart failure. The main focus of the review was on the diagnostic accuracy for suspected cases of heart failure in primary care, we also included studies from all patient settings, including emergency department, hospital and outpatient settings and studies from population cohort or screening studies but grouped data by setting. Studies varied whether they included patients with previously diagnosed heart failure or not; both groups of studies were included in	Symptoms and signs: History of MI, Dyspnoea, Orthopnoea, Paroxysmal nocturnal dyspnoea, Oedema, Tachycardia, Elevated JVP, Cardiomegaly, Added heart sounds, Lung crepitation, Hepatomegaly	Adequate reference standards were considered to be prospective planned evaluation of: a) a clinical diagnosis including all information, for example using ESC (European Society of Cardiology) criteria; b) echocardiographic criteria for left ventricular systolic dysfunction (LVSD) (such as assessment of left ventricular ejection fraction or	See below	HTA

Reference	Study type	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity and specificity Positive and Negative predictive value	Source of funding
***Primary Care*. 2009.**	either met or unclear. 9/15 studies unclear or did not test consecutive patients or a random selection of consecutive patients; 2/15 studies did not describe or had unclear selection criteria; 7/15 studies did not have or were unclear with respect to a short time period between the index and reference test such that the target condition would not have changed between the	**in acute care** n=5 N= 1,890 patients		the review. Exclusion criteria: studies that a) included children; b) used an inappropriate index test, for example urinary natriuretic peptides; c) used a reference standard that was inappropriate for the purposes of this review, such as measures of diastolic function alone or pulmonary capillary wedge pressure; d) used a retrospective study design (for example, a reference standard using a hospital discharge diagnosis of heart failure); e) used a case-control design; or f) that provided results such that 2x2 data could not be extracted. While studies that used echocardiographic criteria for LVSD were included in our principle result tables (in the appendix), the meta-analysis was restricted to studies that used a diagnosis of heart failure as the reference standard.		global assessment of ventricular function); or c) echocardiographic criteria for heart failure with preserved systolic function.		

Reference	Study type	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity and specificity Positive and Negative predictive value	Source of funding
	two tests; 5/15 studies did not or were unclear regarding whether the reference test results were interpreted without knowledge of the results of the index test; and 9/15 did not explain or were unclear with respect to the explanation of withdrawals							

Effect size:

Overall accuracy of clinical features of heart failure.

	Number of Patients (studies)	Sensitivity (%)	Specificity (%)
Dyspnoea	2187 (5)	87	51
Orthopnoea	2901 (6)	44	89

Reference	Study type	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity and specificity Positive and Negative predictive value	Source of funding

Paroxysmal nocturnal dyspnoea	1786 (3)	No summary results	
Oedema	3736 (12)	53	72
Elevated JVP	3353 (7)	52	70
Added heart sounds	2948 (6)	11	99
Lung crepitation	4619 (11)	51	81
Hepatomegaly	1058 (1)	17	97

1. Dyspnoea for the diagnosis of clinically defined heart failure (N=5)

Sensitivity 0.83 (95% CI 0.62-0.94)

Specificity 0.54 (95% CI 0.40-.67)

DOR 5.71 (95% CI 1.78-18.31)

Positive likelihood ratio 1.79 (95% CI 1.30-2.47)

Negative likelihood ratio 0.31 (95% CI 0.12-0.79)

(the results showing considerable heterogeneity)

2. Orthopnoea and Paroxysmal Nocturnal Dyspnoea for the diagnosis of clinically defined heart failure (N=6)

Sensitivity 0.44 (95% CI 0.33-0.56)

Specificity 0.89 (95% CI 0.69-0.96)

DOR 6.23 (95% CI 2.30-16.92)

Reference	Study type	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity and specificity Positive and Negative predictive value	Source of funding
Positive likelihood ratio 3.91 (95% CI 1.51-10.11) Negative likelihood ratio 0.63 (95% CI 0.53-0.74) **3. Oedema (as a symptom or sign) for the diagnosis of clinically defined heart failure (N=12)** Sensitivity 0.53 (95% CI 0.44-0.62) Specificity 0.72 (95% CI 0.62-0.80) DOR 2.91 (95% CI 1.89-4.49) Positive likelihood ratio 1.89 (95% CI 1.42-2.51) Negative likelihood ratio 0.65 (95% CI 0.54-0.78) **4. Elevated jugular venous pressure for the diagnosis of clinically defined heart failure (N=7)** One study defined an elevated JVP as a JVP > 6cm; in the other studies, elevated JVP was not further defined. Sensitivity 0.52 (95% CI 0.41-0.63) Specificity 0.70 (95% CI 0.56-0.80) DOR 2.52 (95% CI 1.51-4.22) Positive likelihood ratio 1.73 (95% CI 1.23-2.43) Negative likelihood ratio 0.68 (95% CI 0.56-0.84) **5. Added heart sounds for the diagnosis of clinically defined heart failure (N=6)** Sensitivity 0.11 (95% CI 0.04-0.24) Specificity 0.99 (95% CI 0.97-1.00) DOR 13.4 (95% CI 6.58-27.3) Positive likelihood ratio 12.1 (95% CI 5.74-25.4)								

Reference	Study type	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity and specificity Positive and Negative predictive value	Source of funding
Negative likelihood ratio 0.90 (95% CI 0.82-0.99) This sign has very low sensitivity but high specificity. This means that if the sign is present it helps to rule the disease in but if absent it does not rule the disease out. **6. Lung crepitations for the diagnosis of clinically defined heart failure (N=11)** Sensitivity 0.51 (95% CI 0.44-0.58) Specificity 0.81 (95% CI 0.71-0.88) DOR 4.34 (95% CI 2.91-6.47) Positive likelihood ratio 2.64 (95% CI 1.86-3.74) Negative likelihood ratio 0.61 (95% CI 0.55-0.68) **7. Hepatomegaly (N=1)** This showed a sensitivity of 17% and a specificity of 97%. **Limitations:** There was considerable variation across the studies. These differences may be due to differing definitions or elicitation 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 be at the more severe end of the heart failure spectrum.								

Madhok V, Falk G, Rogers A et al. The accuracy of symptoms, signs and diagnostic tests in the diagnosis of left ventricular dysfunction in primary care: a diagnostic accuracy systematic review. *BMC Family Practice.* 2008; 9(56)	SR Search until March 2008 The QUADAS quality assessment tool was modified alongside a quality assessment tool for clinical prediction rules- producing a 7 point quality score. The overall quality of included studies: 12/24 provided adequate description and inclusion of important predictors; 12/24 studies had absence of blinding and reference standard test.	N= 24 studies N= 10,710 patients Assessed the usefulness of various symptoms and signs N= 5	The median prevalence of LVSD was 29.9% (inter-quartile range 14-37%)	Inclusion criteria: Population: study participants recruited from a community or primary care setting and had symptoms suggestive of LVSD. Study design and reference standard: studies assessing the diagnostic accuracy by means of a cross-sectional study and echo as reference standard. Index tests: studies assessing the value of symptoms, signs, ECG, chest x-ray and/or natriuretic peptides in diagnosing LVSD. Outcome measures: studies reporting data that allowed a 2×2 table construction for the assessment of diagnostic accuracy for individual symptoms, signs and diagnostic tests. Exclusion criteria: Screening studies in asymptomatic patients, case-control studies, service descriptions, secondary care settings, non-echo reference, population derived from duplicate publication, population including patients previously diagnosed with LVSD.	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	See below	Irish College of General Practitioners and HRB Centre for Primary Care Research; NHS Education for Scotland.

Effect Size:

Clinical value of symptoms, signs and diagnostic tests for LVSD

Diagnostic Test	No. of Studies	No. of Patients	Pooled PLR	(CI) or Range	I-squared	Pooled NLR	(CI) or Range	I-squared
Symptoms								
Fatigue	2	1079	1.03	(0.84 - 1.25)	34.4%	0.98	0.88 - 1.17	52.0%
Dyspnoea	3	1338	1.15	(1.09 - 1.21)	4.8%	0.50	(0.20 - 1.26)	45.8%
Orthopnoea	3	1338	1.59	0.89 - 3.58	83.8%	0.89	0.77 - 1.04	58.6%
PND	3	1338	1.71	1.12 - 2.23	57.4%	0.87	0.75 - 0.99	78.2%
Signs								
Peripheral oedema	4	1721	1.18	0.96 - 1.48	68.0%	0.92	0.74 - 1.05	51.8%
Abnormal Breath Sounds	4	1721	1.53	(1.17 - 1.19)	44.4%	0.85	0.64 - 0.94	75.6%
Raised JVP	3	1338	4.36	2.66 - 7.44	58.1%	0.88	(0.83 - 0.91)	8.2%
Displaced Apex Beat	2	583	15.96	(8.24 - 30.93)	0.0%	0.58	0.35 - 0.93	98.5%
3rd Heart Sound	3	1326	7.34	1.56 - 32.37	87.3%	0.92	0.77 - 0.96	71.4%

- No item from the clinical history or symptoms provided sufficient diagnostic information to rule in or rule out LVSD.
- Clinical signs:
  - Displaced apex beat showed a convincing diagnostic effect with pooled positive likelihood ratio 15.96 (8.24 - 30.93) but this was based on only 2 studies.
  - The presence of a third heart sound showed a wide range of positive likelihood ratios 1.56 - 32.37
  - The presence of a raised jugular venous pressure (JVP) showed a wide range of positive likelihood ratios 2.66 - 7.44
  - Peripheral oedema: the range of positive likelihood ratios 0.96 - 1.48 suggests it is uninformative as a clinical sign of heart failure.

Authors' conclusion: '*likelihood ratios for some clinical signs-raised JVP, displaced apex beat and third heart sound, appear to be more diagnostically useful in ruling in LVSD but are based on a small number of studies in which the prevalence of these clinical signs is low. It is likely these florid clinical signs occur in patients for whom there is little diagnostic uncertainty concerning LVSD compared to the more typical range of patients whose diagnosis needs to be established in routine clinical practice in primary care.'*

Link to Evidence tables of included studies: www.biomedcentral.com/content/supplementary/1471-2296-9-56-S2.doc

Link to methodological standards for included studies: www.biomedcentral.com/content/supplementary/1471-2296-9-56-S3.doc

Wang CS, FitzGerald JM, Schulzer M et al. Does this dyspneic patient in the emergency department have congestive heart failure?[see comment]. [Review] [70 refs]. *JAMA.* 2005; 294(15):1944-1956.	SR The study quality was assessed using the Sackett et al method. Studies were reported as different levels: Level 1: primary prospective studies of the accuracy or precision of the clinical examination that involved comparisons of clinical findings with a reference standard of diagnosis among a large number of consecutive or random patients with dyspnoea. For precision studies 2 or more independent blinded raters of symptoms/signs were needed. Level 2: similar to level 1 but with smaller number of patients. Level 3: comparisons of	N= 22 studies N= 18 studies included in the meta-analysis. Total men (as reported in study): 5,237	Incidence of heart failure, range across studies: 32-83%	**Included studies:** studies evaluating the diagnostic accuracy of some element of medical history, physical examination or readily available diagnostic tests in adult patients with undifferentiated dyspnoea presenting to the emergency department, regardless of whether the patients had known cardiac or pulmonary diseases. **Excluded studies**: studies that: investigated other cardiac neurohormones (ANP, NT-proBNP); review articles with no original data; had no clinical examination performed or reported; used only echo, CT or invasive hemodynamic monitoring alone as a reference standard for HF without clinical correlation because the results from these tests serve as part of the reference standard for a clinical diagnosis; were population based; enrolled patients <18 yrs; did not specifically include patients reporting dyspnoea.	some element of medical history, physical examination or readily available diagnostic tests (chest radiograph, ECG and serum BNP)	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.	See below	New Investigator Award from the Canadian Institute for Health Research and BC Lung Association, scholar award from University of British Columbia Department of Medicine, and a scholar award from th Michael Smith Foundation for Health Research.

	clinical findings with a reference standard among non-consecutive or non-random patients with dyspnoea. Also included retrospective studies. Level 4: comparisons of clinical findings with a reference standard among convenience samples of patients who obviously have the condition. Level 5: comparisons of clinical findings with a reference standard of unknown or uncertain validity among convenience sample. Only studies of Level 1-3 were included in the meta-analysis.							

Effect:

	Sensitivity	Specificity	Positive LR (95% CI)	Negative LR (95% CI)
Symptoms				
Paroxysmal nocturnal dyspnoea	0.41	0.84	2.6 (1.5-4.5)	0.70 (0.54-0.91)
Orthopnoea	0.50	0.77	2.2 (1.2-3.9)	0.65 (0.45-0.92)
Oedema	0.51	0.76	2.1 (0.92-5.0)	0.64 (0.39-0.91)
Dyspnoea on exertion	0.84	0.34	1.3 (1.2-1.4)	0.48 (0.35-0.67)
Fatigue and weight gain	0.31	0.70	1.0 (0.74-1.4)	0.99 (0.85-1.1)
Physical examination/signs				
3rd heart sound	0.13	0.99	11 (4.9-25.0)	0.88 (0.83-0.94)
JVP distension	0.39	0.92	5.1 (3.2-7.9)	0.66 (0.57-0.77)
Rales	0.60	0.78	2.8 (1.9-4.1)	0.51 (0.37-0.70)
Any murmur	0.27	0.90	2.6 (1.7-4.1)	0.81 (0.73-0.90)
Lower extremity oedema	0.50	0.78	2.3 (1.5-3.7)	0.64 (0.47-0.87)
4th heart sound	0.05	0.97	1.6 (0.47-5.5)	0.98 (0.93-1.0)

Subgroup of patients with a history of asthma or COPD:

	Sensitivity	Specificity	Positive LR (95% CI)	Negative LR (95% CI)
Symptoms				
Orthopnoea	0.70	0.44	1.3 (1.1-1.5)	0.68 (0.48-0.95)
Fatigue	0.74	0.34	1.1 (0.96-1.3)	0.79 (0.54-1.2)
Physical examination/signs				
3rd heart sound	0.17	1.00	57.0 (7.6-425)	0.83 (0.75-0.91)
JVP distension	0.41	0.90	4.3 (2.8-6.5)	0.65 (0.54-0.78)
Lower extremity oedema	0.69	0.75	2.7 (2.2-3.5)	0.41 (0.30-0.57)
Rales	0.71	0.73	2.6 (2.1-3.3)	0.39 (0.28-0.55)
Hepatic congestion	0.14	0.94	2.4 (1.2-4.7)	0.91 (0.84-1.0)

Limitations:

- Relevance to this guideline: 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 that made the diagnosis w ere those that usually suggest the presence of chronic heart failure. The results are specific for patients with dyspnoea within the emergency setting and may not generalize to outpatient and inpatient settings or to patients without dyspnoea.
- The overall results had LRs that approximated some of the individual findings therefore it can not be determined whether the symptoms and signs are independently useful.
- The reference standard for heart failure has a level of subjectivity and therefore potential for bias.
- The final diagnosis may not have been made independently of the individual findings, and therefore may over-estimate the sensitivities and specificities.

Authors' conclusion: *'... no individual feature is sufficiently powerful in isolation to rule heart failure in or out.'*

- Features useful in diagnosing HF in adult emergency department patients with dyspnoea-
  - Symptoms: paroxysmal nocturnal dyspnoea, orthopnoea and dyspnoea on exertion
  - Signs/ physical examination: third heart sound, JVP distension, rales, murmur and oedema of legs.

Studies included in meta-analysis (details reported in study): Mueller et al, 2005; Lainchbury et al, 2003; Logeart et al, 2002; Knudsen et al, 2004; Bayes-Genis et al, 2004; Villacorta et al, 2002; Davis et al, 1994; Marantz et al, 1990; Alibay et al, 2005; Ray et al, 2005; Springfield et al, 2004; Morrison et al, 2002; Maisel et al, 2002; McCullough et al, 2002; Dao et al, 2001.

Evidence tables for studies included in Mant et al:

Reference	*N*	*Location*	*Setting*	*Mean age (± SD)*	*Patients*	*Index test*	*Reference test*
General practice setting							

Alehagen et al, 2003	415	Kinda, Sweden	General Practice (primary healthcare centre)	72 ± 6	Pts presenting with symptoms and signs of heart failure with no previous diagnosis	Dyspnoea Peripheral oedema Elevated JVP Lung crepitations	LVEF <40% or atrial fibrillation and symptoms of heart failure
Fonseca et al, 2004	1058	Portugal	General Practice (500 practices)	68 ± 15	Randomly selected pts (stratified by age)	Dyspnoea Orthopnoea PND Oedema (as a symptom) Oedema (as a sign) Weight gain Hypertension (SBP>149mmHg) Tachycardia (HR>90) Elevated JVP Added heart sounds (S3/ gallop) Lung crepitations Hepatomegaly Abdominojugular reflex	ESC criteria (1 clinician)
Galasko et al, 2005	376	Middlesex and London, UK	General Practice (7 practices)	67 ± 11	Pts with symptoms of heart failure or on loop diuretics	History of MI	EF <40% or atrial fibrillation or valve disease and symptoms of heart failure
Hobbs et al, 2002	273	England	General Practice (4 practices)	66 ± 11	Randomly selected pts (stratified by age): Pts presenting with symptoms and signs of heart failure	History of MI Dyspnoea Oedema Crepitations	ESC criteria (panel of 3 clinicians in equivocal cases)

Rutten et al, 2005	405	Netherlands	General Practice (51 practices)	73 ± 5	COPD pts with no previous diagnosis of heart failure	History of MI Orthopnoea Oedema (as a sign) Tachycardia Elevated JVP Displaced apex beat Crepitations	Clinical consensus (2 cardiologists, 1 general practitioner and 1 pulmonologist)
GP pts referred to open access HF or echocardiography clinics							
Cowie et al, 1997	122	London, UK	General Practice (31 practices)	67 ± 12	Pts referred to a rapid access heart failure clinic	History of MI Dyspnoea Oedema	ESC criteria (3 cardiologists)
Fox et al, 2000	383	London, UK	Rapid access heart failure clinic	74 ±10	Pts referred to an open access heart failure clinic	History of MI Peripheral oedema Hypertension Crepitations	ESC criteria (1 cardiologist)
Lim et al, 2006	137	UK	Specialist echocardiography unit	71 ± 13	Pts referred to a specialist unit for echocardiography	Oedema	EF <40% or AF or valve disease and symptoms of heart failure
Wright et al, 2003	305	Auckland and Christchurch, New Zealand	General Practice (92 GPs)	72 ± 12	Pts with dyspnoea and/or oedema referred for assessment in study	Crepitations	Clinical consensus (3 cardiologists and 1 GP)
Zaphiriou et al, 2005	302	Aberdeen, Glasgow and London	Rapid access heart failure clinics in 5	72 ±11	Pts referred to rapid access heart failure clinic	History of MI Oedema (as a sign) Crepitations	ESC criteria (1 cardiologist)

			hospitals				
Emergency department setting							
Jose et al, 2003	119	Vellore, India	ED	54 ± 12	Pts with acute or chronic dyspnoea (excluded pts with ACS, includes pts in outpatient settings)	Orthopnoea Oedema (as a sign) Tachycardia at rest Elevated JVP Added heart sounds Crepitations	Framingham criteria including echocardiogram results
Knudsen et al, 2004	880	USA and Europe (Breathing Not Properly Study)	ED	64 ± 16	Pts with dyspnoea as predominant symptom	History of MI Orthopnoea Oedema (as a sign) Hypertension Elevated JVP (>6cm) Added heart sounds Crepitations	Clinical consensus (2 cardiologists)
Logeart et al, 2002	163	Paris, France	ED	65 ± 15	Pts with acute severe dyspnoea	History of MI Orthopnoea Pedal oedema Elevated JVP Added heart sounds Crepitations	Clinical consensus (2 cardiologists and 1 pneumotologist)
Morrison et al, 2002	276	San Diego, USA	ED	NR	Pts with dyspnoea	Dyspnoea Orthopnoea PND Oedema (as a symptom) Elevated JVP Added heart sounds Crepitations	Clinical consensus (2 cardiologists using Framingham criteria)

Mueller et al, 2005	452	Linz, Austria,	ED	71 ± 15	Pts with dyspnoea	PND Oedema (as a sign) Elevated JVP Added heart sounds Crepitations	Framingham criteria and echocardiographic criteria or systolic or diastolic dysfunction (1 cardiologist)

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Mant J, Doust JA, Roalfe AK et al. *Systematic Review and Individual Patient Data meta-Analysis of Diagnosis of Heart Failure, with Modelling of Implications of Different Diagnostic strategies in Primary Care*. 2009.	HTA Individual patients data analysis	Studies included in the validation: • Cowie, Zaphiriou - UKNP (2005) • Cowie - Hillingdon (1997) • Hobbs - ECHOES (2004) • Hoes (Cost) - Rotterdam	**Study** / **Patient population** / **Signs and symptoms** **Cowie, Zaphiriou -UKNP (2005)** / Referred to cardiologist from primary care / Symptoms not described **Cowie - Hillingdon (1997)** / Referred to cardiologist from primary care / Symptoms not described **Hobbs -** / screening / Shortness	See evidence table on BNP1: signs and symptoms				

		(2000) • Fox - Bromley (2000) • Wright - New Zealand (2003) • Alehagen – Sweden (2003) • Lim – Northwick Park (2006) • Galasko – Northwick Park (2005)	**ECHOES (2004)**	studies where sub-samples of patients with HF symptoms were extracted	off breath (SOB), tiredness, ankle swelling or patients were prescribed diuretics;	
			Hoes (Cost) - Rotterdam (2000)	screening studies where sub-samples of patients with HF symptoms were extracted	Participants who were referred by a GP if they scored 3 or more points on the Rotterdam Heart Failure score or if HF was suspected for other	

					reasons	
			Fox - Bromley (2000)	Referred to cardiologist from primary care	Symptoms not described	
			Wright - New Zealand (2003)	Referred to cardiologist from primary care	Dyspnoea and/or oedema	
			Alehagen – Sweden (2003)	Referred to cardiologist from primary care	SOB and/or bilateral peripheral oedema and/or tiredness.	

			Lim – Northwick Park (2006)	Referred to cardiologist from primary care	Symptoms not described
			Galasko – Northwick Park (2005)	screening studies where sub-samples of patients with HF symptoms were extracted	SOB on level or worse, SOB on hill, SOB plus ankle swelling or prescribed loop diuretics

Effect

The table below gives the characteristics of the datasets utilised in the model derivation and validation.

Characteristics of datasets utilised in the model validations

Variable	UKNP Zaphiriou N=299	Hillingdon Cowie N=105	ECHOES Hobbs N=392	Rotterdam Cost N=143	Bromley Fox N=380	New Zealand Wright N=297
Demographics						

Heart Failure	103 (34)	29 (28)	52 (13)	42 (29)	101 (27)	75 (25)
Age mean (sd)	71.5 (11.5)	66.4 (12.0)	68.0 (10.9)	76.5 (7.2)	73.9 (9.6)	72.0 (11.8)
Gender male	123 (41)	49 (47)	177 (45)	58 (41)	165 (43)	103 (35)
Symptoms and Signs						
Shortness of breath	283 (95)	80 (76)	235 (60)	35 (24)	279 (73)	136 (46)
Ankle oedema	192 (64)	55 (52)	183 (47)	73 (51)	208 (55)	196 (66)*
Previous MI	42 (14)	7 (7)	70 (18)	16 (11)	43 (11)	43 (14)
Crepitations	84 (28)	16 (15)	49 (13)	58 (41)	109 (29)	68 (23)

Figures given are number (%) unless stated otherwise

*Peripheral oedema

The table below presents the results of the logistic model.

Predict heart failure in individual presenting with symptoms suggestive of heart failure, derived from the Zaphiriou (UKNP) dataset

Model	OR (95%CI)
Age	1.00 (0.98, 1.03)
Gender	1.94 (1.11, 3.40)
PMH MI	5.30 (2.49, 11.26)
Ankle oedema	2.55 (1.38, 4.70)
Crepitations	4.84 (2.67, 8.79)
Constant	

2.1 Validation: Area Under the Curve (AUC)

Summary of findings

The AUC for the clinical model is combination with BNP gave an AUC of between 0.85 to 0.94. For the clinical model alone, the AUC ranged from 0.66 to 0.79. Similar results were found for NT-proBNP.

Area under the curve (AUC) for BNP models to predict heart failure in individual presenting with symptoms suggestive of heart failure derived from the Zaphiriou dataset

	Derivation	Validation				
	Zaphiriou	Cowie	Hobbs	Cost	Fox	Wright
Model	AUC (95% CI)	AUC (95% CI)	AUC (95% CI)	AUC (95%CI)	AUC (95% CI)	AUC (95% CI)
BNP only	0.84 (0.79, 0.89)	0.96 (0.92, 0.99)	0.84 (0.79, 0.89)	0.84 (0.77,0.91)		
Clinical only	0.77 (0.72, 0.83)	0.70 (0.57, 0.82)	0.73(0.66, 0.80)	0.73 (0.64, 0.83)	0.66(0.60, 0.72)	0.79 (0.73, 0.86)
BNP + Clinical	0.88 (0.84, 0.92)	0.93 (0.87, 0.98)	0.86 (0.82, 0.91)	0.83(0.76, 0.90)		
BNP + Clinical + ECG	0.89 (0.85, 0.93)	0.94(0.90, 0.98)	0.87 (0.83, 0.92)	0.85 (0.78, 0.91)		

Area under the curve (AUC) for NT-proBNP models to predict heart failure in individual presenting with symptoms suggestive of

heart failure derived from the Zaphiriou dataset

	Derivation	Validation				
	Zaphiriou	Hobbs	Wright	Alehagen	Lim	Galasko
Model	AUC (95% CI)	AUC (95% CI)	AUC (95% CI)	AUC (95% CI)	AUC (95% CI)	AUC (95% CI)
NT-proBNP only	**0.85 (0.81, 0.90)**	0.89 (0.84, 0.93)	0.87 (0.82, 0.92)	0.82 (0.76, 0.87)	0.87 (0.78,0.96)	0.86 (0.81,0.91)
NT-proBNP + Clinical	**0.90 (0.86, 0.93)**	0.91 (0.87, 0.94)	0.90 (0.86, 0.95)			
NT-proBNP + Clinical + ECG	**0.90 (0.86, 0.93)**	0.91 (0.87, 0.94)	0.91 (0.86, 0.95)			

2.2 The model

The following 'weights' were assigned to the four 'feautres':

- Male 2 points
- History of Myocardial Infarction 6 points
- Crepitations 5 points
- Ankle oedema 3 points

* the 4 features can be remembered as MICE: **M**ale **I**nfarction **C**repitations **E**dema

Thus any individual presenting with symptoms of heart failure could be given a clinical score between 0 (female with no history of MI, no ankle oedema, no basal crepitations) and 16 (all features present).

2.3 Performance characteristics of the simple clinical rule

The table below gives the performance characteristics, likelihood ratios of a positive test and post-test probability of HF associated with a pre-test probability of 30%.

Performance characteristics of the simple clinical rule to predict heart failure in individual presenting with symptoms suggestive of heart failure

Cut-point greater than or equal to	Sensitivity (%)	Specificity (%)	LR+	Pre-test probability	Post-test probability
0	100	0	1	30	30
2	96.2	19.8	1.20	30	34
3	92.3	32.7	1.37	30	37
5	79.8	62.9	2.15	30	48
6	60.6	76.7	2.60	30	53
7	59.6	76.7	2.56	30	52
8	53.8	80.7	2.79	30	54
9	35.6	91.1	4.00	30	63
10	30.8	94.1	5.22	30	69

11	19.2	98.5	12.8	30	85
13	8.7	100	> 20	-	> 90
14	6.7	100	> 20	-	> 90
16	2.9	100	> 20	-	> 90

* note: because of division by zero, calculations cannot be made for the last 3 rows

LR+ positive likelihood ratio

A plot of the ROC curve demonstrated that the optimal cut-point on performance characteristics would be 5.

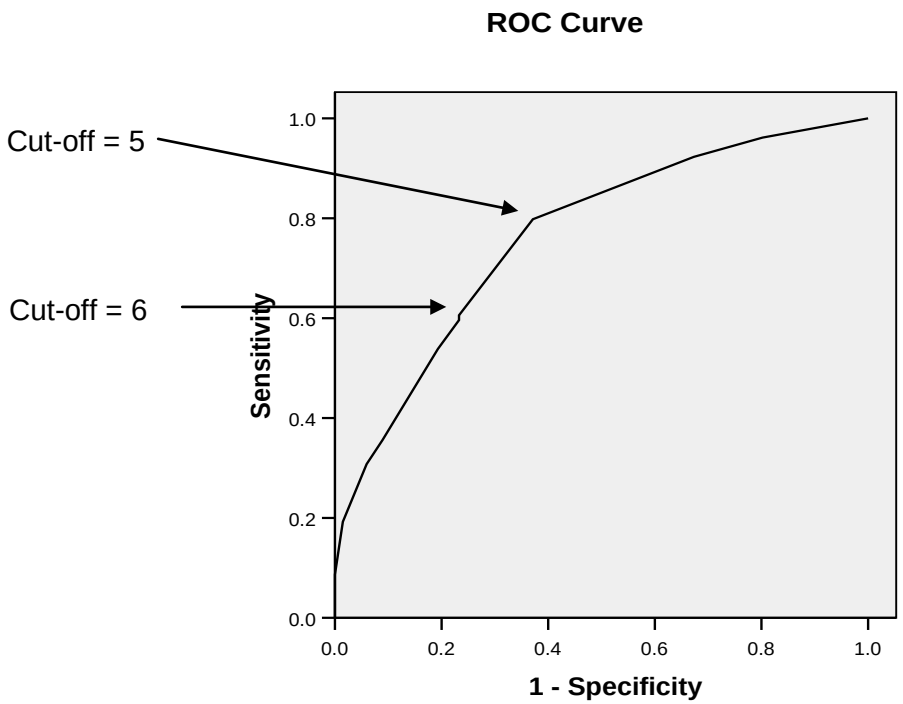

Figure 29 Receiver operating curve of the simple clinical rule predicting HF among patients with symptoms suggestive of heart failure.

This suggested the following simple clinical rule:

2.4 Clinical rule

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

a. a history of MI, or

b. basal crepitations, or

c. is a male with ankle oedema

then refer straight for echocardiography

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

BNP1: natriuretic peptides vs gold standard

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

Bibliographic reference	Study type	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity and specificity Positive and Negative predictive value	Source of funding
BNP vs clinical diagnosis								
Mant J, Doust JA, Roalfe AK et al. *Systematic Review and*	SR Search until July 2006	**TOTAL** N=20 studies	**TOTAL: no. of true positives (%) range minimum -**	Studies were included if they estimated the diagnostic accuracy or reliability of	BNP or NTproBNP	Adequate reference standards was defined as a prospective planned evaluation of: a) a clinical	**See below**	HTA

***Individual Patient Data meta-Analysis of Diagnosis of Heart Failure, with Modelling of Implications of Different Diagnostic strategies in Primary Care*. 2009.**	Studies assessed using the QUADAS tool by two reviewers. If disagreement, by a third reviewer Studies were of moderate to high quality as assessed using the QUADAS checklist: 11/20 studies 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 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 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	N=5030 patients **General practice setting** N=2 N=678 patients **GP patients referred to open access HF or echocardiography clinics** N=3 N=507 patients **Emergency Dept. setting** N=12 studies N=3587 **Inpatient setting** N=3 studies N=258 patients	**maximum** 2056/5030 (40.87%) range 5.49 to 91.67% **General practice setting:** 67/678 (9.89%) range 5.49 to 12.84% **GP referrals:** 152/507 (29.98%) range 22.90 to 50.60% **Emergency Dept. setting:** 1875/3587 (52.27%) range 35 to 91.67% **Inpatient setting:** 114/258 (44.19%) range 28.57 to 49.18%	investigations for detecting heart failure. The main focus of the review was on the diagnostic accuracy for suspected cases of heart failure in primary care, studies were also included from all patient settings, including emergency department, hospital and outpatient settings and studies from population cohort or screening studies. Data is grouped according to setting. Studies included patients previously diagnosed with heart failure or not Inclusion criteria: Studies that compared BNP with an adequate reference standard comprising of either a clinical diagnosis of heart failure Exclusion criteria: studies on a) children b) with an inappropriate reference standard, e.g., measures of diastolic dysfunction alone or pulmonary capillary wedge pressure c)		diagnosis including all information, for example using European Society of Cardiology criteria b) echocardiographic criteria for left ventricular systolic dysfunction (LVSD) (such as assessment of left ventricular ejection fraction or global assessment of ventricular dysfunction);c) echocardiographic criteria for heart failure with preserved systolic dysfunction ECS criteria (2 or more cardiologists) N=4 studies Clinical consensus (typically two cardiologists) N=8 studies		

	withdrawals			retrospective study design, eg reference standard using a hospital discharge diagnosis of heart failure; e) used a case-control design; or f) that provided results such that 2x2 data could not be extracted The meta-analysis was restricted to studies that used a diagnosis of heart failure as the reference standard				

Effect

BNP vs. 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)

Studies of NT-proBNP versus a clinical diagnosis of heart failure

	Studies were of moderate to high quality as assessed using the QUADAS checklist: 6/16 studies unclear or did not test consecutive patients or a random selection of consecutive patients; 3/16 studies	**TOTAL** N=16 studies Total =4280 **General practice setting** N=4 studies	**TOTAL: no. of true positives (%) range minimum – maximum** 1176/4280 (27.48%) range 5.86 to 82.02%	As above	As above	Criteria as above ESC criteria (1 or more cardiologist) N=4 Clinical consensus (2 or more cardiologists) N=6	See below	As above

	did not describe or had unclear selection criteria; 6/16 studies did not have or were unclear with respect to 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 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	N=1469 patients **GP patients referred to open access heart failure of echocardiography clinics** N=4 studies N=1031 patients **Emergency Dept. setting** N=6 studies N=1407 patients **Outpatient setting** N=1 study N=119 **Inpatient setting** N=1 study N=254	**General practice setting** 67/1469 (4.56%) range 5.49 to 12.84 **GP patients referred to open access heart failure of echocardiography clinics** 152/1031 (14.74%) range 22.95 to 50.60% **Emergency Dept. setting** 543/1407 (38.59%) range 27.32 to 82.02% **Outpatient setting** 71/119 (59.66%) **Inpatient setting** 138/254 (54.33%)					

Effect

NT-proBNP vs. clinical diagnosis	Sensitivity	Specificity	Positive likelihood ratio (95%CI)	Negative likelihood	Diagnostic Odd Ratio

Setting	(95%CI)	(95%CI)		(95%CI)	(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)

BNP2: natriuretic peptides vs echocardiography

What is the accuracy of echocardiography *vs* natriuretic peptides in the diagnosis of diastolic dysfunction?

Bibliographic reference	Study type	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity and specificity Positive and Negative predictive value	Source of funding
Islamoglu F, Ozcan K, Apaydin AZ et al. Diagnostic accuracy of N-terminal pro-brain natriuretic peptide in the evaluation of postoperative left ventricular diastolic dysfunction. *Texas Heart Institute Journal.* 2008; 35(2):111-118. Ref ID: 489	Prospective case series Echocardiographers blinded to NT-proBNP results	N=30	Preoperatively: 5/30 (16.7%) Post-operatively:13/30 (43.3%)	**Inclusion criteria**: patients who were undergoing coronary artery bypass graft (CABG) **Exclusion criteria:** Patients who had sustained a myocardial infarction in the preceding 3 weeks, those with unstable angina pectoris, diabetes, or significant systolic dysfunction (left ventricular ejection fraction (LVEF) ≤0.40). Age (mean, range): 60.13 ±	N-Terminal Pro-Brain Natriuretic peptide (NT pro-BNP) 1st sample: obtained prior to surgery 2nd sample: obtained on 7th day postoperatively.	Echocardiogram On admission and on 7th day postoperatively. Early diastolic mitral annular velocity (EA) and peak early diastolic transmittal velocity was measured using tissue Doppler echo and E/Ea ratio was calculated. E/Ea ratio ≤15 cm diastolic	**NT-proBNP:** Sensitivity 87.5% Specificity: 55% (AUC 0.739, P=0.049) **Echo (E/Ea ratio):** Sensitivity 87.5% Specificity: 86.4% (AUC 0.864, P=0.003) Echo + E/Ea ratio was significantly more	Not reported

				8.77 (46-76); >70 yrs: 4 Male/Female: 30/0 Hypertension: 10/30 (33.33%) NYHA functional Class: I: II: III: IV: Number of grafts (mean, range): 3.13 ± 0.89 (2-5%)		functional stage was normal; E/Ea >15 cm diastolic functional stage was defined as abnormal.	sensitive than NT proBNP in the prediction of diastolic functional stage (mean difference 0.12, p=0.024)	
Hettwer S, Panzner GB, Witthaut R et al. Isolated diastolic dysfunction--diagnostic value of tissue Doppler imaging, colour M-mode and N-terminal pro B-type natriuretic peptide. *Clinical Research in Cardiology.* 2007; 96(12):874-882. Ref ID: 241	Case-control study Echocardiographers blinded to NT-proBNP results	N=140	120/140 (85.7%)	<table><tr><td></td><td>No DDF (n=20)</td><td>DDF (n=120)</td><td>P value</td></tr><tr><td>Age: mean/ range</td><td>47.7 ± 35.0 (32-67)</td><td>67.0 ± 45 (38-83)</td><td><0.001</td></tr><tr><td>Male sex (%)</td><td>66.7</td><td>59.2</td><td>0.58</td></tr><tr><td>NYHA class >II at admission (%):</td><td>38.9</td><td>75.4</td><td><0.01</td></tr><tr><td>LVEF</td><td>0.72± 0.0</td><td>0.71 ± 0.0</td><td>0.55</td></tr></table>	NT-proBNP Performed after 10 min rest.	Echocardiogram Measures: - ejection fraction. - parameters of diastolic dysfunction estimated by averaging five consecutive heartbeats. – maximal early and late diastolic transmitral inflow and its ratio E/A. – deceleration time of early inflow (DT) - isovolumetric relaxation time - pulmonary	**NT-pro BNP:** serum over 11.1 pmol/l predicted DDF with a sensitivity: 65.6%, specificity: 77.8% **Echocardiogram:** **1. Myocardial relaxation velocity:** below 6.31 cm/s indicated DDF at any stage with a sensitivity: 82.8% specificity: 77.8% **2. Flow propagation velocity of transmittal**	Roche Diagnostics

				<table><tr><td></td><td>2</td><td>1</td><td></td></tr></table> DFF: diastolic dysfunction LVEF: left ventricular ejection fraction **Inclusion criteria:** Patients admitted to the cardiology department for: 1) dyspnoea of cardiac origin 2) clinical signs of heart failure with normal left ventricular systolic dysfunction 3) longstanding arterial hypertension **Exclusion criteria:** patients with coronary stenoses >60%, with an ejection fraction <50%, with wall motion abnormalities or valve disease; patients with suspected endocarditis or stroke of cardiac origin or patients with prosthetic valves.		flow profile - ratio of maximal systolic to diastolic flow (S-D ratio) - tissue relaxation velocities Diastolic dysfunction diagnosed under 1 of the 3 patterns: 1. impaired relaxation pattern 2. pseudonormal pattern 3. restrictive pattern	**inflow:** below 55.9 cm/s predicted DDF at any stage with a sensitivity: 74.2% specificity: 77.8%	
Tschope C, Kasner M, Westermann D et al. The role of NT-proBNP in the diagnostics of isolated diastolic dysfunction: correlation with echocardiographic and invasive measurements. *European Heart Journal.* 2005;	Prospective Case-control study	N=118 n= 68 patients with diastolic dysfunction (DDF) n=50 controls with normal diastolic function.	68/118 (57.6%)	<table><tr><td></td><td>DDF (n= 68)</td><td>No DDF (n = 50)</td><td>P value</td></tr><tr><td>Age: mean/ range</td><td>51 ± 9 (69-26)</td><td>49 ± 10 (70-28)</td><td>0.091</td></tr></table>	NT-proBNP	Patients with DDF were diagnosed by abnormal values LVEDP, Tau, IVRT, DT, and/or by the E/A ratio (echocardiography) Pseudonormal and restrictive flow pattern	See below	205

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<td>26(21):2277-2284.
Ref ID: 1871</td>
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<tr><td>Female/ Male (%)</td><td>31 (46) /37 (54)</td><td>22 (4 4)/ 28 (5 6)</td><td>0.7 08</td></tr>
<tr><td>NYHA class II-III (%):</td><td>58 (85)</td><td>8 (1 6)</td><td>0.0 01</td></tr>
<tr><td>LVEF (%)</td><td>68 ± 9 (78-51)</td><td>65 ± 10 (8 4-52)</td><td>0.0 93</td></tr>
</table>
DFF: diastolic dysfunction
LVEF: left ventricular ejection fraction

Inclusion criteria: patients with preserved LV function and normal LV dimensions as determined by echocardiography and ventriculography.

Exclusion criteria: patients with atrial fibrillation, lung disease, renal dysfunction, significant heart valve disease, or other severe concomitant diseases.
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<td>were diagnosed using pulmonary vein flow and TDI.</td>
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Results for different NT-proBNP cut-off values:
<table>
<tr><th>NT-proBNP cut-off (pg/ml)</th><th>Sensitivity (%)</th><th>Specificity (%)</th><th>Positive predictive value (%)</th><th>Negative predictive value (%)</th></tr>
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90	75	86	54	94
100	74	88	58	94
110	72	90	61	94
120	69	91	63	93
130	56	92	61	91
140	53	92	59	90
304	19	100	100	85

Results for echocardiogram and NT-pro BNP at a cut off of 120pg/ml;

Parameter	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
LVEDP	0.84 (0.73-0.91)	61	94	69	92
NT-proBNP	0.83 (0.78-0.89)	69	91	63	93
E/A ratio (TDI)	0.81 (0.75-0.90)	71	87	55	93
E/A	0.70 (0.62-0.77)	53	79	36	88
IVRT	0.63 (0.58-0.77)	69	60	27	90
DT	0.59 (0.46-0.68)	33	79	26	84

Echo measures:

LVEDP: left ventricular end-diastolic pressure

E/A ratio: early filling/atrial filling peak velocities

TDI: tissue Doppler imaging

IVRT: isovolumic relaxation time

DT: (early filling) deceleration time

Authors' conclusions:

NT-proBNP:

- had the best negative predictive value of all the methods investigated.
- levels had similar diagnostic accuracy as TDI and were superior to conventional echocardiography.

				• cannot differentiate between diastolic and systolic heart failure and is not surrogate for echocardiography. Can reliably detect the presence of isolated diastolic dysfunction in symptomatic patients and is a useful tool to rule out patients with reduced exercise tolerance of non-cardiac origin.				
Wei T, Zeng C, Chen L et al. Bedside tests of B-type natriuretic peptide in the diagnosis of left ventricular diastolic dysfunction in hypertensive patients. *European Journal of Heart Failure.* 2005; 7(1):75-79. Ref ID: 1927	Prospective BNP was performed right after clinical and echo examinations.	N=135	61/135 (45%)	Consecutive Chinese patients with a history of hypertension for an average of 9.3 ± 7.8 (1-30 yrs). **Exclusion criteria**: patients with chest trauma, pericardial effusion, angina or renal dysfunction prior to the study. **Patient characteristics:** Male/ female: 85/ 135 (63%); 50/185 (27%) Age (range): 70 ± 10 yrs (35-86) Congestive heart failure symptoms: 51% NYHA class I: 35% NYHA class II: 16% Blood pressure <140/90: 47/135 (35%) Blood pressure >160/95: 44/135 (33%) All patients had LVEF>50% **Diagnosis of diastolic**	BNP	Echocardiogram Measures: Doppler echo of transmitral flow, E and A peaks, diastolic time and the isovolumic relaxation time.	BNP cut-off value of 40 pg/ml: Sensitivity: 79% Specificity: 92%	Not reported

				dysfunction: Based on 3 criteria: 1.) the presence of signs or symptoms of congestive heart failure, 2.) the echo measured LVEF >50% 3.) Echo evidence of abnormalities of left ventricular relaxation: 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.				
Dong SJ, de las FL, Brown AL et al. N-terminal pro B-type natriuretic peptide levels: correlation with echocardiographically determined left ventricular diastolic function in an ambulatory cohort. *Journal of the American Society of Echocardiography.* 2006; 19(8):1017-1025. Ref ID: 874	Prospective Echo observer blind to NT-proBNP and other clinical parameters Echo performed after NT-proBNP	N=191	81/191 (42%) LVEF ≥ 55%	Consecutive, clinically stable, ambulatory patients. **Excluded:** Signs and symptoms of concomitant disease including atrial fibrillation, COPD and echo findings of right-sided heart abnormalities and/or valvular heart disease **Control subjects who had no history, symptoms or physical findings of cardiovascular disease (CVD) and**	NT-proBNP Roche	Echo performed within 30 min of blood collection	See below	National Institute of Health, Robert Wood Johnson Foundation, Barnes-Jewish Hospital Foundation and

				normal systolic function (LVEF ≥ 55% and no evidence of segmental wall-motion abnormalities) 43/191 23%) **History, symptoms and/or physical findings compatible with CVD** 148/191 (77%) Of these LVEF > 55% 81/148 (55%), LVEF < 55% 67/148 (45%) **Patients with LVEF ≥ 55%** mean age 60 yrs, male 61%, African American 67%, mean BMI 32 kg/m², dyspnoea 61%, oedema 48%, 66% ACE inhibitor, 15% ARB, 60% beta blocker				Roche supplied the NT-proBNP assays

*denotes optimal threshold values

E/Em mitral early filling wave to Doppler tissue early diastolic mitral annulus velocity ratio

	E/Em ≥ 8			E/Em > 15		
NT-proBNP pg/mL	Sensitivity	Specificity	Accuracy	Sensitivity	Specificity	Accuracy
150	0.74*	0.71*	0.73*	1.0	0.56	0.78
250	0.59	0.80	0.69	1.0	0.68	0.84
350	0.53	0.84	0.68	1.0	0.73	0.87

450	0.49	0.84	0.67	1.0	0.76	0.88
550	0.49	0.88	0.68	1.0*	1.0*	0.89*

Knebel F, Eddicks S, Schimke I et al. Myocardial tissue Doppler echocardiography and N-terminal B-type natriuretic peptide (NT-proBNP) in diastolic and systolic heart failure. *Cardiovascular Ultrasound.* 2008; 6:45. Ref ID: 2794	Prospective Echo blind to BNP Echo and BNP done at the same time but one always after the other	N=137	43/137 diastolic dysfunction Defined as ≥ 55%, E/E′ > 10, E/A < 1	Patients with a clinical indication for Echo from medical and surgical departments who were clinically stable (inpatients and outpatients) 43/137 (31%) **diastolic dysfunction with preserved left ventricular function** 42/137 (31%) healthy controls 52/137 (38%) systolic heart failure EF > 55% **Exclusion criteria:** atrial fibrillation, relevant valvular disease exceeding mild mitral or aortic disease, prosthetic heart valves, pulmonary hypertension, myocardial infarction < 3 months prior to study inclusion, terminal renal failure, creatinine > 2.5 mg/dL, pregnancy, age < 18 yrs	NT-proBNP Roche Drawn after echo	Echo	Diagnostic accuracy to discriminate between normal LVEF (n=88) and reduced LVEF (n=49) AUC 0.84 **Cut-off 489 pg/ml** Sensitivity 81.6% Specificity 85.2% PPV 75.5% NPV 89.3%	None reported

Lubien E, DeMaria A, Krishnaswamy P et al. Utility of B-natriuretic peptide in detecting diastolic dysfunction: Comparison with Doppler velocity recordings. *Circulation.* 2002; 105(5):595-601. Ref ID: 2929	Prospective Echo interpreted blind to BNP	N=294	194/294 (66%) diastolic dysfunction	Patients referred for Echo to evaluate LV dysfunction 1999-2000 **Exclusion criteria:** patients referred to exclude valve disease, to determine whether a vegetation was present, or to rule out a cardiac cause of stroke (~10%). Patients with an ejection fraction <50% or an LV end-diastolic dimension >5.5mm were excluded Referred by physicians or nurse practioners **No diastolic dysfunction:** mean age 60 yrs, male: female 159:16, hypertension 58%, diabetes mellitus 35%, coronary artery disease 26%, shortness of breath 34%, oedema 19%, history of chronic heart failure 1% **Diastolic dysfunction:** mean age 71 yrs, male: female 106:13, hypertension 79%, diabetes mellitus 54%, coronary artery disease 50%, shortness of breath 46%, oedema 29%, history of chronic	Triage BNP assay	Echo Doppler velocity	**Cut-off BNP 17.5 pg/mL** Sensitivity 97 (92 to 99) Specificity 45 (37 to 52) **Cut-off BNP 62 pg/mL** Sensitivity 85 (77 to 90) Specificity 83 (77 to 88) **Cut-off BNP 92 pg/mL** Sensitivity 74 (65 to 81) Specificity 98 (94 to 99) **Cut-off BNP 130 pg/mL** Sensitivity 62 (53 to 71) Specificity 98 (94 to 99) **Cut-off 17.5 pg/mL** Positive predictive value 54 (47 to 81) Negative predictive value	None reported

				heart failure 21%			95% (88 to 98) Accuracy 66% **Cut-off 62 pg/mL** Positive predictive value 78 (70 to 84) Negative predictive value 89 (83 to 93) Accuracy 84% **Cut-off 92 pg/mL** Positive predictive value 96 (89 to 98) Negative predictive value 85 (79 to 89) Accuracy 88% **Cut-off 130 pg/mL** Positive predictive value 95 (87 to 98) Negative predictive value 79 (73 to 84) Accuracy 83%	
Abhayaratna WP, Marwick TH, Becker NG et al. Population-based detection of systolic and diastolic dysfunction with amino-terminal pro-B-type	Prospective ECHO blind to clinical	N=1229 (Total) **N=91**	161/1229 (13.1%)	Population sample of adults 60 to 86 yrs **Total population:**	Amino-terminal pro-BNP	Transthoracic echocardiography	**Men 60 to 86 yr moderate DD** (N=46, 7.7%)	Support from Roche and Sieme

natriuretic peptide. *American Heart Journal.* 2006; 152(5):941-948. Ref ID: 784	data Interobserver reliability	(7.4%) moderate-severe diastolic dysfunction, any EF **N=68** (5.5%) Moderate diastolic dysfunction-no EF **N=2** (0.2%) Severe diastolic dysfunction, no EF		Women 616/1229 (50.1%), mean age 69.4 yrs, hypertension 828/1229 (67%), diabetes 171/1229 (14%), coronary artery disease 214/1229 (17%), BMI ≥ 30 kg/m² 358/1229 (29%), congestive heart failure 86/1229 (7.0%), atrial fibrillation 51/1229 (4.2), crCl < 60 mL/min 308/1229 (25%), EF ≤ 40% 27/1229 2.2%)	Elecsys 100		**NT-pro BNP cutoff 30 pmol/L 240 pg/mL** Sensitivity 83% specificity 85% Women **60 to 86 yr moderate DD** (N=45, 7.3%) **NT-pro BNP cutoff 32 pmol/L 270 pg/mL** Sensitivity 89% specificity 86%	ns Ultrasound

BNP3: natriuretic peptide monitoring (guided therapy) vs standard care

Does serial BNP monitoring (guided therapy) improve outcome compared to standard care in adults with chronic heart failure?

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Lainchbury JG, Troughton RW, Strangman KM et al. *NTproBNP guided treatment for chronic heart failure: results from the Battlescarred trial*. 2009. Ref ID: 4651	RCT Randomisation: 1:1:1 ratio, stratified by age ≤ 75 or > 75 in permuted blocks Double blind Allocation concealment – not specified ITT No power calculation	N=364 All followed-up for at least 12 mths; n=315 for 2 yrs and n=260 for 3 yrs	Patients with symptomatic CHF (Framlingham criteria and ESC guidelines) admitted to hospital. Inclusion criteria: NTproBNP > 50 pmol/L. Exclusion criteria: Active myocarditis/pericarditis, a life expectancy due to nonvascular disease < 24 mths, severe hepatic or pulmonary disease, severe renal impairment, severe valvular disease requiring surgery, severe aortic stenosis, heart failure due to mitral stenosis, or under consideration for cardiac transplantation. Elderly patients and those with preserved LVEF were INCLUDED. BNP-guided: Mean age 76, male 63%, diabetes mellitus 23%, hypertension 55%, prior history of MI 42%, LVEF 40 (SD15)%, NYHA % I 12, II 68, III 18, IV 2, heart failure admission % 0 69%, ≥	Hormone Guided Three monthly visits by the research team in a dedicated outpatient clinic. Intensive assessment was undertaken by staff blinded to the patients' group in order to provide a "heart failure score". Clinical end points were documented and blood drawn for the measurement of NTproBNP and biochemistry. Heart failure score: Derived by assigning a value to	Usual care 3 monthly documentation of medications, readmissions and death by research team but not further contact beyond this. Further management was undertaken by primary care with or without the additional attendance of hospital cardiology or specialist heart failure clinical as requested by their primary care physician	NYHA (3 monthly		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			1 31%, plasma NTproBNP 238pmol/L Clinically guided: Mean age 76, male 67%, diabetes mellitus 20%, hypertension 42%, prior history of MI 47%, LVEF 39% (SD15), NYHA % I 7, II 66, III 25, IV 2, heart failure admission 0 67%, ≥ 1 32%, plasma NTproBNP 236 pmol/L Usual care: Mean age 75, male 62%, diabetes mellitus 22%, hypertension 62%, priory history of MI 44%, LVEF 37% (SD15), NYHA % I 7, II 67, III 25, IV 1, heart failure admission 0 71%, ≥ 1 29%, plasma NTproBNP 238 pmol/L	variables included in the Framingham method for the diagnosis of heart failure with major criteria scoring 1 point and minor 0.5 points. Scores ≥ 2 were indicated decompensation and triggered escalation of drug therapy. Patients were instructed on monitoring weight, dietary sodium restriction, rest after diurectic administration, exercise, avoidance of liquorice, NSAIDs and alcohol and the				

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				need for the flu vaccine Adjustments in dose and visits: these were triggered by an NTproBNP level > 150 pmol/L and/or heart failure score ≥ 2. When results fell below both of these thresholds, treatment was not altered. Drug therapy was escalated according to a preset algorithm (detail not specified). Clinical guided group Regimen as above.				

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				Adjustments in dose: aimed to establish trial-based doses of medications. This included the equivalent of enalapril 10 mg twice daily adjusted for renal function. Beta blockers were introduced with standard titration at 2-weekly intervals towards doses of carvedilol 25 mg twice daily or a sustained release preparation of metoprolol to 190 mg daily. A score of ≥ 2 at any time triggered intensification of therapy				

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				according to a preset algorithm (detail not specified).				

Time - months						
Drug	Treatment Gp	0	3	6	12	24
Furosemide – mg/day	N-BNP	128±23	138±20140±22	140±22	182±22	200±27
	CG	149±23	144±21	134±21	166±23	197±28
	UC	124±22	121±21	134±21	166±23	140±25
ACEI – mg/day	N-BNP	12.7±6	13.0±6	13.3±6	13.1±6	12.4±7
	CG	13.3±6	14.7±6	14.6±6	14.2±6	14.0±7
	UC	10.3±6	11.3±6	11.0±6	11.0±6	10.8±6
Beta blocker – mg/day	N-BNP	76±11	83±9	95±9	95±10	94±11
	CG	80±11	91±9	95±9	95±10	94±11
	UC	73±10	74±9	75±9	73±10	72±10
Spironolactone – mg/day	N-BNP	20±6	22±4	24±5	23±5	20±6
	CG	21±6	22±5	24±5	23±5	20±6
	UC	20±2	20±2	21±2	21±2	21±3

CG – clinically-guided, UC – usual care

Effect

Quality of life –Minnesota Living with heart failure

	Time - months		
	0	6	12
N-BNP	36.5±22.7	28.9±24.5	28.8±21.6
CG	36.6±23.1	27.5±20.0	26.5±22.0
UC	36.5±24.0		

12 mths entered in meta-analysis

Death ± heart failure admission n (%)

		Year		
	Treatment group	1	2	3
N-BNP	All (n=121)	36 (30)	52 (43)	64 (53)
	≤ 75 (n=58)	14 (24)	20 (34)	23 (39)
	> 75 (n=63)	22 (35)	32 (51)	41 (65)
CG	All (n=121)	36 (30)	57 (47)	66 (55)
	≤ 75 (n=55)	15 (27)	25 (45)	28 (51)
	> 75 (n=66)	21 (32)	32 (48)	38 (58)
UC	All (n=122)	42 (34)	57 (47)	66 (54)
	≤ 75 (n=64)	25 (39)	31 (48)	35 (55)
	> 75 (n=58)	17 (29)	26 (45)	31 (53)

1 yr entered in meta-analysis

Heart failure admission n (%)

		Year		
	Treatment group	1	2	3
N-BNP	All (n=121)	29 (24)	38 (31)	44 (36)
	≤ 75 (n=58)	13 (22)	16 (28)	17 (29)
	> 75 (n=63)	16 (25)	22 (35)	27 (43)
CG	All (n=121)	30 (25)	44 (36)	49 (40)
	≤ 75 (n=55)	14 (25)	21 (38)	22 (40)
	> 75 (n=66)	16 (24)	23 (35)	27 (41)
UC	All (n=122)	26 (21)	37 (30)	41 (34)
	≤ 75 (n=64)	18 (28)	22 (34)	23 (36)
	> 75 (n=58)	8 (14)	15 (26)	18 (31)

1 yr entered in meta-analysis

Death

One year-follow-up

N-BNP vs CG vsUC

9.1% (11/121) vs 9.1% (11/121) vs 18.9% (23/122)

		Year		
	Treatment group	1	2	3
N-BNP	All (n=121)	9.1% (11/121)		
	≤ 75 (n=58)	1.7% (1/58)	7.3% (4/58)	15.5% (9/58)
	> 75 (n=63)			49.2% (31/63)
CG	All (n=121)	9.1% (11/121)		
	≤ 75 (n=58)	7.3% (4/58)	20.0% (12/58)	30.9% (17/55)
	> 75 (n=63)			34.9% (23/66)
UC	All (n=122)	18.9% (23/122)		
	≤ 75 (n=58)	20.3% (12/58)	23.4% (14/58)	31.3% (20/64)
	> 75 (n=63)			34.5% (20/58)

1 yr entered in meta analysis

Beck-da-Silva L, de BA, Fraser M et al. BNP-guided	RCT Randomis	N=41 Drop	Patients with HF who were not already on B-blockers and who met the following criteria were eligible for the study.	BNP guided therapy + standard	Standard care [Clinical group].	3 months	Quality of life assessed by the Living with Heart	Not reported

<table>
<tr>
<td>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.</td>
<td>ed

Allocation concealment not reported

Blinding not reported

Sample size calculation reported

ITT not reported

Setting: Heart Foundation Clinic</td>
<td>outs:
After 3 months – N=38</td>
<td>Inclusion criteria: Male or female older than 18 years of age, symptomatic HF (New York Heart Association class II- IV) for at least 3 months or previous hospital admission due to HF, left ventricular ejection fraction (LVEF) of 40% or less assessed by radionuclide ventriculography, treatment with either an angiotensin converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) plus a loop diuretic and digoxin.

Exclusion criteria: Myocardial infarction or unstable angina within 4 weeks, severe stenotic valvular heart disease, hepatic or renal disease (serum transaminase of more than three times normal or serum creatinine >200 mmol/L), or a contraindication for β blockers (asthma, higher than first-degree atrioventricular block, or heart rate below 60 bpm at baseline).

Patient characteristics:

<table>
<tr><th></th><th>BNP group (N=21)</th><th>Clinical group (N=20)</th></tr>
<tr><td>Age (yr) ((m±SD)</td><td>64.5±15.2</td><td>65.6±13.5</td></tr>
<tr><td>Male (n (%))</td><td>7 (33.3%)</td><td>7 (35%)</td></tr>
</table>
</td>
<td>care [BNP group].

β blocker dosage up-titrated according to plasma BNP levels plus standard care (patients clinical status as assessed by the attending physician) *

NB: All but one patient received bisoprolol; the remaining one patient received metoprolol</td>
<td>β blocker dosage up-titrated according standard care</td>
<td></td>
<td>Failure Minnesota Questionnaire.

Hospital admissions (number of patients)

Mortality</td>
<td></td>
</tr>
</table>

			Ischemic aetiology (n (%)) 7 (33.3%) 10 (50%) Diabetes (n (%)) 5 (24%) 5 (25%) LVEF(%)(m±SD) 23.8±8.8 20.9±9.2 NYHA class (m±SD) 2.6±0.7 2.4±0.6 Quality of life (m±SD) 41±24 43±27 Use of ACEI or ARB (n (%)) 21 (100%) 20 (100%) BNP at baseline (pg/ml) (m±SD) 502±411 702±410				

Effect Size

Outcomes Follow-up 3 mths	
Quality of life scores Follow-up 3 mths	BNP group (-11; 95% CI, -1 to -22; p=0.034) Clinical group improved (values not reported) No statistically significant difference between groups.
Hospital admissions (all causes) Follow-up 3 mths	4 out of 20 patients from the clinical group and 2 out of 21 patients from the BNP group were hospitalised. No s significant difference between groups (p=0.34)
Mortality (due to progression	2 out of 20 patients from the clinical group and one out of 21 patients from the BNP group died due to progress

of HF) Follow-up 3 mths	the same period. No statistically significant difference between groups (p=0.52)

* Dose of B-blockers and Furosemide were adjusted. Other medications (ACE inhibitors, ARB's and digoxin) were unchanged.

Clinical group:

Up-titration of B-blocker dose in the clinical group was carried out if the patient did not exhibit signs of deterioration (e.g. worsening functional status, systolic blood pressure below 80mm Hg, heart rate below 55 bpm, or increasing congestion than the previous visit as indicated on the clinical form.)

BNP group:

Up-titration of B-blocker dose in the BNP group was based first on the BNP level. If the BNP was level was lower and the clinical status was unchanged or better, then the dose was increased. The same clinical limitations to B-blocker up-titration as in the clinical group were used. If the patient presented with clinical deterioration as defined above and the serum BNP measurement increased from previous measurement, then the dose of B-blocker was not increased.

B-blockers were successfully up titrated in both groups. No significant difference in the final bisoprolol dosage was found between groups at the end of 3 months (5.9±4.3 mg in the clinical group vs. 4.4±3.4 mg in the BNP group; p=0.22). At the end of the study, 45% of patients in the clinical group and 19% of patients in the BNP group were on the maximal dose of bisoprolol, defined as 10 mg/d (p=0.1).

The dose of furosemide was equally increased in both groups by 20 mg (95% CI, 5.5-34.5 mg; p=0.008) compared with baseline.

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>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.</td>
<td>RCT

Randomised

Double blind

Unclear allocation concealment,
ITT not reported.

Groups matched at baseline for demographic and clinical features, left ventricular function, and functional status.</td>
<td>N=69

No drop-outs.</td>
<td>Inclusion criteria: Patients with impaired LVSD (LVEF <40% on echo), established symptomatic HF (NYHA class II-IV), treated with an ACE inhibitor, loop diuretic +/- digoxin.
Exclusion criteria: recent acute coronary syndrome (within 3 months), pending cardiac transplantation or revascularization, severe stenotic valvular heart disease, or by severe pulmonary (forced expiratory volume in 1 sec <1L), hepatic or renal (plasma creatinine >0.2 mmol/l) disease.

Patient characteristics:
<table>
<tr><th></th><th>BNP (N=33)</th><th>Clinical (N=36)</th></tr>
<tr><td>Age (yrs)</td><td>68</td><td>72</td></tr>
<tr><td>Male</td><td>78 %</td><td>75%</td></tr>
<tr><td>HF</td><td>30 %</td><td>28 %</td></tr>
</table>
</td>
<td>N-BNP guided treatment (BNP group)

The treatment target was N-BNP below 200pmol/l (which corresponds to the concentration of BNP-32 that discriminated decompensated from compensated HF in previous study).

If targets were not achieved, drug treatment was intensified according to a strict and predetermined stepwise protocol comprising: maximisation of ACE (up to enalapril equivalent of 20mg twice/day); increase</td>
<td>Treatment guided by standardised clinical assessment (Clinical group)

The treatment target was clinically compensated heart failure according to an objective score (heart failure score based on Framingham criteria for diagnosing decompensated HF).

If targets were not achieved, drug</td>
<td>Minimum 6 months, median 9.5 months (follow-up every 3 months)</td>
<td>N-BNP concentrations, clinical events, renal and haemodynamic effects; medications, extra visits and adverse events</td>
<td>Health Research Council of New Zealand and Health.</td>
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<table>
<tr><td>admission *</td><td></td><td></td></tr>
<tr><td>LVEF</td><td>28 %</td><td>26%</td></tr>
<tr><td>NYHA class, mean (% in class II)</td><td>2.3 (72%)</td><td>2.3 (67%)</td></tr>
<tr><td>HF score #</td><td>1.2</td><td>1.1</td></tr>
<tr><td>N-BNP (pmol/l)</td><td>217</td><td>251</td></tr>
</table>
* HF admission before index admission at time of recruitment

standardised HF score

(symptom value: orthopnoea 0.5; PND 1.0; reduction in exercise tolerance 0.5; resting sinus tachycardia >100/min 0.5; JVP >4cm 0.5; hepatojugular reflex positive 1.0; 3rd heart sound 1.0; basal crackles 1.0; hepatomegaly 0.5; peripheral oedema 0.5. Decompensated HF indicated by score ≥2.)
</td>
<td>in loop diuretic to furosemide 500mg twice/day; addition of digoxin up to 0.25 mg/day; additional diuretic (spironolactone 25-50 mg once/day, then metolazone 2.5-5mg once a day); then additional vasodilator (isosorbide mononitrate 60-120mg once av day then felodipine 2.5-5mg once a day). If targets were not reached patients were reassessed at 2 week intervals and treatment intensified until targets were met, at which point 3 month reviews were resumed.*</td>
<td>treatment was intensified according to a strict and predetermined stepwise protocol (see intervention)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td colspan="8">Effect Size</td>
</tr>
</table>

Outcomes		
All cause hospital admissions (events) Median 9.5 mths	BNP 17/33; Clinical 25/36; p=0.83	
HF hospital admissions (events) Median 9.5 mths	BNP 5; Clinical 13, p=0.52	
Mortality (cardiovascular death) (number of patients) Median 9.5 mths	BNP 1/33; Clinical 7/36; RR 0.16 [0.02, 1.20]	
Adverse events Median 9.5 mths	13/33 patients in the BNP group experienced adverse events compared with 9/36 in the clinical group (p=0.32). There was no difference in the rate of cough or symptomatic hypotension between groups (21% and 18% in the BNP group vs. 11% and 8% i the clinical group, p=0.73 and 0.34 respectively).	

*ACE inhibitor doses were matched at baseline (15.3 (SD 7.9) mg enalapril-equivalent for BNP group vs. 13.1 (6.7) mg for clinical group, p=0.32)) but increased by 4.8 (5.9) mg in the BNP group vs. 1.2 (6.9) mg in the clinical group at 6 months (p=0.027). Furosemide doses were not significantly different at baseline (p=0.27) and increased (baseline to 6 months) from a mean of 123 (145) mg to 197(237) mg in the BNP group vs. 87 (119) mg to 141 (263) mg in the clinical group (p=0.34). More patients in the BNP group were receiving Spiranolactone at 6 months (6 vs.1, p=0.049). There was no difference in B-blocker use at baseline or 6 months (4 and 4 patients in the BNP group vs. 1 and 2 patients in the clinical group, respectively). Felodipine was not prescribed for any patient.

Additional visits to intensify treatment were needed in 18 patients in the BNP group and 14 patients in the clinical group (p=0.34).

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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.	Multi centre RCT Randomised Unclear allocation concealment Single blind (blind outcome assessment) ITT used Setting: 17 University hospitals in France	N=220 Drop-out: No patient lost to follow-up	Inclusion criteria: Patients older than 18 years with symptomatic (New York Heart Association functional class II to III) systolic heart failure defined by left ventricular ejection fraction (LVEF) <45% assessed by echocardiography using the American Society of Echocardiography guidelines, in stable condition (no hospital stay in the previous month) and treated by optimal medical therapy according to the European guidelines at the time of the study; dosages of medications were to be stable for at least 1 month before inclusion. Patients had to receive diuretics, ACEI's, or angiotensin II receptor blockers (ARB) at the maximum tolerated dosage unless documented intolerance and beta-blockers approved for CHF (carvedilol, bisoprolol, and metaprolol XR-CL), at the maximal tolerated dosage unless documented intolerance or specific contra-indication. Exclusion criteria: Acute coronary syndrome within 3 months, chronic renal failure (plasma creatininemia	BNP group Medical therapy was increased with the aim of lowering plasma BNP levels (target <100 pg/ml). [1]	Clinical group Medical therapy was adjusted according to the opinion of the investigator, on the basis of the physical examination and usual paraclinical and biological parameters.	Minimum 6 months, median 15 months (every month for 3 months, then every 3 months).	CHF related death All cause death Hospital stay for CHF All cause hospital stay	Not reported

>250µmol/l), documented hepatic cirrhosis, asthma, or chronic obstructive pulmonary disease.

Patient characteristics:

	Clinical group (N=110)	BNP group (N=110)
Age (yrs)	66±6	65±5
M/F	62/48	65/45
Smoking (%)	53	39 (p=0.03)
Dyslipidemia (%)	60	46
Duration of heart failure (months)	29	31
Ischaemic heart failure (%)	48	55
Weight (kg)	77±17	76±18
NYHA functional class	2.21±0.62	2.29±0.60
QRS duration (ms)	118±40	119±43
LVEF (%)	31.8 ± 8.4	29.9±7.7 (p=0.05)

			LVED (mm) 69±11 67±12					

Effect Size

Outcomes	
Death related to HF (no. of patients) Median 15 mths	3/110 in the BNP group vs. 9/110 in the clinical group
All cause death (no. of events) Median 15 mths	7/110 in the BNP group vs. 11/110 in the clinical group (p=ns)
Hospital stays for HF (no. of patients) Median 15 mths	22/110 in the BNP group vs. 48/110 in the clinical group (p<0.0001)
Hospitalisation for acute HF decompensation (no. of	2/110 in the BNP group vs. 10/110 in the clinical group (p<0.02)

patients) Median 15 mths	
All cause hospital stays (no. of patients) Median 15 mths	60/110 in the clinical group vs. 52/110 in the BNP group (p=ns)
Composite end point (unplanned hospital stays for HF or death related to heart failure) (no. of patients) Median 15 mths	25/110 in the BNP group vs. 57/110 in the clinical group (p<0.001)

* At baseline, medical treatment was optimised in the population: 99% of patients received an ACEI or an ARB at 94% of the recommended dosage. Similarly 94% of patients received a B-blocker at 58% of the recommended dosage. All the patients received furosemide. No significant difference between groups for any drugs at baseline.

Titration phase: treatment adjustment during the first 3 months

Changes in treatment occurred more frequently in the BNP group compared with the clinical group, 134 vs. 66 occasions (p<0.05). In the BNP group, the treatment was adjusted according to the plasma BNP level in 79% of the cases (106 of the 134 treatment changes).

The most frequently changed pharmacological drugs were diuretics (41% of the changes in the BNP group vs. 39% of the changes in the clinical group, p=ns).

The mean increase in the furosemide dosage was 9±20 mg and was similar in both groups. However, all types of drugs were changed more frequently in the BNP group (furosemide: 55% vs. 26% of the patients; spironolactone: 17% vs. 7% of the patients; ACEI or ARB: 21% vs. 9% of the patients; beta blockers: 36% vs. 20% of the patients).

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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.	Multicentre RCT Randomised Concealed central allocation Single blind (blinding of patients) Power analysis ITT reported Setting:15 out-patient centres in Switzerland and	N=622	Inclusion criteria: Patients aged 60 years or older with dyspnea (New York Heart Association class ≥ II with current therapy), a history of hospitalisation for heart failure within the last year, and an N-Terminal BNP level of 400 pg/ml, or higher in patients younger than 75 years and a level of 800 pg/ml or higher in patients aged 75 years or older. Exclusion criteria: Patients with dyspnea not mainly due to heart failure, with valvular disease requiring surgery, acute coronary syndromes within the previous 10 days, angina pectoris classified as being in the Canadian Cardiovascular Society Class higher than II, revascularisation within the previous month, body mass index higher than 35, serum creatinine level higher than 2.49 mg/dl, a life expectancy of less than 3 years for non cardiovascular diseases, unable give informed consent, no follow-up possible, or participating in another study.	BNP guided + Symptom guided medical therapy (BNP group) Medical therapy to reduce BNP level to 2 times or less the upper limit of normal (<400 pg/ml in patients younger than 75 years and <800 pg/ml in patients aged 75 years or older) and	Symptom guided medical therapy. (Symptom guided group) Medical therapy to reduce symptoms to NYHA class of II or less.	1, 3, 6, 12 and 18 months	All cause hospitalisation Hospitalisation for HF Quality of life (assessed by the Minnesota Living with Heart Failure) Serious adverse events	Not reported

<table>
<tr>
<td>2009; 301(4):383-392.</td>
<td>Germany</td>
<td></td>
<td>Patient characteristics:
<table>
<tr><th></th><th>Symptom guided (n=248)</th><th>BNP group (N=251)</th></tr>
<tr><td>Age (yrs) (m(SD))</td><td>77 (8)</td><td>76(7)</td></tr>
<tr><td>Female</td><td>92 (37.1)</td><td>80 (31.9)</td></tr>
<tr><td>BMI mean (SD)</td><td>25.3 (4.3)</td><td>25.4 (4.0)</td></tr>
<tr><td>NYHA class ≥ III</td><td>185 (74.6)</td><td>186 (74.1)</td></tr>
<tr><td>LVEF, mean(SD)%</td><td>29.7 (7.9)</td><td>29.8 (7.7)</td></tr>
<tr><td>N terminal BNP, median(IQR), pg/ml</td><td>4657 (2455-7520)</td><td>3998 (2075-7220)</td></tr>
<tr><td>COPD</td><td>44 (17.7)</td><td>60 (23.9)</td></tr>
</table></td>
<td>symptoms to NYHA class of II or less. *</td>
<td></td>
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</table>

Effect Size

Outcomes	
Survival free of all cause hospitalisations (no .of events)	/251 BNP vs /248 symptom guided Reported as 41% BNP guided vs. 40% symptom guided; hazard ratio, 0.91 (95% CI, 0.72-1.14); p=0.39

Follow-up 18 months	
Survival free of hospitalisation for HF (no. of events) Follow-up 18 months	Reported as 72% BNP vs. 62% symptom guided; hazard ratio, 0.68 (95% CI, 0.50-0.92); p=0.01
Overall mortality rates (no. of events) Reported: Overall survival rates (no. of events) Follow-up 18 months	16% BNP vs. 22% symptom guided (40/251 vs. 55/248) Reported as: 84% BNP vs. 78% symptom guided ; hazard ratio, 0.68 (95% CI, 0.45-1.02); p=0.06
Heart failure hospitalisation Follow-up 18 months	BNP 30/251vs clinically-guided 40/248 Derived from: Overall survival 84% vs 78% and therefore overall mortality 16% vs 22%. Heart failure hospital-free survival 72% vs 62% and therefore death or hospitalisation for HF 28% vs 38%. HF hospitalisation 12% vs 16%
Quality of Life (Minnesota living with heart failure questionnaire) Follow-up 18 months	Baseline (symptom guided 42.0 (20.3) vs. BNP guided 38.3 (20.2)) ; Month 12 (symptom guided 27.0 (18.6) vs. BNP guided 27.7 (17.9)); Month 18 (symptom guided 27.3 (21.5) vs. BNP guided 28.2 (17.6)) Improved from baseline to 12 months in both groups; p<0.001 and remained unchanged between month 12 and 18. No significant differences between 2 groups.
Serious adverse events	Overall 236 patients had at least 1 serious adverse event (mostly hospitalisation) (47.3%); 49% in the BNP and 45.6% in the symptom guided group (p=0.47)

*Patients were given angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and B-blockers.

Escalation of therapy was suggested as follows: addition of spiranolactone, escalating doses of angiotensin converting enzyme inhibitors, angiotensin II receptor blockers and B-blockers, loop diuretics, low dose digoxin, long acting nitrates, metazolone or another thiazide, molsidomide during nitrate free intervals, and intravenous diuretics or inotropes. Therapy was reduced in cases of significant adverse effects based on the investigators discretion.

At baseline, a high percentage of patients were receiving the recommended heart failure therapy. Up titration of therapy to reduce symptoms was recommended in 192 patients in the symptom guided group at baseline (77%), in 140 of 229 patients at visit month 1 (61%) in 111 of 210 patients at visit month 3 (53%), and in 101 of 194 patients at visit month 6 (52%).

In patients in the N-terminal BNP guided group, an increase in therapy was recommended in 213 patients at baseline, (86%), in 221 of 232 patients at visit month 1 (95%), in 198 of 218 patients at visit month 3 (91%), and in 190 of 211 patients at visit month 6 (90%) ($p<0.001$ between treatment groups at all follow-up visits and $p=0.03$ at baseline).

Doses of drugs with proven prognostic efficacy (ACE-I, ARB, B-blocker) were up titrated to a significantly greater extent in the BNP group vs. symptom guided group.

Spironolactone and eplerenone were given more frequently in patients in the BNP group. Thus, 179 patients received spironolactone (or eplerenone) at any time during the study (72%) vs. 156 in the symptom-guided group (63%, $p=0.05$).

Age

ACE: Angiotensin converting enzyme inhibitors

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

Evidence Tables

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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.	RCT Double-blind, randomised, ITT, unclear allocation concealment	N=74	Inclusion criteria: patients with left ventricular ejection fraction (LVEF) on echo or radionuclide ventriculography ≥ 40%. Where a LVEF could not be measured systolic function had to be preserved or only mildly impaired by direct visualisation of the echo. Exclusion criteria: patients who dies during hospitalization; with haemodynamically significant valvular disease; pulmonary hypertension; right ventricular systolic dysfunction; uncontrolled atrial fibrillation or flutter; unstable angina pectoris; hypotension; myocardial infarction within 1 month; renal failure (serum creatinine >150mmol/L); renal artery stenosis; severe liver or pulmonary disease. Also patients treated with tetracyclines, lithium, benzodiazepines, major tranquillisers, anti-depressants (with the exception of selective serotonin reuptake inhibitors) or major psychoactive drugs.	Quinapril, titrated at 2 week periods from 5 mg to 40 mg within 6 weeks N=36	Placebo N=38	6 months	Echo parameters, 6 minute walk test; Qol	Parke Davis & Co. Ltd

<table>
<tr><th>Reference</th><th>Study type/
Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td></td><td></td><td>Patient characteristics:
<table>
<tr><td></td><td>Placebo</td><td>Quinopril</td><td>P value</td></tr>
<tr><td>Age</td><td>78± 7</td><td>77 ± 7</td><td>0.280</td></tr>
<tr><td>Male (%)</td><td>12 (31.6)</td><td>14 (38.9)</td><td>0.627</td></tr>
<tr><td>NYHA class</td><td></td><td></td><td></td></tr>
<tr><td>I</td><td>0</td><td>2 (5.5%)</td><td></td></tr>
<tr><td>II</td><td>28 (73.7%)</td><td>28 (77.8%)</td><td>0.23</td></tr>
<tr><td>III</td><td>10 (26.3%)</td><td>6 (16.7%)</td><td></td></tr>
<tr><td>IV</td><td>0</td><td>0</td><td></td></tr>
<tr><td>Medications</td><td></td><td></td><td></td></tr>
<tr><td>BB</td><td>3 (7.9)</td><td>7 (19.4)</td><td>1.000</td></tr>
<tr><td>Calcium channel blocker</td><td>7 (18.4)</td><td>15 (41.7)</td><td>1.000</td></tr>
<tr><td>Diuretics</td><td>37 (97.1)</td><td>34 (94.4)</td><td>0.962</td></tr>
<tr><td>Digoxin</td><td>10 (26.3)</td><td>14 (38.9)</td><td>0.322</td></tr>
</table></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Effect Size Outcomes 1. Qol- McMaster quality of life questionnaire: 7 point scale, 1 being worse and 7 the best. Questions divided into 3 dimensions: dyspnoea (5 questions); fatigue (4 questions); emotional function (7 questions): • After 6 months: quinapril: 12.9 ± 3.1; placebo: 13.1 ± 4.7; MD -0.20 [-2.01, 1.61], p=0.83 2. NYHA class • Improvement in NYHA class from III to II: quinapril: 1/36; placebo: 2/38; RR 0.53 [0.05, 5.57], p=0.60 3. Total number of side effects experienced: • Quinapril: 30/36; Placebo: 28/38; RR 1.13 [0.89, 1.44], p=0.31 5. Mortality • Quinapril: 1/36; placebo: 1/38; RR 1.06 [0.07, 16.25], P=0.97								
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.	RCT Double-blind, multicentre, international, randomized, allocation concelament	N=850	Inclusion criteria: patients ≥70 years and treated with diuretics for a clinical diagnosis of CHF due to LV diastolic dysfunction, and a CV hospitalization within the previous 6 months. Patients had to walk without the aid of another person in order to exclude very frail patients who might not respond to any treatment. Clinical criteria needed for diagnosis of diastolic dysfunction (at least 3 of 9 needed and at least 4 additional echo criteria required): exertional breathlessness; orthopnoea or paroxysmal nocturnal dyspnoea; ankle swelling; improved breathlessness with diuretic; increased jugular	Perindopril 4mg/day N=424 assigned (420 assessed for primary outcome)	Placebo N=426	1 year and 18 months	Combined endpoint (all cause mortality, HF hospitalization); CV death; HF hospitalization; hospital bed days for CV reasons or any reason; change in NYHA class	Servier

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<td>venous pressure; prior episode of clinical pulmonary oedema; prior MI; Cardiothoracic ratio >0.55; previous pulmonary oedema. Echo criteria: LV wall motion index 1.4-1.6- roughly equivalent to an LVEF 40-50%; a left atrial diameter >25mm/m² body surface area or>40mm because chronic elevation of LV filling pressure should lead to atrial dilatation; an interventricular septum or posterior LV wall ≥12mm in thickness suggesting hypertrophy; evidence of impaired LV filling by at least one criteria recommended by the European Society of Cardiology study group on Diastolic Heart Failure (E/A ratio <0.5 or DT >280ms from the mitral inflow pattern or an isovolumic relaxation time >105ms.

Exclusion criteria: patients with wall motion index <1.4, roughly equivalent to an LVEF <40%. Patients with AF, haemodynamically significant valve disease, stroke with the previous month, sitting systolic arterial pressure <100mmHg; serum creatinine >200umol/l or potassium >5.4mmol/l, history of ACE I intolerance or use of an ACE I or ARB in the previous week, potassium sparing diuretics (other than low dose spironolactone), or potassium supplements.

Patient characteristics:

<table>
<tr><td></td><td>Placebo</td><td>Perindopril</td></tr>
<tr><td>Age (yrs)</td><td>75 (72-79)</td><td>75 (72-79)</td></tr>
<tr><td>Women (%)</td><td>57%</td><td>54%</td></tr>
<tr><td>NYHA class I/II (%)</td><td>317 (74%)</td><td>327 (77%)</td></tr>
</table>
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</tr>
</table>

			NYHA class III/IV (%)	109 (26%)	97 (23%)					
			LVEF (%)	64 (56-66)	65 (56-66)					
			BB	228 (54%)	235 (55%)					

Effect Size

Outcomes

1. All cause death
   - 1 yr: Placebo: 19/ 426; perindopril 17/420; HR 0.90 (0.47; 1.73), P=0.747
2. CV death
   - 1 yr: Placebo: 17/426; perindopril 10/420; HR 0.59 (0.27, 1.29), p=0.181
3. HF hospitalization
   - 1 yr: Placebo: 53/426; perindopril: 34/420; HR 0.63 (0.41; 0.97); p=0.033
4. Adverse events
   - Perindopril: 9/420; Placebo: 4/426

ALDO: Aldosterone antagonists + optimal medical management vs placebo + optimal medical management

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?

Evidence tables

ALDO: 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?

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>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.</td>
<td>Multicentre, international RCT

Double blinded, allocation concealment unclear, ITT

Original EPHESUS trial

HF post-MI</td>
<td>N=6642

Drop out: during the study 1021 patients (493 in the placebo group and 528 in the eplerenone group) permanently discontinued the study medication (149 in the placebo group and 147 in the eplerenone group due to adverse events)</td>
<td>Inclusion criteria: patients 3-14 days after acute myocardial infarction (MI) as documented according to standard criteria; left ventricular dysfunction as documented by a LVEF ≤40% on echo, radionuclide angiography, or angiography of the left ventricle after the index acute MI and before randomization; and heart failure as documented by the presence of pulmonary rales, chest radiography, showing pulmonary venous congestion, or the presence of a third heart sound. In patients with diabetes who met the criteria for left ventricular dysfunction after acute MI, symptoms of HF did not have to be demonstrated, as these patients have an increased risk of cardiovascular events similar to that of non-diabetic patients with symptoms of HF.

Exclusion criteria: patients on potassium-sparing diuretics; with a serum creatinine concentration >2.5mg per deciliter; a serum potassium concentration >5 mmol/l.

Patient characteristics:

No significant differences between the groups at baseline
<table>
<tr><th></th><th>Eplerenone group (n=3319)</th><th>Placebo group (n=3313)</th></tr>
<tr><td>Age (yr)</td><td>64 ± 11</td><td>64 ± 12</td></tr>
</table>
</td>
<td>Eplerenone

25 mg per day after 4 weeks increased to 50mg/day.

If potassium >5.5mmol/L the dose was reduced or discontinued until potassium <5.5 mmol/L

N=3313 (12 assigned to group did not take treatment)</td>
<td>Placebo

N=3319 (12 assigned to group did not take treatment)</td>
<td>Mean follow-up 16 months (range 0-33)</td>
<td>Time to death from any cause, time to death from cardiovascular cause, or first hospitaliztion for a cardiovascular event. Death from cardiovascular causes, death from any cause or any hospitalization, adverse events.</td>
<td>Not reported</td>
</tr>
</table>

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Race-no. (%)							
			White	2995 (90)	2989 (90)					
			Black	30 (1)	44 (1)					
			Other	294 (9)	280 (8)					
			Sex-no. (%)							
			Male	2380 (72)	2334 (70)					
			Female	939 (28)	979 (30)					
			LVEF (%)	33± 6	33 ± 6					
			Days from MI to randomization	7.3 ±3.0	7.3 ± 3.0					
			Symptoms of HF (%)	90	90					
			Serum creatinine (mg/dl)	1.1 ± 0.3	1.1 ± 0.3					
			Creatinine clearance (ml/min)	79± 60	78±57					
			Medications (%)							
			ACE/ARB	86	87					
			BB	75	75					

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			diuretics 60 61					

Effect size

1. Death from any cause at 16 months

- Eplerenone group: 478/3319; placebo group: 554/3313

2. Sudden death (from cardiac causes) at 16 months

- Eplerenone group: 162/3319; placebo group: 201/3313

3. Any hospitalization (no. of patients) at 16 months

- Eplerenone group: 1493/3319; placebo group: 1526/3313

4. Hyperkalaemia

- Eplerenone group: 113/3307; placebo group: 66/3301

Authors' conclusion: *'eplerenone was beneficial in patients who were receiving optimal therapy including an ACE inhibitor or angiotensin-receptor blocker, a beta-blocker, aspirin, a lipid lowering agent, and coronary reperfusion therapy.'*

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Pitt B, Gheorghiade M, Zannad F et al. Evaluation of eplerenone in the subgroup of EPHESUS patients with	Multicentre RCT EPHESUS subgroup of patients with LVEF <30	N=2106	**Inclusion criteria:** patients 3-14 days after acute myocardial infarction (MI) as documented according to standard criteria; left ventricular dysfunction as documented by a LVEF ≤40% on echo, radionuclide angiography, or angiography of the left ventricle after the index acute MI and before randomization; and heart failure as documented by the presence of pulmonary	Eplerenone 25 mg per day after 4 weeks increased to 50mg/day. If potassium	Placebo N=1058	Mean follow-up 16 months (range 0-33)	All-cause mortality, CV mortality, CV hospitalization, sudden cardiac death, death due to progressive HF, nonfatal	Not reported

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>baseline left ventricular ejection fraction [less-than or equal to] 30%. European Journal of Heart Failure. 2006; 8(3):295-301.</td><td>SEVERE HF (post-MI)</td><td></td><td>rales, chest radiography, showing pulmonary venous congestion, or the presence of a third heart sound. In patients with diabetes who met the criteria for left ventricular dysfunction after acute MI, symptoms of HF did not have to be demonstrated, as these patients have an increased risk of cardiovascular events similar to that of non-diabetic patients with symptoms of HF.

Exclusion criteria: patients on potassium-sparing diuretics; with a serum creatinine concentration >2.5mg per deciliter; a serum potassium concentration >5 mmol/l.

Patient characteristics for patients with LVEF ≤30%:

No significant differences between the groups at baseline

<table><tr><td></td><td>Eplerenone group (n=1048)</td><td>Placebo group (n=1058)</td></tr><tr><td>Age (yr)</td><td>65 ± 11</td><td>65 ± 12</td></tr><tr><td>Race-no. (%)</td><td></td><td></td></tr><tr><td>White</td><td>914 (87)</td><td>922 (87)</td></tr><tr><td>Black</td><td>14 (1)</td><td>18 (2)</td></tr><tr><td>Other</td><td>120 (11)</td><td>118 (111)</td></tr></table></td><td>>5.5mmol/L the dose was reduced or discontinued until potassium <5.5 mmol/L

N=1048</td><td></td><td></td><td>hospitalization for HF, Adverse events

End points reported at 16 month follow-up and 30 days post-randomization.</td><td></td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Sex-no. (%)							
			Male	777 (74)	752 (71)					
			Female	271 (26)	306 (29)					
			LVEF (%)	26 ± 4	26± 5					
			Days from MI to randomization	7.4± 3.0	7.3± 3.0					
			Serum creatinine (mg/dl)	1.2 ± 0.4	1.2 ± 0.4					
			Medications (%)							
			ACE/ARB	92	92					
			BB	73	73					
			diuretics	71	73					
			Digitalis	25	26					
			K+ supplements	18	20					
			Aspirin	87	87					
			Statins	51	50					
			revascularization	44	45					

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Effect Size Outcomes **1. All cause mortality:** • 16 month: eplerenone group 205/1048 (19.6%); placebo group 254/1058 (24%) **2. Sudden cardiac death:** • 16 month: eplerenone group 71/1048 (6.8%); placebo group 103/1058 (9.7%) **3. Nonfatal hospitalization for HF** • 16 month: eplerenone group 152/1048 (14.5%); placebo group 181/1058 (17.1%) **Authors' Conclusions:** *'the results of this analysis suggest an important role for eplerenone both in the early (30 days) as well as late prevention of all-cause mortality, sudden cardiac death, and heart failure mortality/heart failure hospitalizations in patients with heart failure post-AMI and baseline LVEF ≤30%. These findings are of particular importance because patients with severely reduced ejection fraction have a high incidence of sudden death, death due to progressive heart failure, and all cause mortality.'*								
Reference	**Study type**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
Pitt B, White H, Nicolau J et al. Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left	Multicentre RCT EPHESUS – extra outcome	N=6642 139 in placebo group and 134 in eplerenone group discontinued therapy.	**Inclusion criteria:** patients 3-14 days after acute myocardial infarction (MI) as documented according to standard criteria; left ventricular dysfunction as documented by a LVEF ≤40% on echo, radionuclide angiography, or angiography of the left ventricle after the index acute MI and before randomization; and heart failure as documented by the presence of pulmonary rales, chest radiography, showing pulmonary venous congestion, or the presence of a third heart sound. In patients with diabetes who met the criteria for left ventricular dysfunction after acute MI,	Eplerenone 25 mg per day after 4 weeks increased to 50mg/day. If potassium >5.5mmol/L the dose was reduced or discontinued	Placebo N=3319 (12 assigned to group did not take treatment)	Mean follow-up 16 months (range 0-33)	Death from any cause, composite end point of time to death from CV causes or hospitalization for CV events, CV mortality, sudden cardiac death, fatal/nonfatal hospitalization at 30 days.	Not reported

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>ventricular systolic dysfunction and heart failure. Journal of the American College of Cardiology. 2005; 46(3):425-431.</td><td></td><td></td><td>symptoms of HF did not have to be demonstrated, as these patients have an increased risk of cardiovascular events similar to that of non-diabetic patients with symptoms of HF.

Exclusion criteria: patients on potassium-sparing diuretics; with a serum creatinine concentration >2.5mg per deciliter; a serum potassium concentration >5 mmol/l.

Patient characteristics:

No significant differences between the groups at baseline

<table>
<tr><td></td><td>Eplerenone group (n=3319)</td><td>Placebo group (n=3313)</td></tr>
<tr><td>Age (yr)</td><td>64 ± 11</td><td>64 ± 12</td></tr>
<tr><td>Race-no. (%)</td><td></td><td></td></tr>
<tr><td>White</td><td>2995 (90)</td><td>2989 (90)</td></tr>
<tr><td>Black</td><td>30 (1)</td><td>44 (1)</td></tr>
<tr><td>Other</td><td>294 (9)</td><td>280 (8)</td></tr>
<tr><td>Sex-no. (%)</td><td></td><td></td></tr>
<tr><td>Male</td><td>2380 (72)</td><td>2334 (70)</td></tr>
<tr><td>Female</td><td>939 (28)</td><td>979 (30)</td></tr>
<tr><td>LVEF (%)</td><td>33± 6</td><td>33 ± 6</td></tr>
</table>
</td><td>until potassium <5.5 mmol/L

N=3313 (12 assigned to group did not take treatment)</td><td></td><td></td><td></td><td></td></tr>
</table>

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Days from MI to randomization</td><td>7.3 ±3.0</td><td>7.3 ± 3.0</td></tr>
<tr><td>Serum creatinine (mg/dl)</td><td>1.1 ± 0.3</td><td>1.1 ± 0.3</td></tr>
<tr><td>Symptoms of HF (%)</td><td>90</td><td>90</td></tr>
<tr><td>Medications (%)</td><td></td><td></td></tr>
<tr><td>ACE/ARB</td><td>86</td><td>87</td></tr>
<tr><td>BB</td><td>75</td><td>75</td></tr>
<tr><td>diuretics</td><td>60</td><td>61</td></tr>
</table>
</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="9">Effect size
1. All cause mortality at 30 days
• Eplerenone group: 107/3319 (3.2%); placebo group: 153/3313 (4.6%)
2. sudden cardiac death at 30 days
• Eplerenone group: 30/3319 (0.9%); placebo group: 47/3313 (1.4%)
3. fatal/nonfatal HF hospitalization at 30 days
• Eplerenone group: 114/3319 (3.4%); placebo group: 138/3313 (4.2%)
4. hyperkalaemia at 30 days
• Eplerenone group: 23/3319 Placebo: 15/3313</td></tr>
</table>

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td colspan="9">Authors' conclusion: 'thus, in patients with LVSD and signs of heart failure, it would seem prudent to initiate eplerenone in hospital following hemodynamic stabilization after AMI and to continue eplerenone in addition to an ACE inhibitor or an ARB and a beta-blocker over the long term.'</td></tr>
<tr><td>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.</td><td>RCT

Randomized and double blinded (methods unclear)

CHF secondary to CAD</td><td>N=42

2/28 in the spironolactone group required withdrawal from medication due to adverse events.</td><td>Inclusion criteria: patients with CHF secondary to coronary artery disease, documented by coronary angiography. The diagnosis confirmed by an average radionuclide left ventricular ejection fraction of 20%. All patients had congestive symptoms or signs in the past, but at the time were clinically believed to be receiving the optimal diuretic dose.

Exclusion criteria:

Patients with hypertension or any other active medical condition, haematologic abnormality, serum creatinine >200umol/L, or abnormal liver function tests.

Patient characteristics:
<table><tr><td></td><td>Placebo (n=14)</td><td>Spironolactone (n=28)</td></tr><tr><td>Age (yr)</td><td>70 ± 2</td><td>68 ± 3</td></tr><tr><td>M/F</td><td>10/4</td><td>22/6</td></tr><tr><td>Aetiology</td><td></td><td></td></tr><tr><td>Coronary artery</td><td>14</td><td>28</td></tr></table></td><td>Spironolactone 50mg

N=28

All patients had a 1 month run-in before randomization

All patients were treated with a loop diuretic and ACE inhibitors and most low dose aspirin. A constant sodium diet (150mmol/day) was maintained</td><td>Placebo

N=14

See intervention for more details</td><td>8 weeks</td><td>Neurohormonal assays, biochemical assays, cardiac measurements</td><td>British Heart foundation, Scottish Hospitals Endowment Research Trust</td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			disease			by all throughout the study.				
			Previous MI	9	16					
			NYHA class							
			II	6	10					
			III	8	18					
			Furosemide (mg/day)	72 ± 10	75 ± 9					
			Enalapril (mg/day)	17 ± 5	18 ± 4					
			Aspirin	11/14	25/28					
			Calcium antagonist	4/14	7/28					
			Nitrate	6/14	13/28					
			Radionuclide LVEF	21 ± 5	19 ± 7					

Effect Size

- onolactone group: 4/28 patients developed serious hyperkalaemia (>5.5 momol/L), placebo 0/14

2. Creatinine

- Spironolactone group: 4/28 patients had elevated plasma creatinine (>300umol/L), placebo 0/14

Authors' conclusion: '*renal changes occurred in the absence of symptoms; this suggests that a weekly biochemical monitoring is desirable initially after spironolactone therapy is begun, even if renal function is normal at baseline.'*

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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.	RCT Blinding and allocation concealment unclear RALES (dose finding) **SEVERE HF**	N=214 N=212 completed	**Inclusion criteria:** patients with symptomatic heart failure, as defined as New York Heart Association (NYHA) classes II-IV, a LVEF ≤35%, a history of NYHA functional class III or IV within the prior 6 months of enrolment. **Exclusion criteria**: patients were excluded if they (1) were diagnosed with an acute life-threatening disease (including patients with automatic implantable cardioverter/defibrillators), valvular disease, unstable angina pectoris, insulin-dependant diabetes, cancer (without a recurrence within the last 5 years), or primary hepatic failure; (2) were on a waiting list for heart transplant (3) experienced an MI 30 days before the irst dose of study medication, (4) had laboratory values for haematology or biochemical examinations considered abnormal and clinically significant before the first dose of study medication, (5) received a potassium-sparing diuretic within 30 days before the first dose of study medication, (6) were receiving, on a regular basis, either nonsteriodal anti-inflammatory drugs or aspirin (>325mg/day), steroids, dopamine agonists or antagonists, insulin, heparin, or (7) receiving any investigational medication within 30 days of the first dose medication. **Patient characteristics:**	Spironolactone 12.5 mg (n=41), 25mg (n=45), 50mg (n=47), 75mg (n=41) once per day All patients were receiving a stable dose of an ACE I, loop diuretic and optional digitalis for ≥30 days before first dose of placebo or spironolactone.	Placebo n=40 see intervention for more details	12 weeks	Change in vital signs, urinary aldosterone, N-terminal ANF, plasma rennin activity, hematocrit and haemoglobin, serum potassium, serum magnesium, adverse effects	Not reported

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Age (yr): placebo 61 ± 12; 12.5 mg/d group 63 ± 12; 25 mg/d group 61 ± 9; 50mg/d group 62 ± 13; 75 mg/d group 62 ± 13 **White/other (%):** placebo 97/3 ; 12.5 mg/d group 93/7; 25 mg/d group 98/2; 50mg/d group 93/7; 75 mg/d group 88/12 **NYHA class (%)** **II:** placebo 38 ; 12.5 mg/d group 63; 25 mg/d group 60; 50mg/d group 43; 75 mg/d group 49 **III:** placebo 60; 12.5 mg/d group 35; 25 mg/d group 38; 50mg/d group 55; 75 mg/d group 49 **IV:** placebo 2 ; 12.5 mg/d group 2; 25 mg/d group 2; 50mg/d group 2; 75 mg/d group 2 **ACE mean dose (mg)** **Captopril (n=84)** placebo 65.4 ; 12.5 mg/d group 57.3; 25 mg/d group 57.5; 50mg/d group 69.7; 75 mg/d group 59.4 **Enalapril (n=98)** placebo 10.8; 12.5 mg/d group 16.4; 25 mg/d group 13.4; 50mg/d group 14.5; 75 mg/d group 16.3 **Lisinopril (n=22)** placebo 16.4; 12.5 mg/d group 17.5; 25 mg/d group 20.0; 50mg/d group 7.5; 75 mg/d group 13.3 **Quinapril (n=6)** 12.5 mg/d group 10.0; 50mg/d group 12.5; 75 mg/d group 20.0 **Ramipril (n=1)** 25 mg/d group 4.0;					

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Perinidopril (n=1) 25 mg/d group 2.5 **Loop diuretic dose** **Furosemide (mg)** placebo 63.2; 12.5 mg/d group 58.8; 25 mg/d group 82.8; 50mg/d group 76.9; 75 mg/d group 84.9 **Digitalis (%)**placebo 77.5 ; 12.5 mg/d group 78.0; 25 mg/d group 77.8; 50mg/d group 76.6; 75 mg/d group 80.5 **Potassium supplement (%)**placebo 30.0; 12.5 mg/d group 43.9; 25 mg/d group 37.8; 50mg/d group 34.0; 75 mg/d group 39.0					
Effect Size Outcomes 1. **Hyperkalaemia** • All doses of active treatment produced significantly higher serum potassium levels relative to baseline than placebo, p≤0.03 • Incidence of hyperkalaemia (%) in intent-to treat cohort: placebo 1/40 (2.5%), 50mg group 7/47(15%) **Limitations**: • The results of this study are not applicable to patients with HF who are not receiving an ACE as well. • Most patients were white, therefore results may not be applicable to other ethnicities Authors' conclusion: '*we recommend beginning therapy at a dose of 25mg/day in patients maintained with an ACE inhibitor and monitoring serum potassium at 1,4 and 8 weeks.'*								
Pitt B, Zannad F, Remme WJ et	RCT	N=1663	**Inclusion criteria:** patients with a NYHA class IV within 6 months of enrolment, in NYHA class III or IV at enrolment, had a	Spironolactone 25 mg	Placebo	Mean follow up 24 months (the	Death from any cause, death from	Searle, Stokie Ill

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>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.</td>
<td>Randomized (method unclear) double blinded, ITT

RALES

SEVERE HF LVEF <35%</td>
<td>414 patients (200 in placebo and 214 in spironolactone group) discontinued treatment due to lack of response, adverse events or administrative reasons.</td>
<td>diagnosis of HF at least 6 weeks before enrolment, were treated with an ACE inhibitor and a loop diuretic, had LVEF <35% within 6 months before enrolment. Treatment with digitalis and vasodilators was allowed, but potassium sparing diuretics were not permitted.

Exclusion criteria: patients with a primary operable valvular heart disease (other than mitral or tricuspid regurgitation with clinical symptoms due to LVSD), congenital heart disease, unstable angina, primary hepatic failure, active cancer, or any life-threatening disease. Patients who had undergone heart transplantation or were awaiting the procedure. Patients with serum creatinine >2.5mg/dl and a serum potassium >5 mmol/l.

Patient characteristics:
<table>
<tr><th></th><th>Placebo (n=841)</th><th>Spironolactone (n=822)</th></tr>
<tr><td>Age (yr)</td><td>65 ± 12</td><td>65 ± 12</td></tr>
<tr><td>White race %</td><td>86</td><td>87</td></tr>
<tr><td>Male</td><td>614 (73)</td><td>603 (73)</td></tr>
<tr><td>Female</td><td>227 (27)</td><td>219 (27)</td></tr>
<tr><td>NYHA class</td><td></td><td></td></tr>
<tr><td>II</td><td>3 (0.4)</td><td>4 (0.5)</td></tr>
</table>
</td>
<td>N=822

After 8 weeks the dose could be increased to 50mg/day if the patient showed no signs or symptoms of progression of HF without evidence of hyperkalaemia. If hyperkalaemia developed the dose could be decreased to 25mg every other day.</td>
<td>N=841</td>
<td>observed effect of spironolactone on the risk of death from all causes exceeded the pre-specified critical z value, therefore the trial was stopped early)</td>
<td>cardiac causes, hospitalization for cardiac causes, the combined incidence of death from cardiac causes or hospitalization fro cardiac causes, a change in NYHA class.</td>
<td></td>
</tr>
</table>

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			III	581 (69)	592 (72)					
			IV	257 (31)	226 (27)					
			LVEF %	25.2± 6.8	25.6 ± 6.7					
			Cause of HF							
			Ischemic	453 (54)	454 (55)					
			Non-ischemic	386 (46)	368 (45)					
			Medications %							
			Loop diuretics	100	100					
			ACE	94	95					
			Digitalis	72	75					
			Aspirin	37	36					
			Potassium supplements	27	29					
			BB	10	11					
			Mean dose-ACE (mg/day)							
			Captopril	62.1	63.4					
			Enalapril	16.5	13.5					
			lisinopril	13.1	15.5					

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Effect size **1. All cause death** • Placebo group: 386/841 (46%); spironolactone group: 284/822 (35%) **2. Hospitalization** • Cardiac causes - Placebo group: 753/841; spironolactone group: 515/822; 30% reduction in risk of hospitalization for cardiac causes • Heart failure – Placebo group: 300/841, spironactone group 215/822 **3. Hyperkalaemia** • Serious hyperkalaemia: placebo group: 10/841 (1%); spironolactone group: 14/822 (2%) **4. Gynecomastia in men** • Placebo group: 8/614; spironolactone group: 55/603 **Authors' Conclusion:** *'spironolatone reduced the risk of death from all causes, hospitalization for cardiac causes, and the combined endpoint of death from cardiac causes or hospitalization for cardiac causes among patients who had severe heart failure as a result of left ventricular systolic dysfunction and who were receiving standard therapy including ACE inhibitor.'*								
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	RCT- cross-over trial Randomized, double-blinded (unclear method) 25% drop out **MILD HF**	N=57 (43 completed) 14 did not complete the study, 8 in spironolactone group (2 had cramps and 2 had hyperkalaemia) and 6 in the placebo group (1 had lethargy and 1 died). 6 developed	**Inclusion criteria:** patients who at diagnosis their CHF had been at least class II NYHA, but optimising their treatment had improved patients substantially into a stable, less symptomatic state. Left ventricular systolic dysfunction on ~~e~~cho, angiographic, or nuclear imaging was mandatory and taken as a LVEF <50% or fractional shortening <25% at some time in the recent past. All patients were taking ACE inhibitors or ARBs and their individually titrated BB dose for at least 6 months. **Exclusion criteria:** patients with serum sodium concentration <130 mmol/l, potassium >5-mmol/l, urea >10.0mmol/l, or creatinine >221umol/l.	Spironolactone 25 mg N=43 After 2 weeks this doubled to the maximum dose 50mg, if side effects occurred or plasma urea and electrolytes became	Placebo N=43 After 3 months patients were crossed over to spironolactone for 3 months.	6 months	Endothelial function, intra-arterial infusions, BNP, serum pro-collagen II N-terminal peptide (PIINP), QT parameters, heart rate variability, six minute walk, Minnesota living with heart failure questionnaire, hospital	Northwood Trust

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>failure already taking optimal treatment. Heart. 2004; 90(7):765-770.</td>
<td></td>
<td>intercurrent illness and 2 withdrew without giving a reason.</td>
<td>Patient characteristics:
<table>
<tr><td></td><td>Mean (SD)</td></tr>
<tr><td>Age (yrs)</td><td>67.5 (7.05)</td></tr>
<tr><td>M/F</td><td>35/8</td></tr>
<tr><td>NYHA class I/II</td><td>15/28</td></tr>
<tr><td>HF aetiology HT/IHD/dilated cardiomyopathy</td><td>9/29/5</td></tr>
<tr><td>IHD</td><td>38 (88%)</td></tr>
<tr><td>Left ventricular hypertrophy</td><td>9 (21%)</td></tr>
<tr><td>Potassium (mmol/l)</td><td>4.37 (0.34)</td></tr>
<tr><td>Creatinine (umol/l)</td><td>111 (27.2)</td></tr>
<tr><td>Furosemide (mg)</td><td>33.0 (38.0)</td></tr>
<tr><td>Aspirin</td><td>38 (88%)</td></tr>
<tr><td>Warfarin</td><td>3 (12%)</td></tr>
<tr><td>ACE/ARB</td><td>36 (84%)/7 (16%)</td></tr>
<tr><td>Statin</td><td>25 (58%)</td></tr>
<tr><td>BB</td><td>31 (72%)</td></tr>
<tr><td>Digoxin</td><td>4 (9%)</td></tr>
</table>
Systolic and diastolic blood pressures were significantly lower among patients taking spironolactone (p=0.004; p=0.005)</td>
<td>deranged the dose was halved.

After 3 months patients were crossed over to placebo for 3 months.</td>
<td></td>
<td></td>
<td>anxiety and depression questionnaire.</td>
<td></td>
</tr>
</table>

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td colspan="9">Effect Size

1. Minnesota Living with Heart Failure Questionnaire, mean (SD)

• Placebo group: 16.2 (15.9); spironolactone group 18.8 (18.6), p=0.044 (worse with spironolactone)

Authors' conclusion: ' a mega-trial should now be undertaken to establish whether these improvements in surrogate markers translate into a significant prognostic benefit and in particular to see whether any putative benefit outweighs the not inconsiderable and unpredictable risks of hyperkalaemia when spironolactone and ACE inhibitors are given together in certain patients with CHF.'</td></tr>
<tr><td>Agostoni P, Magini A, Andreini D et al. Spironolactone improves lung diffusion in chronic heart failure. European Heart Journal. 2005; 26(2):159-164.</td><td>RCT

Randomised (method unclear), open label (but research personnel involved in the randomization procedure and the personnel that evaluated patients were blinded with regard to study protocol, treatment, and time</td><td>N=30

Drop out: 1 in the spironolactone group due to gynaecomastia</td><td>Inclusion criteria: patients with NYHA class II or III, optimized individually tailored drug treatment, stable clinical conditions for at least 2 months as confirmed by absence of relevant oedema, capability of performing a CPET, lung diffusion for carbon monoxide (DLco) <80% of predicted.

Exclusion criteria: patients with a history of and/or clinical documentation of pulmonary embolism, primary valvular disease, pericardial disease, severe obstructive lung disase, primitive or occupational lung disease, renal failure (serum creatinine >2.0 mg/dl), hyperkalaemia (serum K+>5.5mEq/L), significant peripheral vascular disease, exercise induced angina, ST changes, or severe arrhythmias.

Patient characteristics:
<table><tr><td></td><td>Spironolactone (n=15)</td><td>Placebo (n=15)</td></tr></table></td><td>Spironolactone 25 mg

N=15</td><td>Placebo

N=15</td><td>6 months</td><td>QoI (Minnesota living with heart failure questionnaire), pulmonary function and lung diffusion, cardiopulmonary exercise test.</td><td>Centro Cardiologico Monzino Research Grant</td></tr>
</table>

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td>course of the study), ITT

CHRONIC HF (with reduced lung diffusion)</td><td></td><td>
<table>
<tr><td>Age (yr)</td><td>60.3 ± 9.4</td><td>57.7 ± 7.3</td></tr>
<tr><td>M/F</td><td>10/5</td><td>12/3</td></tr>
<tr><td>EF (%)</td><td>40 ± 19</td><td>35 ± 11</td></tr>
<tr><td>Aetiology</td><td></td><td></td></tr>
<tr><td>Primitive cardiomyopathy</td><td>11</td><td>9</td></tr>
<tr><td>Ischemic cardiomyopathy</td><td>4</td><td>6</td></tr>
<tr><td>ACE</td><td>14</td><td>8</td></tr>
<tr><td>BB</td><td>12</td><td>7</td></tr>
<tr><td>Diuretic</td><td>9</td><td>15</td></tr>
<tr><td>AT1 blockers</td><td>1</td><td>4</td></tr>
<tr><td>Digoxin</td><td>2</td><td>3</td></tr>
<tr><td>Amiodarone</td><td>3</td><td>5</td></tr>
</table>
</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="9">Effect Size
1. Minnesota Living with Heart Failure Questionnaire:
• Spironolactone group: basal: 27 ± 16; 6 months 27 ± 15
• Placebo group: basal: 26 ± 16; 6 months 27 ± 17
• Changes from baseline: spironolactone group: 1 ± 9; placebo group 2 ± 12, NS
2. Creatinaemia (mg/dl) (Raised creatinine)
• Changes from baseline: spironolactone group: 0 ± 0.22; placebo group 0.03 ± 0.30, NS, MD -0.03 (-0.22, 0.16)</td></tr>
</table>

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Study Limitations: • Only HF patients with low DLco included, therefore results cannot be extended to patients with normal DLco • The spironolactone effects in HF are potentially ubiquitous and they limited there evaluation to the lungs.								

ARB1: angiotensin II receptor antagonists vs placebo

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

Evidence Tables

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Granger CB, McMurray JJ, Yusuf S et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function	RCT Powered International, multicentre trial Randomised	N=2028 2 lost to follow up in candersartan group; 1 lost to follow up in placebo group	Inclusion criteria: patients ≥18 years who had symptomatic HF (NYHA class II-IV)m of at least 4 weeks' duration, LVEF ≤ 40%, intolerance to ACE inhibitors (defined as having an ACE inhibitor discontinued by a physician because of intolerance, with specific cause classified). Exclusion criteria (from CHARM overall study): serum creatinine 265 umol/l or more, serum potassium 5.5 mol/l or more, known bilateral renal artery stenosis symptomatic hypotension, women of childbearing	Candesartan Started at 4 or 8mg daily and doubled every 2 weeks according to titration	Placebo Matching Candesartan dosing N=1015	2 Years Median 33.7 months	1◦ outcome: cardiovascular death or unplanned admission to hospital for the management of worsening CHF. 2◦ outcomes: cardiovascular death,	AstraZeneca R&D

<table>
<tr><th>Reference</th><th>Study type/ Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet. 2003; 362(9386):772-776.

CHARM-Alternative</td>
<td>(computer-generated), double-blinded, ITT, allocation concealment</td>
<td>N=2025 completed</td>
<td>potential not using adequate contraception, critical aortic or mitral stenosis, myocardial infarction, stroke, or open heart surgery in the previous 4 weeks, use of an angiotensin-receptor blocker in the previous 2 weeks, any non-cardiac disease judged likely to limit 2 year survival, and unwillingness to consent.

Patient characteristics:
<table>
<tr><th></th><th>Candesartan (n=3830)</th><th>Placebo (n=3796)</th></tr>
<tr><td>Mean age (years)</td><td>66.3 (11.0)</td><td>66.8 (10.5)</td></tr>
<tr><td>≥75 years</td><td>233 (23.0%)</td><td>239 (23.5%)</td></tr>
<tr><td>Men/women</td><td>691 (68.2%)/ 322 (31.8%)</td><td>691 (68.1%)/ 324 (31.9%)</td></tr>
<tr><td>NYHA Class II</td><td>487 (48.1%)</td><td>479 (47.2%)</td></tr>
<tr><td>III</td><td>490 (48.4%)</td><td>479 (47.2%)</td></tr>
<tr><td>IV</td><td>36 (3.6%)</td><td>37 (3.6%)</td></tr>
<tr><td>Mean (SD) LVEF (%)</td><td>29.8 (7.6)</td><td>30.0 (7.2)</td></tr>
</table>
</td>
<td>protocol.
Target dose 32mg from 6 weeks onwards

N=1013</td>
<td></td>
<td></td>
<td>admission to hospital for CHF, or non-fatal myocardial infarction; cardiovascular death, admission to hospital for CHF, non-fatal myocardial infarction, or non-fatal stroke; cardiovascular death, admission to hospital for CHF, non-fatal myocardial infarction, non-fatal stroke, or coronary revascularization; death (any cause) or admission to hospital for CHF; and development of new diabetes; causes for discontinuation</td>
<td></td>
</tr>
</table>

<table>
<tr><th>Reference</th><th>Study type/
Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Background medication</td><td></td><td></td></tr>
<tr><td>Diuretic</td><td>864 (85.3%)</td><td>869 (85.6%)</td></tr>
<tr><td>BB</td><td>553 (54.6%)</td><td>553 (54.5%)</td></tr>
<tr><td>Spironolactone</td><td>250 (24.7%)</td><td>233 (23.0%)</td></tr>
</table>
</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="9">
Effect Size
Outcomes
Composite outcome
Cardiovascular death or hospital admission for CHF: candesartan 334/1013; placebo: 406/1015; hazard ratio 0.77 (CI 0.67-0.89) p=0.0004 adjusted hazard ratio 0.70 (CI 0.60-0.81) p=<0.0001
RR 0.82 [0.73, 0.93], P=0.001
Cause for discontinuation:
Hypotension: candesartan 37/1013; placebo 9/1015, p<0.0001
Increase in creatinine: candesartan: 62/1013; placebo 27/1015, p<0.0001
Hyperkalaemia: candesartan: 19/1013; placebo 3/1015, RR 6.35 [1.88, 21.38], P=0.003
All cause death
Candesartan: 265/1013; placebo: 296/1015
</td></tr>
</table>

<table>
<tr><th>Reference</th><th>Study type/ Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td colspan="9">HF hospitalization
Candesartan: 207/1013; placebo: 286/1015</td></tr>
<tr><td>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</td><td>RCT

Multicentre, double-blind, parallel-group, randomized, allocation concealment, ITT

(NOT ON ACEI)</td><td>N=844

(55 discontinued early)

(629 included in the per protocol analysis)</td><td>Inclusion criteria: male and female patients 21-80 years of age with mild to moderate symptomatic CHF (NYHA class II or III). LVEEF 30-45% confirmed by echo, ventriculography or scintigraphy.

Exclusion criteria: severe or malignant hypertension; symptomatic hypertension, myocardial infarction within 3 months of the trial; hemodynamically relevant arrhythmias and the use of pacemakers or implanted cardioverters, hemodynamically relevant valvular defect or insufficiency; angina pectoris; clinically significant diseases; autoimmune or wasting disease; psychological illness; drug or alcohol addiction; type I diabetes mellitus; uncontrolled diabetes mellitus or diabetes requiring insulin therapy; and limitation of exercise capacity for a reason other than CHF; pregnant/lactating women; those unable to comply.

Patient characteristics:
<table>
<tr><th></th><th></th><th colspan="3">Candesartan</th></tr>
<tr><th></th><th>Placebo</th><th>4 mg</th><th>8mg</th><th>16mg</th></tr>
<tr><td>Age, yr</td><td>62.1 ± 9.3</td><td>62.4 ± 9.3</td><td>61.5 ± 9.5</td><td>61.6 ± 9.4</td></tr>
</table></td><td>Candesartan cilexetil 4 (n=208), 8 (n=212) or 16mg (n=213) (initially 4 mg then 8mg after 1 week and than 16mg after another week)</td><td>Placebo

N=211</td><td>12 weeks</td><td>Exercise tolerance, signs and symptoms, NYHA class, cardiothoracic ratio, neuroendocrine parameters, blood pressure, heart rate.</td><td>Not reported</td></tr>
</table>

<table>
<tr><th>Reference</th><th>Study type/
Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Sex (M/F)</td><td>153 (72.5%) / 58 (27.5)</td><td>128 (61.5%) / 80 (38.5)</td><td>151 (71.2%) / 61 (28.8%)</td><td>145 (68.1%) / 68 (31.9%)</td></tr>
<tr><td>Ejection fraction</td><td>39.0 ± 4.8</td><td>38.6 ± 4.2</td><td>38.8 ± 4.5</td><td>38.8 ± 4.6</td></tr>
<tr><td>NYHA class</td><td></td><td></td><td></td><td></td></tr>
<tr><td>I</td><td>167 (79.1%)</td><td>172 (82.7%)</td><td>166 (78.3%)</td><td>180 (84.5%)</td></tr>
<tr><td>II</td><td>44 (20.9%)</td><td>36 (17.3%)</td><td>46 (21.7%)</td><td>33 (15.5%)</td></tr>
<tr><td>ACE I</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Diuretics</td><td>123 (58.3%)</td><td>126 (60.6%)</td><td>133 (62.7%
0</td><td>123 (57.7%)</td></tr>
<tr><td>BB</td><td>1 (0.5 %)</td><td>1 (0.5 %)</td><td>1 (0.5 %)</td><td>0</td></tr>
</table>
</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="9">Effect Size
Outcomes
1. NYHA class
• Improved: placebo: 28/201; 4mg: 39/203; 8mg 41/202; 16mg: 34/201; 16mg vs. placebo: RR 1.21 [0.77, 1.92], p=0.41
• No change: placebo: 170/201; 4mg: 162/203; 8mg: 161/202; 16mg: 165/20; 16mg vs. placebo : RR 0.97 [0.89, 1.06], p=0.50
• Deterioration: 3/210; 4mg: 2/203; 8mg: 0/202; 16mg: 2/201; 16mg vs. placebo: RR 0.67 [0.11, 3.95], p=0.65
2. Increase in creatinine:
• Placebo: 4/211; 4mg: 6/208; 8mg: 9/212; 16mg: 2/213; total in candesartan group: 17/633</td></tr>
</table>

<table>
<tr><th>Reference</th><th>Study type/
Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td colspan="9">3. All cause mortality
• Candesartan: 10/633; placebo: 1/211</td></tr>
<tr><td>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</td><td>RCT

Randomised, double-blind, unclear allocation concealment, ITT</td><td></td><td>Inclusion criteria: men and women ≥ 20 years, with symptomatic CHF due to previous MI, hypertensive heart disease, dilated cardiomyopathy or valvular disease. NYHA class II or III with LVEF ≤ 45% measured by echo, radionuclide imaging or contrast ventriculography within 2 months of enrolment.

Exclusion criteria: patients with unstable angina, life-threatening ventricular arrhythmias, severe valvular stenosis; hypertrophic obstructive cardiomyopathy; advanced respiratory disease; MI within 1 month; cardiogenic shock or severe hypotension; symptomatic cerebrovascular disease within 3 months; serum creatinine >2 mg/dl; hyperkalaemia; advanced hepatic dysfunction; history of drug allergy or hypersensitivity; pregnant/nursing women; patients treated with another investigational drug.

Patients who had been treated with an ACE I were enrolled in the study if (a) their symptoms were not adequately controlled, (b) they were intolerant to ACE I, (c) they were willing to participate.

Patient characteristics:
<table><tr><td></td><td>Candesartan</td><td>Placebo</td></tr></table></td><td>Candesartan cilexetil 4mg for 2-4 weeks, 8mg for 24 weeks

N=148</td><td>Placebo

N=144</td><td>Up to 30 weeks</td><td>Composite score (patient hospitalization, increase in any medications); CV events, adverse events</td><td>Takeda Chemical Industries</td></tr>
</table>

<table>
<tr><th>Reference</th><th>Study type/
Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Age, yrs</td><td>63.1 ± 11.3</td><td>64.4 ± 10.9</td></tr>
<tr><td>M/F</td><td>78/22</td><td>77/23</td></tr>
<tr><td>NYHA class II/III</td><td>76/24</td><td>72/28</td></tr>
<tr><td>LVEF % (median)</td><td>35.3 (34.6)</td><td>34.1 (33.9)</td></tr>
<tr><td>Previous treatment with ACE-I</td><td>43.9</td><td>52.8</td></tr>
<tr><td>Ambient drug therapy</td><td></td><td></td></tr>
<tr><td>Diuretic</td><td>84.5</td><td>81.9</td></tr>
<tr><td>Beta-adrenergic blocker</td><td>18.9</td><td>21.5</td></tr>
</table>
</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="9">Effect Size
Outcomes
1. Hypotension
• Candesartan: 10/151; placebo: 2/147
2. All cause mortality
• Candesartan: 2/148; placebo: 3/144
3. HF hospitalization
• Candesartan: 8/148; placebo: 17/144</td></tr>
</table>

<table>
<tr><th>Reference</th><th>Study type/
Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>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 analysis-subgroup not on ACE I)</td><td>Subgroup analysis of multicentre RCT- Val-HeFT</td><td>N=366</td><td>Inclusion criteria: men and women ≥ 18 yrs old with a history and clinical findings of HF for at least 3 months; NYHA class II to IV; clinically stable; receiving a fixed dose regimen that might include ACE inhibitors, diuretics, digoxin and B blockers for at least 2 weeks; LVEF <40% and echo measured LVIDD/BSA >2.9 cm/m². This reported subgroup were not treated with ACE I.

Patient characteristics:
<table><tr><td></td><td>Valsartan</td><td>Placebo</td></tr><tr><td>Age (yrs)</td><td>66.6 ± 10.3</td><td>67.7 ± 10.4</td></tr><tr><td>Females (%)</td><td>24.3</td><td>33.1</td></tr><tr><td>Whites (%)</td><td>95.1</td><td>95.0</td></tr><tr><td>NYHA class III-IV</td><td>41.1</td><td>53.0 *</td></tr><tr><td>BB</td><td>39.5</td><td>37.0</td></tr><tr><td>LVEF %</td><td>27.6 ± 6.7</td><td>28.7 ± 6.6</td></tr></table>* P<0.05</td><td>Valsartan 40mg twice daily, doubled every 2 weeks to target of 160mg twice daily

N=185</td><td>Placebo

N=181</td><td>24 months</td><td>Time to death, time to composite outcome (morbidity and mortality); change in EF, LV diastolic volume, QoI, neurohormonal profile, adverse events.</td><td>Novartis Pharma AG</td></tr>
<tr><td colspan="9">Effect Size
Outcomes
1. All cause mortality</td></tr>
</table>

<table>
<tr><th>Reference</th><th>Study type/ Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td colspan="9">
Valsartan: 32/185; placebo: 46/181; RR (95% CI) 0.67 (0.42-1.06); P=0.017
2. change in QoL (Minnesota Living with Heart Failure Questionnaire) at 1 yr
Valsartan: -4.15 ± 1.78 (n=86); placebo: 1.01 ± 2.11 (n=73), p=0.047
MD -5.16 [-5.77, -4.55], P<0.0001
3. mean increase in creatinine
Valsartan: 0.18 ± 0.02; placebo: 0.10 ± 0.02, p=0.009
MD: 0.08 [0.08, 0.08], p<0.001
4. Hypotension
Valsartan: 1/185; placebo: 1/181, RR 0.98 [0.06, 15.52]p=0.988
</td></tr>
<tr><td>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.</td><td>RCT

Randomized, double-blinded, unclear allocation concealment, ITT</td><td>N=116 (103 completed)</td><td>Inclusion criteria: men and women aged 18-80 years with stable CHF, NYHA class II-IV for at least 1 month; mean pulmonary capillary wedge pressure ≥15 mmHg.

Exclusion criteria: patients on ACEI or in the previous 6 months; history of acute MI or unstable angina in the last 3 months; acute pulmonary oedema or decompensated congestive heart failure in the previous month; angina pectoris; clinically significant primary valvular dysfunction; restrictive cardiomyopathy; constrictive pericarditis; life-threatening ventricular arrhythmias or sustained ventricular tachycardia; non-cardiac dyspnoea; hepatic or renal impairment; uncontrolled hypertension; history of cerebrovascular accident; gastrointestinal disease; malignancy or clinically significant allergies.

Patient characteristics:<table><tr><td></td><td>Valsartan</td><td></td></tr></table></td><td>Valsartan 40mg (n=24), 80mg (n=24), 160mg (n=27) twice daily OR ACE I lisinopril (n=15) once daily 5mg for 7 days followed by 10mg for 3 weeks.</td><td>Placebo (n=26)</td><td>28 days</td><td>Mean pulmonary capillary wedge pressure, cardiac output, systemic vascular resistance, adverse events, changes in body weight, heart rate, blood pressure, laboratory parameters.</td><td>Not reported</td></tr>
</table>

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			<table><tr><td></td><td>40mg</td><td>80mg</td><td>160mg</td><td>Placebo</td></tr><tr><td>Male (%)</td><td>18 (75)</td><td>23 (95.8)</td><td>22 (81.5)</td><td>23 (88.5)</td></tr><tr><td>Age, yrs (Mean ± SD)</td><td>58.8 ± 11.1</td><td>53.9 ± 10.6</td><td>56.3 ± 9.3</td><td>53.3 ± 11.1</td></tr></table>					

Effect Size

Outcomes

1. hypotension:

- Valsartan 40mg: 0/24; 80mg: 1/24; 160mg: 0/27 (total: 1/75); placebo:0/26

2. All cause mortality

- Valsartan: 1/75; placebo: 1/26

POPULATION: PRESERVED LVEF

Ref ID: 1902								
Reference	**Study type/ Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
Yusuf et al Effects of candesartan in patients	RCT Powered	Total: 3025 No data: 2 Candesartan: 1514 (2 lost	Inclusion criteria: Eligible patients were aged 18 years or older, had New York Heart Association functional class II-IV of at least 4 weeks' duration, had a history of hospital admission for a cardiac reason, and had	Candesartan Started at 4 or	Placebo Matching	2 years Median	1◦ outcome: cardiovascular death or unplanned admission to	AstraZeneca R&D

<table>
<tr><td>Ref ID: 1902</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Reference</td><td>Study type/
Evidence level</td><td>Number of patients</td><td>Patient characteristics</td><td>Intervention</td><td>Comparison</td><td>Length of follow-up</td><td>Outcome measures</td><td>Source of funding</td></tr>
<tr><td>with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial
Ref ID 2</td><td>International, multicentre trial

Randomised (computer-generated), double-blinded, ITT, allocation concealment</td><td>to follow up)
Placebo: 1509 (1 lost to follow up)</td><td>LVEF higher than 40%.
Exclusion criteria: not mentioned, but taken to be the same as the overall programme exclusion criteria: serum creatinine 265 umol/l or more, serum potassium 5.5 mol/l or more, known bilateral renal artery stenosis symptomatic hypotension, women of childbearing potential not using adequate contraception, critical aortic or mitral stenosis, myocardial infarction, stroke, or open heart surgery in the previous 4 weeks, use of an angiotensin-receptor blocker in the previous 2 weeks, any non-cardiac disease judged likely to limit 2 year survival, and unwillingness to consent.

Patient characteristics:<table><tr><td></td><td>Candesartan (n=1514)</td><td>Placebo (n=1509)</td></tr><tr><td>Mean age (years)</td><td>67.2 (11.1)</td><td>67.2 (11.1)</td></tr><tr><td>≥75 years</td><td>407 (26.9%)</td><td>400 (26.5%)</td></tr><tr><td>Men/women</td><td>920 (60.8%)/ 594 (39.2%0</td><td>891 (59.0%)/ 618 (41.0%)</td></tr><tr><td>NYHA Class</td><td></td><td>905</td></tr></table></td><td>8mg daily and doubled every 2 weeks according to titration protocol.
Target dose 32mg from 6 weeks onwards.

N=1512</td><td>candesartan dose

N=1508</td><td>follow up was 36.6 months</td><td>hospital for the management of worsening CHF.
2◦ outcomes: cardiovascular death, admission to hospital for CHF, or non-fatal myocardial infarction; cardiovascular death, admission to hospital for CHF, non-fatal myocardial infarction, or non-fatal stroke; cardiovascular death, admission to hospital for CHF, non-fatal myocardial infarction, non-fatal stroke, or coronary revascularization; death (any cause) or admission to hospital for CHF; and development of new diabetes; causes for</td><td></td></tr>
</table>

Ref ID: 1902								
Reference	**Study type/ Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
			II: 931 (61.5%) / (60.0%0 III: 556 (36.7%) / 584 (38.7%) IV: 27 (1.8%) / 20 (1.3%) Mean (SD) LVEF (%): 54.0 (9.4) / 54.1 (9.4) Background medication: ACE inhibitor: 296 (19.6%) / 280 (18.6%) Diuretic: 1138 (75.2%) / 1121 (74.3%) BB: 847 (55.9%) / 837 (55.5%) Spironolactone: 171 (11.3%) / 181 (12.0%)				discontinuation	

Ref ID: 1902								
Reference	**Study type/ Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
Effect Size **Combined outcome** Cardiovascular death or hospital admission for CHF: candesartan: 333/1514; placebo: 366/1509; hazard ratio 0.89 (CI 0.77-1.03) p=0.118 adjusted hazard ratio 0.86 (CI 0.74-1.00) p=0.051 **Cardiovascular death:** Candesartan: 170/1514; placebo: 170/1509; hazard ratio 0.99 (CI 0.80-1.22) P=0.918 adjusted hazard ratio 0.95 (CI 0.76-1.18) p=0.635 **Hospital admission for CHF:** Candesartan 241/1514; placebo: 276/1509; hazard ratio 0.85 (C I 0.72-1.01) p=0.072 adjusted hazard ratio 0.84 (CI 0.70-1.00) p=0.047 **Cause of discontinuation** Hypotension: candesartan: 37/1514; placebo: 17/1509, p=0.009 Increase creatinine: candesartan: 72/1514; placebo: 36/1509, RR 1.99 [1.34, 2.96] p=0.0006 Hyperkalaemia: candesartan: 22/1514; placebo: 9/1509, p=0.029 **All-cause mortality (taken from the health economic paper of this trial McMurray et al– Ref ID 361)** Candesartan 237/1514; placebo: 244/1509;								
Massie BM, Carson PE, McMurray JJ et al. Irbesartan in patients with heart failure and	RCT International, multicentre, Randomised, allocation concealment,	N=4128	Inclusion criteria: patients were at least 60yrs, and had heart failure symptoms and a LVEF ≥45%. Patients must have been in hospital for heart failure during the previous 6 months and have a NYHA class II, III or IV; if they had not been hospitalized they were required to be NYHA class III or IV with corroborative evidence (pulmonary	Irbesartan 75mg, double to 150mg after 1-2 weeks and doubled again to 300mg after a further 1-2weeks	Placebo N=2061	Mean 49.5 months	Composite score (all cause death and HF hospitalization); all cause death; HF hospitalization; composite HF	Bristol-Myers Squibb and Sanofi-Aventis

<table>
<tr><td>Ref ID: 1902</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Reference</td><td>Study type/
Evidence level</td><td>Number of patients</td><td>Patient characteristics</td><td>Intervention</td><td>Comparison</td><td>Length of follow-up</td><td>Outcome measures</td><td>Source of funding</td></tr>
<tr><td>preserved ejection fraction. New England Journal of Medicine. 2008; 359(23):2456-2467

I-PRESERVE</td><td>single-blind, ITT</td><td></td><td>congestion on radiography, left ventricular hypertrophy or left atrial enlargement on echo or left ventricular hypertrophy or left bundle branch block on electrocardiography. ACE I treatment was permitted only if it was considered essential for an indication other than uncomplicated hypertension.

Exclusion criteria: previous intolerance to an ARB; an alternative probable cause of the patient’s symptoms; any previous LVEF <40%; a history of acute coronary syndrome; coronary revascularization or stroke within the last 3 months; substantial valvular abnormalities; hypertrophic or restrictive cardiomyopathy; pericardial disease; cor pulmonale or other cause of isolated right heart failure; systolic blood pressure <100mgHg or >160mmHg or a diastolic blood pressure >95mmHg despite anti-hypertensive therapy; other systemic disease limiting life expectancy <3 years; haemoglobin <11g/dl; creatinine >2.5mg/dl; liver function abnormalities; poor compliance.

Patient characteristics:
<table><tr><td></td><td>Placebo</td><td>Irbesartan</td></tr><tr><td>Mean age.</td><td>72 ± 7</td><td>72 ± 7</td></tr></table></td><td>N=2067</td><td></td><td></td><td>outcome (CV death, HF hospitalization); Qol; NT-proBNP; composite vascular score (CV death-MI/stroke)</td><td></td></tr>
</table>

<table>
<tr><td>Ref ID: 1902</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Reference</td><td>Study type/
Evidence level</td><td>Number of patients</td><td>Patient characteristics</td><td>Intervention</td><td>Comparison</td><td>Length of follow-up</td><td>Outcome measures</td><td>Source of funding</td></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>yrs</td><td></td><td></td></tr>
<tr><td>Female (%)</td><td>1264 (61)</td><td>1227 (59)</td></tr>
<tr><td>White (%)</td><td>1925 (93)</td><td>1934 (94)</td></tr>
<tr><td>Black (%)</td><td>43 (2)</td><td>39 (2)</td></tr>
<tr><td>Asian</td><td>15 (1)</td><td>19 (1)</td></tr>
<tr><td>other</td><td>78 (4)</td><td>75 (4)</td></tr>
<tr><td>NYHA class</td><td></td><td></td></tr>
<tr><td>II</td><td>445 (22)</td><td>426 (21)</td></tr>
<tr><td>III</td><td>1562 (76)</td><td>1582 (77)</td></tr>
<tr><td>IV</td><td>53 (3)</td><td>59 (3)</td></tr>
<tr><td>Ejection fraction</td><td>0.60 ± 0.09</td><td>0.59 ± 0.09</td></tr>
<tr><td>diuretic</td><td>1721 (84)</td><td>1696 (82)</td></tr>
<tr><td>ACE I</td><td>510 (25)</td><td>538 (26)</td></tr>
<tr><td>BB</td><td>1202 (58)</td><td>1225 (59)</td></tr>
</table>
</td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="9">Effect Size:
1. Death all cause
• Placebo: 436/2061; irbesartan: 445/2067; Hazard ratio: 1.00 (0.88-1.14); p=0.98
• Irbesartan vs. placebo: RR 1.02 [0.91, 1.14], P=0.77
2. CV death
• Placebo: 302/2061; irbesartan: 311/2067; Hazard ratio: 1.01 (0.86-1.18); p=0.92
3. Composite outcome: death from HF or HF hospitalization</td></tr>
</table>

Ref ID: 1902								
Reference	**Study type/ Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
• Placebo: 438/2061; irbesartan: 428/2067; Hazard ratio: 0.96 (0.84-1.09); p=0.51 4. HF hospitalization • Placebo: 336/2061; irbesartan: 325/2067; Hazard ratio: 0.95 (0.81-1.10), p=0.50 5. Hypotension • Placebo: 62/2061; irbesartan: 60/2067, p=0.84 6. Hyperkalaemia • Placebo: 9/2061; irbesartan: 12/2067, p=0.34 7. Mean Creatinine (at last visit) • Placebo: 0.98 ± 0.34 mg/dl; irbesartan: 1.02 ± 0.46 mg/dl, p=0.11 • Irbesartan vs. Placebo: MD 0.04 [0.02, 0.06], P=0.001								

ARB2: a) angiotensin-II receptor antagonists + angiotensin converting enzyme inhibitor vs placebo + angiotensin converting enzyme inhibitor;

b) angiotensin-II receptor antagonists + angiotensin converting enzyme inhibitor + beta blocker vs placebo + angiotensin converting enzyme inhibitor + beta blocker

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

Evidence Tables

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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. Ref ID: 1	RCT + Powered International, multi-centre trial	Total: 2548 Candersartan: 1276 Placebo: 1272	Inclusion criteria: patients were aged 18 yrs or older, had left-wentricular ejection fraction 40% or lower measured within the past 6 months, New York Heart Association functional class II-IV (if class II, patients had to have admission to hospital for a cardiac reason in the previous 6 months), and treatment with an ACE inhibitor at a constant dose for 30 days or longer. Exclusion criteria: included serum creatinine 265 umol/l or more, serum potassium 5.5mmol/l or more, known bilateral renal artery stenosis, symptomatic hypotension, women of childbearing potential not using adequate contraception, critical aortic or mitral stenosis, myocardial infarction, stroke, or open heart surgery in the previous 4 weeks, use of an angiotensin-receptor blocker in the previous 2 weeks, any non-cardiac disease judged likely to limit 2 year survival, and unwillingness to consent.	Candesartan Started at 4 or 8mg daily and doubled every 2 weeks according to titration protocol. Target dose 32mg from 6 weeks onwards **BACKGROUND MEDICATION OVERALL IN BOTH GROUPS: ACEi - 100%** **BB – 55%**	Placebo Matching Candesartan dosing	Median follow up 41 months	1◦ outcome: cardiovascular death or unplanned admission to hospital for the management of worsening CHF. 2◦ outcomes: cardiovascular death, admission to hospital for CHF, or non-fatal myocardial infarction; cardiovascular death, admission to hospital for CHF, non-fatal myocardial infarction, or non-fatal	AstraZeneca R&D

Reference	Study type/ Evidence level	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				Candesartan (n=3830)	Placebo (n=3796)				stroke; cardiovascular death, admission to hospital for CHF, non-fatal myocardial infarction, non-fatal stroke, or coronary revascularization; death (any cause) or admission to hospital for CHF; and development of new diabetes	
			Mean age (years)	64.0 (10.7)	64.1 (11.3)					
			≥75 years	212 (16.6%)	245 (19.3%)					
			Men/women	1006 (78.8%)/ 270 (21.2%)	100 (78.6%)/ 272(21.4 %)					
			NYHA Class II	312 (24.5%)	302 (23.7%)					
			III	931 (73.0%)	925 (72.7%)					
			IV	33 (2.6%)	45 (3.5%)					

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Effect Size Outcomes (intention to treat population) Cardiovascular death or hospital admission for CHF: candesartan 483/1276; placebo 538/1272; hazard ratio 0.85 (CI 0.75-0.96) p=0.011 adjusted hazard ratio 0.85 (CI 0.75-0.96) p=0.010 Cardiovascular death: hazard ratio 0.84 (CI 0.72-0.98) p=0.029 adjusted hazard ratio 0.83 (CI 0.71-0.97) p=0.021 Hospital admission for CHF: hazard ratio 0.83 (CI 0.71-0.96) p=0.014 adjusted hazard ratio 0.83 (CI 0.71-0.97) p=0.018 Cardiovascular death, hospital admission for CHF, MI: hazard ratio 0.85 (CI 0.76-0.96) p= 0.010 adjusted hazard ratio 0.85 (CI 0.75-0.96) p=0.007 Cardiovascular death, hospital admission for CHF, MI, stroke: hazard ratio 0.87 (CI 0.77-0.98) p=0.020 adjusted hazard ratio 0.86 (CI 0.76-0.97) p=0.015 Cardiovascular death, hospital admission for CHF, MI, stroke, coronary revascularisation procedure: hazard ratio 0.87(CI 0.77-0.97) p=0.015 adjusted hazard ratio 0.87 (CI 0.77-0.98) p=0.018 Number of patients with increased creatinine: Candesartan 100/1276; placebo 52/1272 Number of patients with hypotension: Candesartan 58/1276; placebo 40/1272 Hospitalisation: Candesartan 309/1276; placebo 356/1272 All-cause mortality: Candesartan 377/1276; placebo 412/1272								
A. R. Houghton, M. Harrison, A. J. Cowley, and J. R. Hampton.	RCT Randomised, double-blinded, ITT	N=20 N=2 (10%) drop-outs – n=1	Inclusion criteria: Age ≥18 years, NYHA functional calss II or III, heart failure at least 12 weeks duration, LVSD, had to be taking a minimum of 40 mg furosemide (or equivalent) daily and be treated with maximally tolerated doses of either enalapril or captopril for at least	Losartan (titrated to dose 25 mg at 1 week then to 50 mg 1 week later)	Placebo n=10	12 weeks	Creatinine, QoL, hyperkalemia,	None mentioned

<table>
<tr><th>Reference</th><th>Study type/
Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>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.

ID 4468</td><td>analysis, allocation concealment, powered study, acceptable (<20%) drop-outs, small trial</td><td>in each group.</td><td>3 months before randomisation and be taking stable does of these drugs for at least 4 weeks.

Exclusion criteria: haemodynamically significant obstructive valvular disease or recent (within 12 weeks) MI, stroke or symptomatic arrhythmia.

Patient characteristics:
<table><tr><td></td><td>Losartan</td><td>Placebo</td></tr><tr><td>Age (yrs)</td><td>70 ± 2</td><td>62 ± 2</td></tr><tr><td>Females (%)</td><td>10</td><td>0</td></tr><tr><td>NYHA class
II
III</td><td>
60%
40%</td><td>
70%
30%</td></tr></table>*p=0.02

There were NS differences between the groups for baseline characteristics except for age (placebo group were 8 years younger)</td><td>+ACE (as patients already on this background medication)

n=10

Randomisation preceded by a run-in phase continuing all usual medication. Patients only eligible for randomisation if passed the criteria of this phase (exercise tolerance was limited by dyspnea or fatigue and if treadmill exercise duration was consistent)</td><td>BACKGROUND MEDICATION OVERALL IN BOTH GROUPS:
ACEi - 100%
BB – 0%</td><td></td><td></td><td></td></tr>
</table>

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				N=179				
Effect Size Outcomes 1. Change in QoL (scale not mentioned) • NS difference between groups (change from baseline): Losartan: +2.0; placebo: -1.0, p=0.09; (no SD given) 2. Mean increase in serum creatinine • NS changes in either group: Losartan: 1.00 umol/L; placebo: 3.0umol/L (no SD given) 3. Hyperkalemia • Losartan: 1/10; placebo: 0/10								
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.	RCT Double-blinded, no mention of allocation concealment, power study, seems like ITT and seems like no drop-outs (as all patients accounted for in analysis)	N=48 Seems like no drop-outs as all patients accounted for in aanalysis	Inclusion criteria: ages 50 to 72 years with moderate to severe cardiac failure, stable LV dysfunction, resting EF ≤40% within 4 weeks of randomisation., NYHA class III to IV. Exclusion criteria: not reported Patient characteristics:	Cilazapril + placebo + BB (n=16) Initial dose 5 mg/day Cilazapril/valsartan + BB (n=16) Initial dose 2.5 mg/40 mg each day	Placebo + placebo + BB (n=16) **BACKGROUND MEDICATION OVERALL IN BOTH GROUPS: ACEi - 100%**	8 weeks (6 weeks at maximum tolderated dose)	AEs, NYHA class, creatinine	None mentioned

<table>
<tr><th>Reference</th><th>Study type/
Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>*HeartDrug* 2 (6):286-294, 2002.

ID 865</td>
<td></td>
<td></td>
<td>
<table>
<tr><th></th><th>Cilazapril</th><th>Cilazapril/ valsartan</th><th>Placebo</th></tr>
<tr><td>Sex M/F (%)</td><td>10 (63)/6 (37)</td><td>11 (69)/ 5 (31)</td><td>10 (63)/ 6 (37)</td></tr>
<tr><td>Age, yrs</td><td>64</td><td>64</td><td>62</td></tr>
<tr><td>NYHA class
II
III
IV</td><td>
1
13
2</td><td>
3
10
3</td><td>
1
14
1</td></tr>
</table>
</td>
<td>All patients were on beta-blockers as concomitant medication, depending upon patient’s clinical condition, the dose of the test drugs were increased at weekly intervals (cilazipril to 10 and 15 mg; cilazapril/valsartan to 5/80 mg and 10/160 mg). The highest dose was chosen according to lack of relevant side-effects.</td>
<td>BB – 100%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td colspan="9">Effect Size
Outcomes
1. NYHA class
• Placebo: improved by 1 class 2/16, unchanged 10/16, worsened by 1 class 4/16
• Cilazapril: improved by 1 class 4/16, improved by 2 classes 2/16, (improved by any class overall is therefore 6/16), unchanged 8/16, worsened by 1 class 2/16
• Cilazapril/valsartan: improved by 1 class 7/16, improved by 2 classes 5/16 (improved by any class overall is therefore 12/16), unchanged 4/16; worsened 0/16</td>
</tr>
</table>

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

- Combination treatment (cilazapril/valsartan) improved functional class significantly more (p<0.005) than the monotherapy with cilazapril

2. Serum creatinine

- No clinically significant changes (small fluctuations)

3. Dizziness probably due to hypotension

- Placebo 2/16, cilazapril 4/16, cilazapril/valsartan 3/16)

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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	Subgroup analysis of an RCT **Val-HeFT subgroup analysis (those not on concomitant beta-blockers)**	N=3034	Inclusion criteria: Eligible patients were thosein Val-HeFT receiving ACEi but not BB on entry (this was 61% patients randomised to valsartan and 60% to placebo). Patient characteristics: Valsartan (n=1532) / Placebo (n=1502) Mean age (years): 63 (10.8) / 63.9 (10.8) Men/women: 80.4%/ 19.6% / 79.3%/20.7%	Valsartan (+ ACEi: no BB) n=1532 All patients were on concomitant ACEi **BACKGROUND MEDICATION OVERALL IN BOTH GROUPS: ACEi - 100%**	Placebo (+ACEi: no BB) n=1502 All patients were on concomitant ACEi	**Mean 23 months**	QoL, NYHA, hospitalisation for HF mortality, AEs	Novartis

<table>
<tr><th>Reference</th><th>Study type/
Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>patients with heart failure: results from Val-HeFT. European Journal of Heart Failure 6 (7):937-945, 2004.

ID 396</td><td></td><td></td><td><table>
<tr><td>NYHA Class II</td><td>60.4</td><td>61.1%</td></tr>
<tr><td>III</td><td>37.5%</td><td>36.8%</td></tr>
<tr><td>IV</td><td>2.0%</td><td>2.1%</td></tr>
<tr><td>Mean (SD) LVEF (%)</td><td>26.2 (7.3)</td><td>26.5 (6.9)</td></tr>
</table></td><td>BB – 0%</td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="9">Effect Size
Outcomes
1. Mortality
• Placebo: n=338 (22.5%), valsartan n=334 (21.8%); HR 0.959 (0.824 to 1.116)
2. QoL (MLHQ)
• Significantly improved in valsartan compared to placebo: change –0.96 vs 1.82, p=0.0006; (no SD given)
3. Risk of first hospitalisation for HF:
• Valsartan n=224/1532, placebo n=315/1502: HR reduced by 34.4% (p=0.0007) with valsartan compared to placebo</td></tr>
</table>

<table>
<tr><th>Reference</th><th>Study type/
Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>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.

VaL-HeFT

ID 4470</td><td>RCT

Randomised, double blind, unclear allocation concealment, powered, unclear ITT</td><td>N=5010</td><td>Inclusion criteria: men and women ≥18 yrs with a history and clinical findings of heart failure for at least 3 months before screening, NYHA class II, III, IV and clinically stable. For at least 2 weeks prior they had to be receiving a fixed-dose regimen that could include and ACE I, diuretic, digoxin and B-blocker. LVEF <40% and a left ventricular dilation with an echo measured short-axis internal dimension at end diastole >2.9cm/m² of body-surface area.

Patient characteristics:
<table><tr><td></td><td>Valsartan</td><td>Placebo</td></tr><tr><td>Age (yr)</td><td>62.4 ± 11.1</td><td>63.0 ± 11.0</td></tr><tr><td>Male sex (%)</td><td>79.9</td><td>80.0</td></tr><tr><td>Race %</td><td></td><td></td></tr><tr><td>White</td><td>89.8</td><td>90.9</td></tr><tr><td>Black</td><td>7.2</td><td>6.5</td></tr><tr><td>Other</td><td>2.9</td><td>2.6</td></tr><tr><td>NYHA class %</td><td></td><td></td></tr><tr><td>II</td><td>62.1</td><td>61.4</td></tr><tr><td>III</td><td>36.1</td><td>36.3</td></tr><tr><td>IV</td><td>1.7</td><td>2.2</td></tr></table></td><td>Valsartan

40mg twice daily, and then doubled every 2 weeks to reach target of 160mg twice daily

N=2511

BACKGROUND MEDICATION OVERALL IN BOTH GROUPS: ACEi - 100%

BB – 0%</td><td>Placebo

N=2499</td><td>Mean 23 months</td><td>Mortality, combined endpoint (mortality and morbidity); change in EF, NYHA class, QoI and signs and symptoms</td><td>Novartis Pharma</td></tr>
</table>

Reference	Study type/ Evidence level	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Ejection fraction %	26.6 ± 7.3	26.9 ± 7.0					
			ACE I (background medication)	92.6	92.8					
			BB (background medication)	34.5	35.3					

Effect Size

Outcomes (intention to treat population)

1. All cause mortality
   - Valsartan: 495/2511; placebo: 484/2499
2. HF hospitalization
   - Valsartan: 346/2511; placebo: 455/2499
3. Mean change in creatinine concentration
   - Valsartan: +15.9umol/L; placebo: +8.8umol/L, p<0.001 (no SD given)
4. Mean change in Potassium
   - Valsartan: +0.12mmol/l; placebo: -0.07mmol/l, p<0.001
5. NYHA class
   - Improvement: valsartan: 580/2511(23.1%); placebo: 517/2499(20.7%)
   - Worsening: valsartan: 254/2511(10.1%); placebo: 320/2499 (12.8%)

<table>
<tr><th>Reference</th><th>Study type/
Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>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</td>
<td>RCT

Multicentre, international trial

Randomised, double blind, allocation concealment, powered (for mortality any cause), ITT analysis (mortality and CV outcomes)

Withdrawals due to any reason:</td>
<td>N=14,703</td>
<td>Inclusion criteria: Age ≥18 years; acute MI (between 0.5 to 10 days previously) that was complicated by clinical or radiologic signs of heart failure, evidence of LVSD (EF ≤0.35 on echocardiography or contrast angiography and ≤0.40 on radionucleotide ventriculography) or both. At randomisation patients had to have systolic BP >100 mm Hg and serum creatinine <2.5 mg/dL. Patients were permitted to recive ACEi or ARB up to 12h before randomisation.

Exclusion criteria: previous intolerance or contraindication to an ACEi or ARB, clinically significant valvular disease, another disease known to limit life expectancy severely, and the absence of written informed consent.

Patient characteristics:
<table>
<tr><th></th><th>Valsartan</th><th>Captopril</th><th>C + V</th></tr>
</table>
</td>
<td>Valsartan (ARB)
N=4909

20 mg increased in 4 steps to target of 160 mg twice/day

BACKGROUND MEDICATION OVERALL IN ALL GROUPS:
BB – 70%

Treatment with ACE + ARB was stopped before randomisati</td>
<td>Captopril (ACE)
N=4909

6.25 mg increased in 4 steps to target of 50 mg three times/day

Valsartan + captopril (ACE + ARB)
N=4885

20 mg + 6.25 mg increased in 4 steps to target of 80 mg</td>
<td>Median 24.7 months</td>
<td>Primary: Mortality from any cause.

Secondary: HF hospitalisation, yperkalemia, hypotension</td>
<td>Novartis Pharmaceuticals</td>
</tr>
</table>

<table>
<tr><th>Reference</th><th>Study type/
Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>ventricular dysfunction, or both. N Engl J Med 349 (20):1893-1906, 2003.

ID 4524</td><td>V 20.5%, V+C 23.4%, C 21.6%</td><td></td><td>
<table>
<tr><td>Age (yr)</td><td>65.0 ± 11.8</td><td>64.9 ± 11.8</td><td>64.6 ± 11.9</td></tr>
<tr><td>Male sex (%)</td><td>68.5</td><td>68.7</td><td>69.5</td></tr>
<tr><td colspan="4">Race %</td></tr>
<tr><td>White</td><td>9.38</td><td>93.5</td><td>93.2</td></tr>
<tr><td>Black</td><td>2.5</td><td>3.0</td><td>2.8</td></tr>
<tr><td>Other</td><td>3.7</td><td>3.5</td><td>4.0</td></tr>
<tr><td>LVEF %</td><td>35.3 ± 10.4</td><td>35.3 ± 10.4</td><td>35.3 ± 10.3</td></tr>
<tr><td>BB (background medication)</td><td>70.6</td><td>70.1</td><td>70.4</td></tr>
</table>
</td><td>on</td><td>twice/day + 50 mg three times/day

In all groups – doses were adjusted (increased or decreased) at the discretion of the investigators</td><td></td><td></td><td></td></tr>
<tr><td colspan="9"><u>Comparisons: ACE + ARB + BB vs ACE + BB</u>

Effect Size</td></tr>
</table>

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Outcomes (intention to treat population) 1. All cause mortality • Captopril: 958/4909; Valsartan + Captopril: 941/4885: HR 0.98, 95% CI 0.89 to 1.09, p=0.73 (NS) 2. HF hospitalization • Captopril: 945/4909; Valsartan + Captopril: 834/4885 ; p=0.005 3. Hyperkalaemia (NOT ITT population) • Captopril: 4/4879; Valsartan + Captopril: 12/4862 4. Hypotension • Captopril: 41/4879; Valsartan + Captopril: 90/4862								

BB: beta blockers vs placebo, optimal medical management or other beta blockers

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?

Evidence tables

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

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

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

Evidence tables:

Beta blockers

Outcomes

1. all cause death up to 5 yrs
2. all cause hospitalization
3. sudden death
4. Quality of life
5. Adverse event

Older adults

Bibliographic reference	Study type	Number of patients	Patient characteristics	Comparison	Intervention	Length of follow-up	Outcomes	Source of funding
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;	Post-hoc sub-group analysis of RCT	N=1982	Patients ≥ 65 yrs with EF ≤ 30% and NYHA II to IV On optimum standard therapy of diuretics and an ACEI. If ACEI not tolerated then vasodilators, preferably angiotensin II receptor	Metroprolol CR/XL 25 mg NYHA II 12.5 mg NYHA III and IV Dose doubled at each 2-week period until target dose of 200 mg or highest tolerated	Placebo	Mean one year	Mortality Sudden death All cause hospitalization Discontinuation of study medication Adverse events	Astra Zeneca

25(15):1300-1309. Ref ID: 2710			blockers. Digitalis could be prescribed					

	Metoprolol CR/XL N=990	Placebo N=992
Mean age yrs	72 (4.0)	72 (4.1)
Female %	24	26
NYHA % II III IV	 36 60 4	 37 59 4
Ejection fraction	0.28 (0.07)	0.28 (0.08)
Systolic blood pressure mm Hg Diastolic blood pressure	132 (18) 77 (9.1)	132 (18) 77 (8.9)
BMI	26	27
Medications Diuretics ACEI ACEI or All blocker Digitalis ASA	 93 87 94 63 48	 87 95 62 49 23

Effect BB vs placebo Mortality (mean follow-up one year) 87/990 vs 134/992 Sudden death 42/990 vs 72/992 All cause hospitalization (no. of patients) 345/990 vs 368/992 (p>0.2) Discontinuation of study medication 17.8 vs 20.3% Any adverse event 121/990 vs 132/992								
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	RCT Double blind Parallel group ITT Power analysis but study population underpowered	N=260 (ITT population) Withdrawals: N=24	Patients with chronic heart failure aged more than 65 yrs 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 Titration period of 8 weeks. 1.25 mg double every 14 days until highest tolerated or maximum of 10 mg/day Treatment period of 8 months Follow-up. End of	Placebo	40 weeks	Quality of life – Minnesota Living with Hear failure 21 items 0 to 5 point scale	Berlin-Chemie AG

			Exclusion criteria: MI within past 3 months, beta blocker therapy in the 4 weeks prior to trial	treatment followed by an observation period of 2 months. Study medication gradually discontinued during first 14 days of this observation period				

	Nebivolol N=134	Placebo N=126
Age yrs	72 (5.0)	72.2 (5.2)
Male %	70%	77%
HYHA % II III IV	 52 46 2	 45 48 7
Quality of life Minnesota Questionnaire mean	 32.3 (19.7)	 35.6 (21.3)
Medications %		

ACEI ARB ACEI + diuretic or ARB + diuretic Digitalis	91 5 83 60	90 7 85 53						
Effect Nebivolol(n=134) vs placebo (n=126) **Quality of life (difference between week -2 (screening) and week 40)** -9.13 (13.78) vs -11.01 (14.66) **Adverse events (no of patients with adverse events)** 81/134 vs 75/126 (p=0.790)								
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 **In the sub-**	RCT post-hoc sub group analysis Double blind Centralised computerised random no. generation ITT analysis	N=539 (total population in RCT N=2647) Drop-outs withdrawal Bisoprolol N=305 died or permanent treatment withdrawal + N=41 treatment withdrawn early Placebo N=372 died or permanent	Patients ≥ 71 yrs with chronic heart failure Inclusion criteria: NYHA II, IV EF ≤35% Concomitant medication diuretics and ACEI No details of patient population provided	Bisoprolol 1.25 mg to a maximum of 10 mg/day N=264	Placebo N=275	Mean 1.3 yrs	Deaths All cause hospital admission	Merck

group of patients ≥ 71 yrs		treatment withdrawal + N=28 treatment withdrawn early						
Bisoprolol (n=61) vs placebo (n=61) (mean follow-up 1.3 yrs) **All cause mortality** 10/61 vs 15/61 **All cause hospitalisation** 25/61 vs 31/61								
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.	RCT Double-blind Parallel groups Randomisation 1:1 Concealment allocation – central list by treatment no. corresponding to treatment pack	N=2128 Drop-outs etc: N=7 after randomisation N=37 lost to follow-up	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 N=1067 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	Placebo N=1061	Mean 21 months (SD 9)	Death or hospitalisation Death (all cause) Sudden death Hospitalisation Adverse events	Menarini Ricerche SpA

Ref ID: 2849			Exclusion criteria: new drug therapy for CHF within the 6 wks prior to randomisation, any change in cardiovascular drug therapy in the two weeks prior to randomisation, heart failure due to uncorrected valve disease, current use of beta blockers or medical condition that may reduce survival during the study					

	Nebivolol (n=1067)	Placebo (n=1061)
Age yrs	76.1 (4.8)	76.1 (4.6)
Women	38%	35%
NYHA class (%) II III	 3 57	 3 56

IV	39	39
Ejection fraction ≤ 35% (%) > 35% (%)	 64% 36%	 65% 35%
Blood pressure Systolic Diastolic	 138.6 (20.1) 80.5 (10.8)	 78.9 (13.7) 139.5 (35.2)
Prior coronary artery disease (%)	69	68
Prior MI (%)	44	44
Diabetes (%)	27	25
Renal function Creatinine µmol/L	 102.0 (35.1)	 103.5 (34.8)
Medications for heart failure (%) Diuretic (inclusion criteria) ACEI (inclusion criteria) Angiotensin receptor blocker Digitalis Nitrates Aldosterone antagonists B blockers (stopped prior to study)	 86 4	 99 91 7 58 33 11 4
Effect BB vs placebo (mean follow-up 21 mths)		

Primary outcome – all cause mortality of CV hospitalisation (adjusted for gender, age and LVEF)

332/1067 (31.1%) vs 375/1061 (35.3%) (HR 0.86 (95%CI 0.74 to 0.99; p=0.039)

all cause death (adjusted)

169/1067 (15.8%) vs 192/1061 (18.1%) (HR 0.85 (95%CI 0.71 to 1.08; p=0.21)

all cause hospitalization (adjusted)

359/1067 (33.6%) vs 364/1061 (34.3%) (HR 0.95 (95%CI 0.82 to 1.10; p=0.047)

sudden death - cardiac (adjusted)

44/1067 (4.1%) vs 70/1061 (6.6%)

QoL

Not reported

Adverse event

Cardiac failure – aggravated

256/1067 (24.0%) vs 265/1061 (25.0%)

Dizziness (excluding vertigo)

166/1067 (15.6%) vs 142/1061 (13.4%)

For patients with LVEF ≤ 35% and LVEF > 35% from 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 Rehospitalization in Seniors With Heart Failure). *Journal of the American College of Cardiology.* 2009; 53(23):2150-2158. Ref ID: 36

LVEF ≤ 35%

Nebivolol vs placebo – 21 mths
All cause mortality of CV hospitalisation
218/678 vs 247/681
All cause mortality
115/678 vs 135/681
All cause mortality or HF hospitalisation
170/678 vs 181/681
All cause hospitalisation
229/678 vs 232/681
LVEF > 35%
Nebivolol vs placebo – 21 mths
All cause mortality of CV hospitalisation
110/380 vs 125/372
All cause mortality
52/380 vs 55/372
All cause mortality or HF hospitalisation
81/380 vs 88/372
All cause hospitalisation
127/380 vs 130/372

Selective vs non selective BBs

Bibliographic reference	Study type	Number of patients	Patient characteristics	Comparison	Intervention	Length of follow-up	Outcomes	Source of funding
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	RCT Double blind Parallel group No power analysis No ITT analysis	N=51 Withdrawals: N=7	Patients with typical symptoms of heart failure and reduced LV ejection fraction (0.45)	Metoprolol N=26 Four week titration period increasing the dose from 3.125 to 25 mg twice daily at weekly intervals	Carvedilol N=25 Titration as for intervention. Dose titrated from 6.25 to 50 mg twice daily.	12 weeks	Quality of life – Minnesota Heart Failure Questionnaire	Boehringer

	Metoprolol N=26	Carvedilol N=25
Age yrs	60.4 (2.3)	58.7 (3.0)
Gender male:female	23:3	17:8
NYHA II III	 7 19	 10 14

IV	0	1
Symptom questionnaire score	13.1 (1.8)	17.2 (3.0)
Baseline BP (mm Hg) Sitting Standing	 126(3)/75(3) 127(3)/78(3)	 130(5)/78(3) 130(5)/83(3)
LVEF (%)	25.5 (1.8)	26.4 (1.8)
Treatment Frusemide ACEI/Angiotensin receptor antagonist Nitrates	 24 25 16	 24 24 16

The group were well matched at baseline

Effect

Quality of life

Metoprolol vs carvedilol (12 weeks)

4.8 (1.4) vs 8.1 (2); p<0.001

Poole-Wilson PA SK. Comparison of carvedilol and metoprolol on clinical outcomes in patients with	RCT Randomised – permuted blocks by centre Concealment allocation – numbered	N=3029 Lost to follow-up N=5 N=28 withdrew consent for further follow-up	Adults with symptomatic chronic heart failure (NYHA II to IV), at least one cardiovascular admission during the past 2 yrs, on stable heart failure	Carvedilol N=1511 3.125 mg bd Target dose: 25	Metroprolol N=1518 5 mg bd Target dose:	58 months	All deaths All deaths and all-cause admission Patients with at least one adverse event	F Hoffmann La Roche and GlaxoSmithKline

chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet.* 2003; 362(9377):7-13. Ref ID: 2158	treatment kits Multicentre Double-blind Parallel groups Power analysis ITT	during study	treatment with ACEI for at least 4 weeks unless contraindicated, and on treatment with diuretics (≥40 mg of frusemide or equivalent) for at least 2 weeks. Digitalise, angiotensin II inhibitors, or other vasodilators could be used at the discretion of the investigators. Left ventricular ejection fraction had to be 0.35 or lower measured within the previous 3 months Exclusion criteria: Recent change of treatment, unstable angina, myocardial infarction or stroke within the past two months, uncontrolled hypertension	mg bd	50 mg bd		No of adverse events Sudden death	

Patient population

	Carvedilol (n=1511)	Metroprolol (n=1518)
Age yrs	62 (11.3)	62 (11.4)
Male	79%	80%
BMI	26.9 (4.5)	26.8 (4.4)
Primary cause of heart failure (%)		
Ischemic heart disease	51	54
Hypertension	18	18
Dilated cardiomyopathy	44	44
Previous valve surgery	3	2
NYHA class (%)		
II	48	49
III	48	47
IV	3	4
Diabetes (%)	24	24
Ejection fraction (%)	0.26 (0.07)	0.26 (0.07)
Blood pressure		
Systolic	126 (19.3)	126 (19.7)
Diastolic	77 (11.0)	77 (10.9)
Medications for heart failure (%)		

Diuretic (inclusion criteria)	99	99
ACEI (inclusion criteria)	92	91
Angiotensin	6	7
Digitalis	61	58
Nitrates	33	33
Aldosterone antagonists	11	11
B blockers (stopped prior to study)	4	4

Effect

Carvedilol vs metroprolol (58 months)

All deaths

512/1511 (34%) vs 600/1518 (40%) [HR 0.83 (0.74 to 0.93); p=0.002)

All deaths and all-cause admission

1116/1511 (74%) vs 1160/1518 (76%) [HR 0.94 (0.86 to 1.02); p=0.122)

Patients with at least one adverse event

94 vs 96%

No of adverse events

8469 vs 8808

Sudden death

Carvedilol vs metroprolol (58 months)

512/1511 vs 600/1518 {HR 0.83 (95%CI 0.74 to 0.93); p=0.0017)

BB then ACEI vs ACEI then BB

Willenheimer R, van Veldhuisen DJ, Silke B et al. Effect on survival and hospitalization 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 **CIBIS III**	RCT Multicentre Open-label Blind end-point Randomisation – dynamic balance algorithm, stratified by NYHA II or III Concealment allocation – random numbers allocated centrally Power analysis ITT – per protocol	N=1010 Withdrawals N=9 excluded from per protocol analysis (never took study medication) Beta blocker N=60 ACEI N=59	Adults of 65 yrs or older with mild to moderate CHF (NYHA II or III) and LVEF ≤ 35%. Inclusion criteria: clinically stable, without clinically relevant fluid retention or diuretic adjustment in the 7 days before randomisation Exclusion criteria: treatment with ACEI, angiotensin-receptor blocker, or beta blocker for > 7 days during 3 months before randomisation	Beta blocker first Bisorprolol 1.25 mg QD N=503 Progressively titrated at two week intervals (or slower if intolerant) Target dose 10 mg QD Maintenance period 16 weeks if drug used first During the 6 month monotherapy phase, initiation of	ACEI first Enalapril 2.5 mg BID N=498 Progressively titrated at two week intervals (or slower if intolerant) Target dose 10 mg BID Maintenance period 22 weeks if drug used first Procedure as for beta blocker Combination	Mean 1.22 yrs (max 2.1)	Primary end point of time-to-the-first event of combined all-cause mortality or all-cause hospitalisation Mortality – all cause Hospitalisation – all cause Permanent discontinuation of drug during monotherapy phase Serious adverse event during monotherapy phase Sudden death	Merck

			Patient population: Mean age 72 yrs, 68% male. Most common cause of DHF ischemic heart disease 62% and 37% hypertension. Mean LVEF 29% and the patients were evenly distributed between NYHA II and III. Approximately half of the patients had a history of acute MI. Baseline cardiovascular medication was similar between the two groups. A total of 84% were receiving diuretic treatment; < 15% aldosterone-receptor blocker. The use of aldosterone-receptor blocker and digoxin changed very	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 Combination therapy: Addition of enalapril and up titration as for monotherapy phase	therapy: beta-blocker introduced as for intervention			

			little during the study.					

	Bisoprolol-first	Enalapril-first
Mean age (years)	72.4	72.5
Males (%)	66	71
NYHA class II (%)	49	50
NYHA class III (%)	51	50
Median duration of CHF (months)	20	18
Mean LVEF (%)	28.8	28.8
Mean serum creatinine (mmol/L)	99.6	101.9
Mean systolic BP (mmHg)	134.5	133.7
Coronary artery disease (%)	61.2	63.6
Hypertension (%)	39.0	34.1
Diuretic treatment (%)	85	83
Aldosterone-receptor (%)	14	12

Table 1 Baseline data in the CIBIS III trial

Effect

Primary end point of time-to-the-first event of combined all-cause mortality or all-cause hospitalisation

BB-first vs ACEI-first (ITT)

178/505 (35.2%) vs 186/505 (36.8%) (absolute difference -1.6%; 95%CI -7.6 to 4.4%; HR 0.94; 95%CI 0.77 to 1.16; p=0.019)

Mortality – all cause

65/505 vs 73/505 (HR 0.88; 95%CI 0.63 to 1.22; p=0.44)

Hospitalisation – all cause

151/505 vs 157/505 (HR 0.95; 95%CI 0.75 to 1.19; p=0.66)

Permanent discontinuation of drug during monotherapy phase

39/505 (6.9%) vs 49/505 (9.7%)

Serious adverse event during monotherapy phase

113/505 (22.4%) vs 111/505 (22.1)

Sudden death (from conference presentation/website)

29/505 vs 34/505

QOL

Not reported

ISO: isosorbide/hydralazine vs placebo or ACE or placebo+optimal medical treatment

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

Evidence Tables

Black population

isosorbide + hydralazine in comparison to placebo

isosorbide + hydralazine in comparison to ACEI

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;	RCT Randomised, Double-blinded	VHEFT I: N=642 VHEFT II: N=804	**Inclusion criteria:** male patients with a history of heart failure or documentation of left ventricular enlargement or dysfunction by chest radiography, 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, defined as	**VHEFT I:** - prazosin 5mg 4×day OR - combination of hydralazine 75mg + isosorbide dinitrate 40mg 4× day. **VHEFT II:** - combination of hydralazine 75mg + isosorbide dinitrate	**VHEFT I:** - placebo **VHEFT II:** - enalapril 10mg 2×day	Minimum 6 months or until death	Mortality, hospitalizations, EF, exercise tolerance	Veterans Affairs Cooperative Studies Program

5(3):178-187. Ref ID: 650 **V-HeFT I and II**			a measured peak oxygen consumption (VO^2) <25 mL/kg/min during a progressive bicycle ergometer exercise test. **Exclusion criteria**: not mentioned **Patient Characteristics**: Nearly all patients were receiving background therapy with diuretics and/or digoxin. **VHEFT I:** 642 male patients (NYHA classes I+II) Black/white: 180/450 Age: o White: 59.2 ± 6.9 o Black: 56.3 ± 9.0 o p<0.01 Coronary artery disease (CAD)(%): o White: 53.2 o Black: 20.8 o p<0.01 History of hypertension (%) o White: 37.3 o Black: 46.6 o NS	40mg 4× day				

			VHEFT II: 804 male patients (NYHA classes I+II) Black/white: 215/574 Age: o White: 61.1 ± 8.0 o Black: 58.8 ± 9.0 o NS Coronary artery disease (CAD)(%): o White: 61.6 o Black: 28.4 o p<0.01 History of hypertension (%) o White: 41.5 o Black: 64.9 o p<0.01					
Effect Size Outcomes **1. Mortality** (end period reported 66months- 5.5yrs) **VHEFT I** • Black patients: o HI group: deaths 15/49 (annual mortality rate (AMR) 9.7%) o Placebo: deaths 35/79 (AMR 17.3%)								

- p=0.04
- White patients:
  - HI group: deaths 56/132 (AMR 16.9%)
  - Placebo: deaths 85/192 (AMR 18.8%)

VHEFT II

- Black patients:
  - HI group: deaths 39/109 (AMR 12.9%)
  - Enalapril: deaths 39/106 (AMR 12.8%)
  - p=NS
- White patients:
  - HI group: deaths 112/282 (AMR 14.9%)
  - Enalapril: deaths 90/292 (AMR 11.0%)
  - P=0.09
- A trend for a significant interaction between race and treatment was shown, p=0.09

2. Hospitalization for CHF

VHEFT I

- White
  - Placebo 49 (25.5)
  - HI 32 (24.2)
  - p=0.8
- Black
  - Placebo 16 (20.3)
  - HI 11 (22.4)
  - p=0.77
- White vs. black p=0.18

VHEFT II

- White

- Enalapril 51(17.5)
- HI 51 (18.1)

- Black
  - Enalapril 24 (22.6)
  - HI 23 (21.1)
- White vs. black p=0.20
- No difference in hospitalization for HF between black vs. white patients

3. Hospitalization for any reason

VHEFT I

- White
  - Placebo 67 (34.9)
  - HI 56 (42.4)
- Black
  - Placebo 39 (49.4)
  - HI 20 (40.8)
- White vs. black p=0.10

VHEFT II

- White
  - Enalapril 181 (62.0)
  - HI 165 (58.5)
- Black
  - Enalapril 65 (61.3)
  - HI 59 (54.1)
- White vs. black p=0.51
- No difference in all cause hospitalization between black vs. white patients

4. Exercise tolerance-change in Maximal VO2 (figures taken from graph)

VHEFT II

- **6 months:**
  - white enalapril + 0.3

<table>
<tr><td colspan="9">

o white HI + 0.7
o black enalapril + 0.3
o black HI + 0.3

12 months:

o white enalapril -0.1
o white HI + 0.2
o black enalapril -0.1
o black HI + 0.6

24 months (1 year):

o white enalapril -0.7
o white HI + 0.2
o black enalapril + 0.4
o black HI + 0.2

Authors' Conclusion: 'the H-I combination appears to be particularly effective in prolonging survival in black patients and is as effective as enalapril in this subgroup. In contrast, enalapril shows its more favourable effect on survival, particularly in the white population.'
</td></tr>
<tr>
<td>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

A-HeFT</td>
<td>RCT

Mult-centre

Double blind

Randomisation – stratified by use or nonuse of beta blockers as background therapy. Blocks of 4 per stratum were used, with each site allowed to randomise upto 6 blocks of patients (24 patients) in the non-beta block group and up to 10</td>
<td>N=1050

No. of centres N=161</td>
<td>Screening criteria: 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

Inclusion criteria: On standard therapy for heart failure, as deemed appropriate by their physicians;</td>
<td>Fixed-dose combination of isosorbide dinitrate plus hydralazine

N=518

37.5 mg hydralazine hydrochloride + 20 mg isosorbide dinitrate three times daily</td>
<td>Placebo

N=532</td>
<td>Upto 18 mths (mean 10 mths)</td>
<td>Primary: Composite score made up of weighted values for death from any cause, a first hospitalisation for heart failure during the 18-month follow-up period, and a change in quality of life at 6 months

Quality of life – Minnesota Living with Heart Failure questionnaire, 21</td>
<td>Nitromed</td>
</tr>
</table>

	blocks (40 patients) in the beta blocker groups Treatment allocation – performed centrally Power analysis (N=400 per group) Full ITT analysis		such therapy included angiotensin-converting-enzyme inhibitors (ACEIs), beta blockers for at least three months before randomisation, digoxin, spronolactone and diurectics Evidence of left ventricular ejection fraction (LVEF) within the six months preceding 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) Exclusion criteria:	Dose increased to two tables three time daily, total dose 225 mg hydralazine and 120 mg isosorbide Increase in dose was dependent on the absence of drug-induced side effects			items (self-administered). Higher score = poorer quality of life Composite score Death (any time during trial) -3 Survival to end of trial 0 First hospitalisation for heart failure -1 No hospitalisation 0 Change if quality of life at 6 mths (or last measurement): Improvement by ≥ 10 units, +2, improvement by 5 to 9 units +1, change by < 5 units 0. worsening by 5 to 9 units -1, worsening by ≤ 10 units -2 (score -6 to +2) Secondary endpoints: individual components of the composite score, the total number of	

			acute myocardial infarction, acute coronary syndrome, or stroke within the preceding three months; cardiac surgery or percutaneous coronary intervention within the preceding three months or the likelihood of a requirement for such procedures during the study period; clinically significant valvular heart disease, hypertrophic or restrictive cardiomyopathy, active myocarditis, or uncontrolled hypertension; a history of cardiac arrest or life threatening arrhythmias within the preceding three months (unless treated with an implantable defibrillator); treatment with parental inotropic agents within the one month before				hospitalisations for heart failure, total number of hospitalisations for any reason, overall quality of life throughout the trial, the number of unscheduled emergency room and office or clinic visits	

			randomisation, a potential need for cardiac transplantation; the presence of symptomatic hypotension; the presence of an illness other than heart failure that was likely to result in death within the study period					

Patient population

	Isosorbide plus hydralazine	Placebo
Age yrs	56.7 (12.7)	56.9 (13.3)
Male sex (%)	58.8*	63.9
Weight (kg)	92.5 (21.4)	94.2 (25.5)
Primary cause of heart failure (%)		
Ischemic heart disease	23.4	22.7
Hypertension	40.0	37.4
Idiopathic	24.5	27.6
Valvular cause	2.5	3.2
Other	9.7	9.0
NYHA class (%)		
I	0	22.7
II	0.2	0
III	96.7	0

IV	3.1	94.7 5.3
Diabetes (%)	44.8**	37.0
Renal insufficiency (%)	16.2	18.2
Atrial fibrillation (%)	15.0	18.0
Cardiac resynchronisation therapy (%)	2.0	2.1
Implantable cardiac defibrillator (%)	16.6	17.3
Ejection fraction (%)	23.9 (7.3)	24.2 (7.5)
LVIDD (cm)	6.5 (0.9)	6.5 (1.0)
Blood pressure Systolic Diastolic	 127.2 (17.4) 77.6 (10.3)***	 125.3 (18.1) 75.6 (10.5)
Minnesota Living with Heart Failure Questionnaire score (0 to 105)	50.9 (24.9)***	50.7 (25.5)
Medications for heart failure (%) Diurectic ACEI ARB Beta blocker Carvedilol Digoxin Spironolactone	 88.0 69.4 17.2 74.1 55.2 58.5 40.2	 91.5 69.5 16.5 73.5 55.8 60.7 37.6

*p=0.008 vs placebo; ** p=0.01 vs placebo; *** p=0.002 vs placebo

Effect

The trial was halted early due to the significantly higher mortality in patients given placebo compared to isosorbide plus hydralazine

(planned recruitment N=1100, actual N=1050)

Isosorbide plus hydralazine (N=518) vs placebo (N=532)

Primary composite score (range -6 to 2) mean (SD), mean duration of follow-up 10 months (range 0 to 18)

Isosorbide plus hydralazine vs placebo

-0.1 (1.9) vs 0.5 (2.0); p=0.01

Mortality (any cause), mean duration of follow-up 10 months (range 0 to 18)

Isosorbide plus hydralazine vs placebo

At the time the trial was halted 32/518 (6.2%) vs 54/532 (10.2%)

Change in quality of life score at six months mean (SD) (n=742 completed and for rest earlier assessment used or worst possible score used)

Isosorbide plus hydralazine vs placebo

-5.6 (20.6) vs -2.7 (21.1); p=0.02

Adverse events, mean duration of follow-up 10 months (range 0 to 18)

Isosorbide plus hydralazine vs placebo

Headache 47.5 vs 19.2; p<0.001

Dizziness 29.3 vs 12.3; p<0.001

TAKEN FROM Taylor AL, Ziesche S, Yancy CW et al. Early and sustained benefit on event-free survival and heart failure hospitalization from fixed-dose combination of isosorbide dinitrate/hydralazine: consistency across subgroups in the African-American Heart

Failure Trial. *Circulation.* 2007; 115(13):1747-1753. Ref ID: 14

Mortality (cardiovascular death), mean duration of follow-up 10 months (range 0 to 18)

Isosorbide plus hydralazine vs placebo

26/518 (5.0%) vs 45/532 (8.5%); p=0.027

TAKEN FROM: 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. Ref ID: 423

Mean follow-up 12.8 months

Total number of hospitalisations for heart failure (by total no. of patients)

Iso/Hyd vs placebo

173/518 vs 251/532

Total number of ER and unscheduled office visits (by total no. of patients)

Iso/hyd vs placebo

32/518 vs 43/532

Age subgroup

isosorbide + hydralazine in comparison to placebo

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 **V-HeFT I**	RCT Treatment allocation – centralised Randomisation – seven-subject and six-subject permuted block designs NOTE: Prazosin group not reported	N=459 One or both placebo medication discontinued in 22% (mostly due to increasing congestive hart failure), a cardiac event or side effects) Hydralazine/isosorbide: 17% taken off both drugs mostly due to headahce	Men between the ages of 18 to 75 yrs with chronic heart failure 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 Exclusion criteria: myocardial infarction or cardiac surgery within the three months previous, angina pectoris limiting exercise or requiring long term	Hydralazine 75 mg plus isosorbide dinitrate 40g Four times daily N=186 Baseline: Period of at least 4 weeks to allow optimal therapy with digoxin and diurectic and for non study drugs to be discontinued	Placebo N=273 Baseline as for HYD/ISO	Mortality Mortality by age	mean 2.3 yrs (range 6 mths to 5.7 yrs)	Cooperative Studies Program, Medical Research Service

			medical therapy, serious obstructive lung disease (ratio of forced vital capacity <0.60), or other diseases likely to limit life expectancy. The patients were asked not to take vasodilators or antihypertensive drugs					

	Placebo	Hydralazine plus isosorbide
Age, yrs	58.5	58.3
Coronary artery disease, %	44.3	44.1
History of alcohol excess, %	38.2	43.0
History of hypertension, %	42.6	43.0
Previous cardiac surgery, %	17.6	16.7
Previous vasodilator therapy, %	36.3	41.9
Previous antiarrythmic therapy, %	26.7	27.4
Cardiothoraic ratio, %	52.9	52.8
Ejection fraction, %	30.4	30.3
Left ventricular diastolic diameter, cm/m²	3.5	3.5
VO_2	15.0	14.4

Effect

Hydralazine/isosorbide vs placebo

Mortality (annual mortality rate assuming exponential model)

14.5 vs 18.2%

Mortality according to age (assuming exponential model)

> 60 yrs

Hyd/iso (n=93) vs placebo (n=137)

16/93 vs 26/137

< 60 yrs

Hyd/iso (n=93) vs placebo (n=136)

12/93 vs 24/136

Effect

	V-HeFT I		V-HeFT II	
	Hyd/Iso vs placebo		Hyd/iso vs enalapril	
Age group	RR	P	RR	P
≤ 55	0.60	0.06	1.21	0.47
56 to 60	1.00	0.99	1.28	0.33
61 to 65	0.73	0.30	1.39	0.15
> 65	1.00	0.99	1.10	0.66

Age

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
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	RCT VHEFT II post hoc subgroup analysis	N=804	**Inclusion criteria:** male patients between 18-75 yrs old with chronic CHF. Patients had to have demonstrable cardiac dysfunction confirmed by radionuclide ejection 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.) **Exclusion criteria:** myocardial infarction or cardiac surgery in the preceding 3 months; angina pectoris limiting exercise or requiring long-term nitrates; hypertension requiring treatment other than diuretics, ß blockers, or calcium antagonist; serious obstructive valvular disease; obstructive lung disease (FEV1:FVC >0.60); other life threatening conditions or failure to give consent.	Enalapril 20mg plus 2 placebos **Run-in period**: All patient had at least 4 weeks to establish optimal therapeutic dosages of digoxin and a diuretic agent, and any conflicting or nonstudy drugs were discontinued.	Hydralazine 300mg + isosrbide dinitrate 160mg + one placebo. See intervention for details of run-in period for all patients	2 yrs	All cause mortality.	Veterans Affairs Cooperative Studies Program

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			Patient characteristics: Age: enalapril 60.6; Iso/hydral 60.5 Sex: all male NYHA classification (%): I – enalapril 6.0; Iso/hydral 5.5 II – enalaparil 49.6; Iso/hydral 52.4 III – enalapril 44.2; Iso/hydral 41.6 IV – enalapril 0.2; Iso/hydral 0.5 Duration of CHF (years): enalapril 3.1; Iso/hydral 3.7, p<0.05 Ejection fraction (%): enalapril 28.6; Iso/hydral 29.4					

Effect Size

Outcomes

All cause mortality:

- ≤ 55 years:
  - Enalapril: no deaths./no. at risk: 27/86; annual mortality rate (AMR): 11.1
  - Iso/hydral: no deaths./no. at risk: 31/89; AMR: 13.2
  - Risk ratio (enalapril vs. iso/hydral): 0.83
  - 95% CI 0.49-1.38

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
• >55- ≤ 60 years: o Enalapril: no deaths./no. at risk: 29/86; AMR: 11.7 o Iso/hydral: no deaths./no. at risk: 34/87; AMR: 14.6 o Risk ratio (enalapril vs. iso/hydral): 0.78 o 95% CI 0.47-1.28 • >60- ≤ 65 years: o Enalapril: no deaths./no. at risk: 32/117; AMR: 9.7 o Iso/hydral: no deaths./no. at risk: 43/114; AMR: 13.3 o Risk ratio (enalapril vs. iso/hydral): 0.72 o 95% CI 0.45-1.13 • >65 years: o Enalapril: no deaths./no. at risk: 44/114; AMR: 14.4 o Iso/hydral: no deaths./no. at risk: 45/111; AMR: 15.7 o Risk ratio (enalapril vs. iso/hydral): 0.91 o 95% CI 0.60-1.38 **Authors' Conclusion**: *'in no patient subgroup was the mortality with enalapril treatment significantly higher than the mortality with hydralazine/isosorbide dinitrate treatment.'* **Limitations:** • Increasing the number of subgroups analysed reduced the power to detect a significant effect within these groups. (increased risk of type II error) and also increased the chances of a significant finding (type I error)								

MONIT: patient telemonitoring vs out patient monitoring

What is the efficacy and safety of patient telemonitoring in comparison to outpatient monitoring for adults with chronic heart failure?

Evidence tables

Bibliographic reference	Study type	Number of patients	Patient characteristics	Comparison	Intervention	Length of follow-up	Outcomes	Source of funding
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	RCT Randomisation – no details - sealed envelope - No drop-outs reported and therefore no ITT	N=284	Patients admitted for skilled home care with a diagnosis of heart failure Mean age 78 yrs No further details provided	Usual care N=110 Routine home visits. No further details provided,	Telemonitoring Included education on HF and when to notify home care nurse or personal physician Monitoring N=126 One-way monitoring – patient took their own measurements which were then transmitted. This occurred typically once every day at predetermined time. Monitoring and video	120 days	Hospitalisation (all cause) (No. of events)	Robert Wood Johnson Foundation

					N=44 Two-way monitoring – included video camera and digital stethoscope monitoring device. Patients chose the frequency of their own monitoring but they also had scheduled sessions two or three times a week. Monitoring included blood pressure, weight, pulse, heart rate, blood sugar.			
Effect Control vs monitor only (data for monitoring plus video phone and digital stethoscope not reported) Mean no. of hospitalisations (all cause) – follow-up 120 days 0.60 (0.91) vs 0.54 (0.78) Mean total no of emergency department visitis 0.48 (0.75) vs 0.35 (0.58)								
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	RCT Randomised 1:1 Allocation concealment not specified Single blind 8/315 drop-outs ITT	N=315	The population was elderly, women and non-Caucasian males, primarily African Americans and Hispanics with a diagnosis of heart failure secondary to predominately systolic	Usual care N=155 Included 1 to 1 education, availability of education to physicians, an effort to use evidence-based optimal medical treatment and a	Telemonitoring N=160 Usual care plus Home-based disease management	6 months	Mortality Hospital admissions (No. of events)	Medicare and Medicaid

Monitoring System in Older Minorities and Women. *J Card Fail.* 2008; 14(9):711-717. Ref ID: 453	Power analysis		dysfunction Inclusion criteria: aged 65 yrs or older, evidence of systolic dysfunction, current symptoms, receiving optimal medical care Exclusion criteria included: symptomatic ischemic heart disease, uncorrected thyroid disease, COPD and white non-Hispanic men	commercially available digital home scale. Patients were instructed to weight themselves daily and record symptoms.	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			

	Usual care	Telemonitoring
Mean age	76	77
Female %	61	69
Race		
White	48%	58%
Black	52%	42%
Medication		
ACEI	79%	82%
B blocker	47%	44%

ARBs Hydralazine	21% 10%	21% 11%						
Effect Telemoniitoring vs usual care Mortality – follow-up 6 months 11/160 vs 17/155 (p=0.24) Any hospital admissions – follow-up 6 months 68/160 vs 73/155 46.8% vs 42.5% (p=0.44)								
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	RCT - no details of randomisation or allocation concealment - no drop-outs reported - blinding unclear - power analysis (nearly all variables)	N=57	Patients aged 70 yrs or older admitted for worsening symptoms and signs of chronic heart failure. Patients with NYHA II-IIII who had an ejection fraction > 40% and evidence of diastolic LV dysfunction were also included Exclusion criteria included: chronic renal function requiring dialysis and unstable	Usual care N=29 Standard care based on routinely scheduled clinic visits performed by a team specialised in CHF management. CHF outpatient clinic outpatient appointment were every four months with additional visits when required i.e. due to changes in condition	Telemonitoring N=28 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	12 month	Mortality Hospital admissions (No. of patients)	Italian Ministry of Health

			angina Telemonitoring: mean age 77 yrs, male 57%, NYHA IV 4%, mean ejection fraction 35% Usual care: mean age 79 yrs, male 66%, NYHA IV 7%, mean ejection fraction 37%					
Telemonitoring vs usual care Hospital readmission – follow-up ten months 9/28 vs 26/29 (p<0.05) Mortaltiy all cause – follow-up 12 months 3/28 vs 5/29 (ns)								
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	RCT -sealed envelopes - 5/148 drop-outs - ITT	N=148	Patients hospitalised due to HF and: able to participate in telemonitoring	Usual care N=49 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.	Telephone N=47 Video N=52 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	12 months	Hospital readmission (unplanned or planned not stated) (No. of events) All cause mortality MLHF	None reported

ID: 4530					on diet and medication compliance Telephone or videophone used for contact			

Variable	Usual care N=49	Telephone N=47	Videophone N=52
Mean age yrs	67	72	69
Male %	48	47	51
Comorbidities Previous myocardial infarction Chronic lung disease	 53 15	 51 17	
Prior year hospitalisations for HF %	6%	4%	0%
NYHA IV	 6%	 6%	 8%
LVEF mean	43%	43.5%	38%

Effect

Telephone only vs usual care

Mortality, 12 months

21.3% vs 22.4%

10/47 vs 11/49

MLHF – 90 days

44.4 (27.1) vs 53.4 (24.1)

MLHF – 180 days

Telephone vs usual care

41.5 (26.9) vs 56.6 (23.9)								
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	RCT -randomisation method not given - sealed envelope - 2/102 withdrawals - no ITT	N=102 N=84 at follow-up	Patients and caregiver dyads over > 65 yrs with: NYHA II to IV, functionally impaired on at least one activity of daily living (ADL) or one instrumental ADL necessitating assistance of a family caregiver Exclusion criteria: planned discharge to a nursing home, independence on ADL or no caregiver, use of hospice care Intervention: mean age 77 yrs, 43% female, 80% white, ADL/IADL 6.5, NYHA IV 31%, comorbidities 4.2, heart medications 5.6 Usual care: mean age 79 yrs, 61%	Usual care N=40 No details provided	Telemonitoring N=44 Weight and symptoms monitored. Values outside range triggered call from nurse	90 days	Hospital admissions (No of people and No. of events) MLHF	National Institute for Nursing Research, National Institute for Health

			female, 82% white, ADL/IADL 8.1, NYHA IV, comorbidities 4.9, heart medications 5.4 The group were well matched at baseline					
Effect Compliance Telemonitoring vs usual care – 90days Hospital readmission (no. of patients) 12/44 vs 13/40 Hospital readmission (no of events) 0.32 (0.6) vs 0.33 (0.6) ED visits (no. of events) 0.34 (0.6) vs 0.38 (0.5) Minnesota Living with Heart Failure – 90 days 27.4 (21.7) vs 27.3 (21.6)								
Mortara A, Pinna GD, Johnson P et al. Home telemonitoring in heart failure patients: the HHH study (Home or Hospital in Heart	RCT Randomised 1: 2 - central computerised allocation - no ITT - 18/461 withdrawals (all	N=254	Patients > 18 and < 85 yrs with NYHA II to IV. Inclusion criteria included LVEF < 40%, hospitalisation for HF or	Usual care N=160 This was provided by at least one cardiologist or a physician with a special interest in HF, and one specialist nurse. Regular clinical	Home telemonitoring N=94 Usual care plus telemonitoring including changes in weight, blood pressure and symptoms weekly	Mean 11.6 mths	Unplanned hospitalisations (No of patients)	EC grant

Failure). *European Journal of Heart Failure.* 2009; 11(3):312-318. Ref ID: 4525	groups – only two reported here)		decompensation in the previous 12 months and optimised medical therapy Exclusion criteria: insulin-dependent diabetes or life-limiting condition	review and telephone support. Frequency of follow-up was at the discretion of the heart failure team	PLUS monthly telephone contact from the study nurse			

Variable	Home-based telemanagement N=94	Usual care N=160
Mean age yrs	60	60
> 65 yrs	35%	39%
Female %	11%	17%
NYHA ≥ 3	36%	34%
Medications BB Angiotensin-converting enzme	 87 82	 84 82

Effect

Data reported for one intervention strategy (no. 2) only

Telemonitoring vs usual care

No of patients hospitalised all cause – mean 11.6 months

34/94 vs 48/160

No. of patients hospitalised (heart failure) – mean 11.6 months

17/94 vs 28/160

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	RCT Randomised in blocked stratified by hospital site - central computerised allocation - ITT - 4/182 withdrawals	N=182	Patients admitted to hospital with a diagnosis of heart failure Inclusion criteria: home telephone line, NYHA II to IV Exclusion criteria: cognitive impairment that would hinder use of equipe=ment	Usual care N=91 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 N=91 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	180 days	Unplanned hospitalisations (No. of patients) Minnesota Living with Heart Failure Questionnaire	Honeywell HomMed

Variable	Home-based telemanagement N=91	Usual care N=91
Mean age yrs	70	72
≥ 75 yrs	42	48
Male %	68	65
South Asian	20	21
Comorbidities Previous myocardial infarction Chronic lung disease	 40 9	 48 9
Pts with > 1 hospitalisations for HF in the previous yr	8%	5%
Medications BB	 57	 55

Angiotensin-converting enzme Aldosterone antagonists	82 43	93 38						
Compliance 95% using the telemonitoring system for > 90% of the time Telemonitoring vs usual care No. of patients hospitalised (all cause) – follow-up 180 days 33/91 vs 23/91 No. of patients hospitalised (HF) – follow-up 180 days 17/91 vs 10/91 Minnesota Living with Heart Failure questionnaire There were no significant differences (data not shown/reported)								
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	RCT - permuted block randomisation - unclear allocation concealment - unclear blinding - ITT - usual care 1/230 and tele 4/230 lost to follow-up	N=460	Hospitalised patients with a confirmed diagnosis of CHF, LVEF < 40% and at least one hospitalisation for acute HF in the previous year Inclusion criteria: clinically stable with optimised oral therapy inc angiotensin inhibitors and beta blockers Exclusion criteria included: non-cardiac debilitating	Usual care N=230 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 the discharge. Education on heart failure including advice on daily weights, daily self-management of blood pressure, dietary restrictions and signs and symptoms	Home-based telemanagement (HBT) N=230 Telemonitoring Scheduled appointments every weeks of every 15 days for NYHA III-IV and 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.	One year	Unplanned hospitalisation (No. of patients)	National Ministry of Health

			illness, cognitive impairment clinically evident		Teleassistance: Occasional appointments when signs and symptoms of possible decompensation were present. Format as for telemonitoring Education as for comparison			

Variable	Home-based telemanagement N=230	Usual care N=230
Mean age yrs	58	56
> 65 yrs	73%	82%
Women %	16	14
Comorbidities		
Previous myocardial infarction	53	51
Chronic lung disease	15	17
Pts with > 2 hospitalisations for HF in the previous yr	48%	52%
NYHA		
II	54%	65%
III-IV	46%	35%
Discharge medications		
Digitalis	34%	50%

BB Angiotensin-converting enzme Aldosterone antagonists	85% 95% 69%	60% 94% 55%						
Effect home-based telemanagement (HBT) vs usual care All cause mortality – one year 9 vs 14% 21/230 vs 32/230 All cause hospital readmissions 67/230 vs 96/230 Heart failure admissions 43/230 vs 73/230								
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*	RCT - Permuted blocks (size concealed) - no details of concealment - 4/426 lost to follow-up - ITT	N=253	Patients hospitalised due to or complicated by worsening heart failure lasting > 48 hrs within the last six weeks, a LVEF < 40% and LV end-diastolic dimension > 30 mm/m (height) and to be receiving furosemide at a dose equal to or greater than 40 mg/day equiv. plus at least one of: unplanned CV admission lasting	Usual care N=85 Individualised written management plan describing medication regimen sent to primary care physician. Patients assessed at research clinic every four months	Home telemonitoring N=168 Usual care plus telephoned each month by a nurse specialist to assess symptoms and medication. The nurse could also be contact 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	240 days	Total hospitalisations (No. of patients), all cause mortality	European Union Trans European Network and Philips Medical Systems

of Cardiology. 2005; 45(10):1654-1664. Ref ID: 155			> 48 hrs within the previous 2 yrs, an LVEF < 25%, or treatment with furosemide > 100 mg/day or equiv.					

Variable	Usual care N=85	Nurse telephone support N=173	Home telemonitoring N=168
Mean age yrs	68	67	67
≥ 70 yrs	49	47	54
Women %	18	28	20
Comorbidities			
Previous myocardial infarction	67%	52%	56%
Chronic lung disease	29%	22%	24%

Effect

Telemonitoring vs usual care

No. of hospitalisations (unplanned or planned not stated) (no.of patients) – 240 days

80/163 vs 46/85

No. of hospitalisations (heart failure) (no. of patients) – 240 days

40/163 vs 24/85

All cause mortality – 240 days

28/163 vs 20/85

No. of hospitalisations (unplanned or planned not stated) (no. of patients)– 450 days

75/106 vs 40/55

No. of hospitalisations (heart failure) (no of patients) – 450 days

38/106 vs 23/55

All cause mortality – 450 days

36/106 vs 28/55

REHAB: exercise based cardiac rehabilitation

What is the safety and efficacy of exercise based cardiac rehabilitation in adults with chronic heart failure?

Evidence Tables

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
C. M. O'Connor, D. J. Whellan, K. L. Lee, S. J. Keteyian, L. S. Cooper, S. J. Ellis, E. S. Leifer, W. E. Kraus, D. W. Kitzman, J. A. Blumenthal, D. S. Rendall, N. H. Miller, J. L. Fleg, K. A. Schulman,	RCT Multicentre (USA, Canada and France) Randomised, No blinding, ITT, drop outs given (5%), unclear allocation concealment	N=2331 (5% drop-outs in each arm)	**Inclusion criteria:** patients with CHF, NYHA class II-IV, LVEF≤ 35% despite optimal HF therapy for at least 6 weeks. **Exclusion criteria:** major comorbidities or limitations that could interfere with exercise training, recent (≤ 6 weeks) or planned (≤ 6 months) major cardiovascular events or procedures, performance of regular exercise training, or use of devices that limited the ability to achieve target heart rates. **Patient Characteristics:** Training | Control	N=1159 Training group (structured then home-based) The patients began with a structured group-based supervised exercise program, with a goal of 3 sessions/week for a total of 36	N=1172 Control group (usual care): patients had no formal exercise prescription, they all received self-management educational materials including information on	Median 30 months (up to 4-year follow-up)	All-cause mortality; 6 minute walking test (6MWT); change in NYHA class; all cause hospitalisation	The National Heart, Lung and Blood Institute

<table>
<tr><th>Reference</th><th>Study type/
Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>R. S. McKelvie, F. Zannad, I. L. Pina, and ACTION Investigators HF. 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.

ID 13</td>
<td></td>
<td></td>
<td>
<table>
<tr><td></td><td>group</td><td>Group</td></tr>
<tr><td>Male/female</td><td>70/30%</td><td>73/27%</td></tr>
<tr><td>Age median (yr)</td><td>59.2</td><td>59.3</td></tr>
<tr><td>NYHA class %
II
II
IV</td><td>
62.4
36.4
1.2</td><td>
64.3
34.9
0.8</td></tr>
<tr><td>LVEF median (IQR) %</td><td>24.6
(20-30)</td><td>24.9
(20-30)</td></tr>
</table>
</td>
<td>sessions in 3 months. Patients performed walking, treadmill or stationary cycling exercise as their primary training mode. Exercise was initiated at 15-30 mins/session and increased after 6 sessions to 30-35 mins.

Patients then began home-based exercise after 18 supervised sessions</td>
<td>exercise, they also received comparable levels of attention from study personnel as the exercise group (by telephone calls)

NOTE: a minority of patients in the usual care group also exercised (22-28% range at each assessment) – only 8% however reported that they</td>
<td></td>
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</tr>
</table>

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				and fully home-based after 36 supervised sessions. They were provided with home exercise equipment (cycle or treadmill). Target was 5 times/week of 40 minute sessions. Both exercise phases had target heart rates.	were exercising continuously throughout the trial.			
Effect Size Outcomes 1. Mortality (all cause)								

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
• Training group: 189/1159; Control group: 198/1172 2. Mortality (CV) • Training group: 131/1159; Control group: 143/1172 3. All hospitalization • Training group: 729/1159; Control group: 760/1172 4. 6 minute walking test (metres, median change from baseline at 12 months) • Training group: 12 (IQR -30 to 55); Control group: 13 (-28 to 61), p=0.26 5. Change NYHA class (post-hoc analysis) • Improvement (by 1 class or more): Training group: 30%; Control group: 25%								
Reference	**Study type/ Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
Corvera TT, Doering LV, Woo MA et al. Effects of a home walking exercise program on functional status and symptoms in heart	RCT Randomized, ITT, drop outs given, unclear allocation concealment	N=79 (n=68 completed)	Inclusion criteria: patients with CHF, NYHA class II-IV, LVEF≤ 40% and HF duration ≥ 3 months. Exclusion criteria: Myocardial infarction or recurrent angina within 3 months; orthopedic, neurologic, or pulmonary conditions limiting exercise; peak expiratory flow rate <50%, uncorrected peripheral vascular disease; uncontrolled ventricular	Training group: home walking exercise 1/day, 5 days/week, with an exercise duration and intensity initiated at 10 mins and	Control group: patients were instructed to maintain their normal daily activities and asked not to	12 weeks	Cardiopulmonary exercise test; 6 minute walking test (6MWT); heart failure functional status inventory; dyspnoea-fatigue score; adverse	Veterans Affairs Health Services Research and Development: Nursing Research Initiative

<table>
<tr><th>Reference</th><th>Study type/
Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>failure. American Heart Journal. 2004; 147(2):339-346.</td><td></td><td></td><td>tachyarrhythmias; current involvement in an exercise program; and/or cognitive impairment defined by a mini-mental state score <20.
Patient Characteristics:<table><tr><td></td><td>Training group</td><td>Control Group</td></tr><tr><td>Male/female</td><td>42/0</td><td>36/1</td></tr><tr><td>Age (yr)</td><td>63.8 ± 10.1</td><td>61.3 ± 11.1</td></tr><tr><td>NYHA class II</td><td>32 (76)</td><td>31 (84)</td></tr><tr><td>NYHA class III/IV</td><td>9 (24)</td><td>6 (16)</td></tr><tr><td>LVEF (%)</td><td>29.1 ± 8.5</td><td>24.7 ± 8.8</td></tr></table></td><td>40% maximal heart rate and progressively increased up to 60 mins and 65% maximal HR in the last 6 weeks of the program. Patients were instructed to 1) wear the pedometer for the walking exercise and immediately record walking data, 2) reset the pedometer (after walking exercise) and record all-day data</td><td>begin a regular exercise program. Patients were asked to provide only the all-day pedometer data. During each home visit, the nurse 1) obtained vital signs and performed a brief physical assessment 2) reinforced maintenance of daily activities and 3) reviewed all-day</td><td></td><td>events</td><td></td></tr>
</table>

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				before bedtime. During home visits the nurse 1) provided weekly walking prescription including duration, and intensity 2) walked with the patient to evaluate exercise tolerance and validate self-reported protocol compliance 3) conducted a brief physical assessment immediately before and after walking exercise and 4) reviewed	pedometer data			

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				pedometer data and counselled patients about incomplete data. N=42 (n=32 completed)				
Effect Size Outcomes 1. Death (CV) • Training group: 2/42; Control group: 1/37 2. All hospitalization • Training group: 3/42; Control group: 4/37 3. 6 minute walking test (feet) • Training group: baseline: 1219.0 ± 241.5, 3 months: 1337.1 ± 272.2; Control group: baseline: 1273.2 ± 249.2, 3 months: 1263.9 ± 254.5, p=0.001 • IN METRES: Training group: baseline: 371.55 ± 73.6, 3 months 407.55 ± 82.97; Control group: baseline: 388.7 ± 75.96, 3 months: 385.24 ± 77.57								
Jolly K, Taylor RS, Lip GY et al. A	RCT Randomised 1:1	N=169	Patients with LVEF ≤ 40 and NYHA of II or more in the previous 12 months. Clinically stable and on optimal medical	Exercise training	Specialist care	12 months	MLHF questionnaire	Department of Health

<table>
<tr><th>Reference</th><th>Study type/
Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>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.</td><td>Computerised, central randomisation
Power analysis of QoL measure
Sensitivity analysis to look at the effect of missing values</td><td></td><td>therapy. All patients had to complete a shuffle walking test supervised by a trained nurse in order to identify any contraindications.

<table><tr><td></td><td>Exercise</td><td>Control</td></tr><tr><td>Male</td><td>76%</td><td>73%</td></tr><tr><td>Age</td><td>66 yrs</td><td>70 yrs</td></tr><tr><td>NYHA iii</td><td>20%</td><td>20%</td></tr><tr><td>Diurectic</td><td>93%</td><td>92%</td></tr><tr><td>ACEI or ARB</td><td>99%</td><td>94%</td></tr><tr><td>Beta-blockers</td><td>74%</td><td>61%</td></tr></table></td><td>N=84

Care from a specialised heart failure nurse plus
Exercise started with three sessions to plan an individualised programme. Followed by home-based programme. The aim was to achieve continuous bouts of exercise (20 to 30 min) five times a week after 6 months of the home programme.</td><td>Care from a specialised heart failure nurse
N=85</td><td></td><td></td><td></td></tr>
</table>

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Telemonitoring plus specialist care vs specialist care Distance on the Incremental Shuffle Walking Test (ISWT), 6 month follow-up 226.95 (SD 120.3) vs 206.18 (135.2) MLHF, 12 month follow-up 37.61 (20.97) vs 34.91 (24.8) All cause hospitalisation, follow-up twelve months 16/84 vs 20/85 Hospitalisation (cardiac), follow-up twelve months 11/85 vs 11/84								
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*	RCT: follow up study (see below) Randomized, allocation concealment, ITT	N=80	Inclusion criteria: patients with stable CHF, NYHA classes II-IIIB, on optimal treatment including BB and ACE inhibitors. LVEF<40% or ≥40% with clinical symptoms of HF. Exclusion criteria: acute MI within 4 weeks, unstable angina pectoris, uncontrolled atrial fibrillation, symptomatic peripheral vascular disease, obstructive pulmonary disease forced expiratory vital capacity <50% of predicted, 6 minute walking distance >550m, and work load on the ergometer cycle	Exercise group: underwent standard care plus group-based high-intensity interval training. The Norwegian Ullevaal Model was used: high intensity 16 week aerobic	Standard care: outpatient monitoring of clinical status and uptitration of medication by a specialist nurse supervised by a cardiologist. Follow-up care	12 months	6 minute walking test, cycle ergometry, Qol (MLWHFQ),	Eastern Norwegian Health Authority, Norwegian Foundation for Health and Rehabilitation, Centre for Clinical Research, Ullevaal University Hospital

<table>
<tr><th>Reference</th><th>Study type/
Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Cardiology. 2008; 102(9):1220-1224.</td><td></td><td></td><td>test >100 W. Patients with a significant co-morbidity, terminal disease or inability to exercise.
Patient characteristics
<table>
<tr><td></td><td>Exercise group</td><td>Control group</td></tr>
<tr><td>Mean age (yrs)</td><td>69 ± 8</td><td>72 ± 8</td></tr>
<tr><td>Men/women</td><td>31/9</td><td>32/8</td></tr>
<tr><td>NYHA class II/III</td><td>21/19</td><td>26/16</td></tr>
<tr><td>Ejection fraction</td><td>30 ± 8</td><td>31 ± 9</td></tr>
</table></td><td>interval training (2 days/week) each 50 mins, followed by 15-30 mins of counselling about how to cope with CHF under supervision of physical therapist. A total of 32 sessions were offered. Exercise training consisted of group-based simple aerobic dance movements (with music) and involved the use of upper and</td><td>provided by primary care physician and patients were not discouraged from exercise but did not receive supervised exercise.

N=40
(N=37 completed 6 months)</td><td></td><td></td><td></td></tr>
</table>

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				lower extremities, including strength, endurance and stretching exercises. The Borg scale and beats per min were used to adjust exercise intensity. Heart rate was recorded using a portable heart rate monitor to measure the assigned exercise intensity. Exercise training included 3				

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				intervals of high intensity and 2 intervals of moderate intensity. All patients were guided to exercise at their individual level based on baseline tests and their health on the day. In addition patients were offered up to 4 individual counselling sessions with a CHF nurse, including information and discussions regarding				

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				medication, dietary behaviour, and monitoring and interpretation of symptoms. N=40 (N=35 completed 6 months)				
Effect Size Outcomes (ITT analysed) 1. 6MWT (m)- 12 months • Control group: 435 ± 117; Exercise group: 598 ± 100, p<0.001 2. Qol: MLWHFQ 12 months • Control group: 28 ± 20; Exercise group:23 ± 14, p=0.003								
Nilsson BB, Westheim A, Risberg MA. Effects of group-	RCT Randomized, allocation	N=80	Inclusion criteria: patients with stable CHF, NYHA classes II-IIIB, on optimal treatment including BB and ACE inhibitors. LVEF<40% or ≥40% with clinical	Exercise group: underwent standard care plus	Standard care: outpatient monitoring of clinical	24 weeks	6 minute walking test, cycle ergometry, Qol	Eastern Norwegian Health Authority, Norwegian

<table>
<tr><th>Reference</th><th>Study type/
Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>based high-intensity aerobic interval training in patients with chronic heart failure. American Journal of Cardiology. 2008; 102(10):1361-1365.</td><td>concealment, ITT</td><td></td><td>symptoms of HF.

Exclusion criteria: acute MI within 4 weeks, unstable angina pectoris, uncontrolled atrial fibrillation, symptomatic peripheral vascular disease, obstructive pulmonary disease forced expiratory vital capacity <50% of predicted, 6 minute walking distance >550m, and work load on the ergometer cycle test >100 W. Patients with a significant co-morbidity, terminal disease or inability to exercise.

Patient characteristics
<table>
<tr><th></th><th>Exercise group</th><th>Control group</th></tr>
<tr><td>Mean age (yrs)</td><td>69 ± 8</td><td>72 ± 8</td></tr>
<tr><td>Men/women</td><td>31/9</td><td>32/8</td></tr>
<tr><td>NYHA class II/III</td><td>21/19</td><td>26/16</td></tr>
<tr><td>Ejection fraction</td><td>30 ± 8</td><td>31 ± 9</td></tr>
</table></td><td>group-based high-intensity interval training.

The Norwegian Ullevaal Model was used: high intensity 16 week aerobic interval training (2 days/week) each 50 mins, followed by 15-30 mins of counselling about how to cope with CHF under supervision of physical therapist. A total of 32 sessions were offered. Exercise</td><td>status and uptitration of medication by a specialist nurse supervised by a cardiologist. Follow-up care provided by primary care physician and patients were not discouraged from exercise but did not receive supervised exercise.

N=40

(N=38</td><td></td><td>(MLWHFQ),</td><td>Foundation for Health and Rehabilitation, Centre for Clinical Research, Ullevaal University Hospital</td></tr>
</table>

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				training consisted of group-based simple aerobic dance movements (with music) and involved the use of upper and lower extremities, including strength, endurance and stretching exercises. The Borg scale and beats per min were used to adjust exercise intensity. Heart rate was recorded	completed, 1 died and 1 dropped out due to dissatisfaction with group allocation)			

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				using a portable heart rate monitor to measure the assigned exercise intensity. Exercise training included 3 intervals of high intensity and 2 intervals of moderate intensity. All patients were guided to exercise at their individual level based on baseline tests and their health on the day. In addition patients were offered				

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				up to 4 individual counselling sessions with a CHF nurse, including information and discussions regarding medication, dietary behaviour, and monitoring and interpretation of symptoms. N=40 (N=38 completed, drop outs: 1 no reason and 1 had stroke just after randomisatio				

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				n)				
Effect Size Outcomes (ITT analysed) 1. 6MWT (m) • Control group: baseline: 455 ± 83; follow up: 440 ± 100; Exercise group: baseline 457 ± 77; follow up: 515 ± 93, p<0.001 2. Qol: MLWHFQ • Control group: baseline: 22 ± 17*; follow up: 23 ± 20; Exercise group: baseline 33* ± 18; follow up: 22 ± 12, p=0.033 * p>0.005 between groups at baseline								
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-	RCT Randomised, allocation concealment, ITT	N=200	Inclusion criteria: patients >60 yrs with heart failure, NYHA class II-III and LVEF ≤40% confirmed by echo. The sources of recruitment reflected a diversity of healthcare so that results would be reflective of a conventional programme. Exclusion criteria: patients with diastolic dysfunction, a significant co-morbidity either a terminal disease or an inability to exercise (severe musculoskeletal condition, unstable ischaemic heart disease, advanced valvular disease)	Experimental regimen: standard care plus an 8 week cardiac rehabilitation programme co-ordinated by clinical nurse specialist. Patients attended classes twice weekly for 2.5 hrs.	Standard group: 8 weekly monitoring of clinical status (functional performance, fluid status, cardiac rhythm, laboratory assessment) in the cardiology outpatients	24 weeks	6 minute walking test, NYHA class, Qol (MLWHFQ), cost utility, perceived exertion (Borg RPE), death, hospitalization	Not reported

<table>
<tr><th>Reference</th><th>Study type/
Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>417.</td><td></td><td></td><td>Patient Characteristics:
<table><tr><td></td><td>Standard care</td><td>Experimental</td></tr><tr><td>Mean Age (yrs) (SD)</td><td>71.8 (6.8)</td><td>71.9 (6.3)</td></tr><tr><td>Male</td><td>42 (64)</td><td>44 (67)</td></tr><tr><td>Source of recruitment</td><td></td><td></td></tr><tr><td>Outpatients</td><td>62</td><td>61</td></tr><tr><td>Ward</td><td>28</td><td>23</td></tr><tr><td>General practice</td><td>10</td><td>16</td></tr><tr><td>LVEF ≤40-35%</td><td>18</td><td>15</td></tr><tr><td>LVEF <35-30%</td><td>41</td><td>49</td></tr><tr><td>LVEF <30%</td><td>41</td><td>36</td></tr><tr><td>NYHA class II</td><td>47</td><td>56</td></tr><tr><td>NYHA class III</td><td>53</td><td>44</td></tr></table></td><td>(Transport provided by hospital if unable to make their own way). After 8 weeks patients began a 16 week community based care regimen of weekly 1hr exercise sessions supervised by a British Association of Cardiac Rehabilitation exercise instructor.
Patients were encouraged to attend with their spouse or</td><td>by the clinical nurse specialist. Participants also given an explanation of HF and its treatment-self monitoring (fluid overload, dietary advice, patient health record containing list of drugs, weights, blood test results, hospital appointments and nurse</td><td></td><td></td><td></td></tr>
</table>

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				partner. Patients performed aerobic endurance training and low resistance training/high repetitive muscular strength work. Patients were issued with guidance to promote exercise for an additional 3 times/week at home. During first 8 weeks patients also received additional education input in weekly group	specialist contact details) N=100 (n=86 received intervention : 4 died, 3 cancer diagnosis, 1 fractured femur, 1 moved, 5 withdrew)			

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				sessions on topics such as medication, diet and exercise from members of the MDT. If required patients also received individual counselling from the dietician, psychotherapist and occupational therapist. N=100 (n=99 received intervention-1 died)				

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Effect Size Outcomes 1. 6 min walking test (metres): • Standard care: baseline: 259.4 (95% CI 236.3-282.5); at 24 weeks: 252.7 (95% CI 226.7-278.5) • Experimental group: baseline: 275.5 (95% CI 254.1-298.8); at 24 weeks: 320.4 (95% CI 298.5-342.2) p<0.001 2. Qol: MLWHFQ • Standard care: baseline: 44.3 (39.5-49.1); 24 weeks: 36.9 (32.2-41.6), p<0.05 • Experimental group: baseline: 41.0 (36.0-46.0); 24 weeks: 22.9 (19.5-26.4), p<0.01 3. change NYHA class (baseline to 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 4. Mortality • standard group: 4/94; experimental: 5/85 5. Total admissions/hospitalization • standard group: 33/94; experimental: 11/85								
Cider A, Schaufelberger M, Sunnerhagen KS et al. Hydrotherapy--a new approach to	RCT Randomised, ITT, drop outs given, unclear allocation	N=25	Inclusion criteria: patients with stable CHF in NYHA class II-III, EF <45% and 60 yrs of age or older. Medication for HF had to be stable for the previous 3 months. Exclusion criteria: patients with	Training programme: 45 mins sessions in a heated pool (33-34 °C), 3 times/week over an 8	Control group: instructed to live their life as normal for 8 weeks and were	8 weeks	Exercise tolerance (6MWT), muscle function, Qol,	Vardalstiftelsen VD-98, Askers Foundation, The Cardiac research found SU/ Sahlgrenska

<table>
<tr><th>Reference</th><th>Study type/
Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>improve function in the older patient with chronic heart failure. European Journal of Heart Failure. 2003; 5(4):527-535.</td><td>concealment</td><td></td><td>diabetes, peripheral arterial disease, chronic pulmonary disease and status post stroke, or other disabling diseases that might interfere with the exercise protocol.
Patient characteristics:<table><tr><td></td><td>Training</td><td>Control</td></tr><tr><td>Age (yrs)</td><td>70.2 ± 5.2</td><td>75 ± 6.4</td></tr><tr><td>Sex F/M</td><td>5/11</td><td>3/6</td></tr><tr><td>LVEF (%)</td><td>31 ± 8.3</td><td>Not reported</td></tr><tr><td>NYHA class (II/III)</td><td>3/12</td><td>1/9</td></tr></table></td><td>week period. Patients trained as a group following a low to moderate exercise level (40-70% of maximal heart rate reserve). The basis posture was standing with water just below neck level. The exercise regime used muscles required for activities of daily living such as walking, dressing and household activities.</td><td>not allowed to increase their habitual physical activity during this period.

N=10</td><td></td><td></td><td>, Renee Eanders Foundation and Hjalmar Svenssons foundation, LSR memorial foundation and Gustav V memorial foundation.</td></tr>
</table>

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				Included peripheral muscle training and central circulatory exercises- to improve aerobic capacity, peripheral muscle strength and endurance. The physiotherapist used music to facilitate the correct pace of exercise. A heart rate recorder, sport tester was used to monitor intensity. (full protocol provided in paper				

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
				appendix) N=15 (1 drop out: due to new episode of arrhythmia)				

Effect Size

Outcomes

1. 6MWT (m)

- Training group: baseline 421 ± 115; follow up: 450 ± 94, p value within group: p=0.02
- Control group: baseline 329 ± 98; follow up 335 ± 95, p value within group: p=0.4
- P value training vs. control p=0.055

2. Qol (MLWHFQ)

- Training group: baseline 33.3 ± 15.9; follow up: 24.5 ± 16.9, p value within group: p=0.01
- Control group: baseline 32.7 ± 21.7; follow up 27.8 ± 16.8, p value within group: p= 0.1
- P value training vs. control NS

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

<table>
<tr><th>Reference</th><th>Study type/
Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>E. Collins, W. E. Langbein, Koetje J. Dilan, C. Bammert, K. Hanson, D. Reda, and L. Edwards. Effects of exercise training on aerobic capacity and quality of life in individuals with heart failure. Heart & Lung 33 (3):154-161,</td>
<td>RCT
(Single centre USA)
• No mention of allocation concealment
• No mention of blinding
• <20% drop-outs (19%)
• Not true ITT analysis
• Power study for peak oxygen and change in physical</td>
<td>N=31
(N=6 drop-outs; 19%)</td>
<td>Inclusion criteria: patients from Veteran’s Hospital, age ≥18 years, LVEF ≤40%, NYHA class II and III; stable medication regimen.

Exclusion criteria: unstable HF, unstable dysrhythmia, unstable angina, uncontrolled diabetes, uncontrolled hypertension, anaemia, exercise-limiting concurrent condition, cardiac transplant and current participation in a supervised exercise programme.

<table>
<tr><th>Baseline</th><th>Exercise (n=15)</th><th>Control (n=16)</th></tr>
<tr><td>Mean age (years)</td><td>62.7 (11.2)</td><td>66.2 (9.8)</td></tr>
<tr><td>Men/women</td><td>100% / 0%</td><td>100%/0%</td></tr>
</table>
</td>
<td>N=15

Rehabilitation programme: supervised moderate aerobic exercise programme

Polestriding and treadmill walking (3 times/week; duration gradually increased to 45-50 mins by 12 weeks). An exercise physiologist or nurse supervised training sessions (this was</td>
<td>N=16

Control
(Attention control)

Patients seen bi-weekly by the study nurse. Patients asked not to change their level of exercise.</td>
<td>12 weeks</td>
<td>Secondary outcome: change in QoL (MLHFQ)</td>
<td>Grant from Department of Veterans Affairs, USA.</td>
</tr>
</table>

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
2004. **REF ID: 606**	function)			tapered to fortnightly by 12 weeks)				
Effect size Effect size Outcomes 1. QoL (MLHFQ) – lower score is better score • Change in exercise group –3.2 (13.7); change in control group –0.1 (13.4); NS difference (p=0.75).								
Sarullo F. Maria, T. Gristina, I. Brusca, S. Milia, R. Raimondi, M. Sajeva, Chiusa S. Maria La, G. Serio, S. Paterna, Pasquale	RCT (Single centre, Italy) • Allocation concealment • Single blind (physicians)	N=60 No drop-outs	**Inclusion criteria:** patients were clinically stable on medical therapy in 3 months before the study; documented clinical signs and symptoms of HF, LVEF <40%, NYHA class II-III and sinus rhythm. **Exclusion criteria:** unstable angina, recent acute MI, decompensated congestive HF, haemodynamically significant valvular heart disease, poorly controlled cardiac arrythmias, significant chronic pulmonary illness, renal insufficiency, inability to attend regular exercise training sessions, exercise	N=30 Supervised physical training programme (bicycle ergometer 30mins 3 times/week)	N=30 Control (no change in physical activity)	3 months	Secondary outcome: change in QoL (MLHFQ); NYHA class	None mentioned

<table>
<tr><th>Reference</th><th>Study type/
Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>P. Di, and A. Castello. Effect of physical training on exercise capacity, gas exchange and N-terminal pro-brain natriuretic peptide levels in patients with chronic heart failure. European Journal of Cardiovascular Prevention & Rehabilit</td>
<td>• No drop-outs therefore is an ITT analysis</td>
<td></td>
<td>testing limited by angina or leg claudication, abnormal blood pressure response to exercise testing and neurological or orthopaedic limitations.
<table>
<tr><th>Baseline</th><th>Exercise (n=30)</th><th>Control (n=30)</th></tr>
<tr><td>Mean age (years)</td><td>53.1 (6.1)</td><td>52.9 (4.9)</td></tr>
<tr><td>Men/women</td><td>77% /23%</td><td>74%/25%</td></tr>
<tr><td>NYHA class
II
III</td><td>
17
13</td><td>
18
12</td></tr>
</table>
NS differences at baseline</td>
<td></td><td></td><td></td><td></td><td></td>
</tr>
</table>

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
ation 13 (5):812-817, 2006. **ID 311**								
Effect Size Outcomes 1. NYHA class • 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 2. QoL (MLHFQ) • Exercise: improvement (change from baseline) of 35.5 (1.9); Control: improvement 31.2 (2.6).								
K. Dracup, L. S. Evangelista, M. A. Hamilton, V. Erickson, A. Hage, J. Moriguchi, C. Canary, W. R.	RCT (Multicentre, USA) • No mention of allocation concealment • No mention of blinding	N=173 No drop-outs	**Inclusion criteria:** patients aged 18-80 years, HF NYHA class II to IV, LVSD (LVEF ≤40%) within previous 6 months. **Exclusion criteria:** unstable angina or recurrent MI in last 3 months, orthopaedic limitations to exercise, severe COPD, stenotic valvular disease, history of uncontrolled tacharrhthmias or absence of an ICD despite a history of sudden cardiac death; not enrolled if judged stable by their cardiologist.	N=86 Low-level aerobic and resistive/strength training programme Aerobic training (walking) gradually	N=87 Control (no change in physical activity)	1 year	Secondary outcomes: change in QoL (MLHFQ); 6-min walk test, hospitalisataion, mortality	American Heart Association

<table>
<tr><th>Reference</th><th>Study type/
Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr>
<td>MacLellan, and G. C. Fonarow. Effects of a home-based exercise program on clinical outcomes in heart failure. American Heart Journal 154 (5):877-883, 2007.

ID 4495</td>
<td>• No drop-outs therefore is an ITT analysis

• Power study (for composite endpoint)</td>
<td></td>
<td>
<table>
<tr><th>Baseline</th><th>Exercise (n=86)</th><th>Control (n=87)</th></tr>
<tr><td>Mean age (years)</td><td>53.3 (12.7)</td><td>54.6 (12.5)</td></tr>
<tr><td>Men/women</td><td>73% /27%</td><td>70%/30%</td></tr>
<tr><td>NYHA class
II
III
IV</td><td>
32.6
59.3
8.1</td><td>
21.8
66.7
11.5</td></tr>
</table>
NS differences at baseline
</td>
<td>increased up to 45 mins at 12 weeks; exercsie sessions 4 times/week. Then resistance programme added – weights for upper nd lower extremities – performed 3 days/week (on days they did not walk)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td colspan="9">Effect Size
Outcomes
1. 6-minute walk test at 6 months
• NS difference between groups: Exercise: baseline 1350.7 (297.4), 6 months 1422.9 (354.3); control: baseline 1332.4 (293.5), 6 months 1385.6 (317.3); p=0.275
• In metres: Exercise: 6 months: 433.7 (108.0); control: 6 months: 422.3 (96.7)</td>
</tr>
</table>

<table>
<tr><th>Reference</th><th>Study type/
Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td colspan="9">2. All-cause hospitalisations (over 1 year)
• NS difference between groups: Exercise: 35/87; control: 37/86, p=0.752
3. Mortality (over 1 year)
• NS difference between groups: Exercise: 9/87; control: 8/86, p=0.720
4. QoL (MLHFQ) at 6 months
• NS difference between groups: Exercise: baseline 46.7 (23.8), 6 months 35.7 (23.7); control: baseline 49.2 (22.4), 6 months 43.2 (27.3); p=0.819</td></tr>
<tr><td>OLDER PATIENTS THUS POSS REPORT SEPARATELY

M. D. Witham, J. M. Gray, I. S. Argo, D. W. Johnston, A. D. Struthers, and M. E. T. McMurdo. Effect of</td><td>RCT
(Twin centre, UK)
• Allocation concealment
• Single blind (assessor)
• No mention of ITT analysis
• Larger dropouts in 1 arm (12% exercise</td><td>N=82

Drop-outs: Exercise 12%, control 22%</td><td>Inclusion criteria: patients aged ≥70 years, clinical diagnosis of HF, NYHA class II or III, LVSD.

Exclusion criteria: uncontrolled AF, significant aortic stenosis, sustained ventricular tachycardia, recent MI, inability to walk without human assistance, those currently undergoing physiotherapy or rehabilitation.

<table><tr><th>Baseline</th><th>Exercise (n=41)</th><th>Control (n=41)</th></tr><tr><td>Mean age (years)</td><td>80 (6)</td><td>81 (4)</td></tr><tr><td>Men/women</td><td>63% /37%</td><td>46%/54%</td></tr><tr><td>NYHA class
II
III</td><td>
25
16</td><td>
21
20</td></tr></table></td><td>N=41

Physiotherapist delivered the exercise intervention – was divided into supervised and home phases. Supervised phase (0-3 months) classes as outpatients of small groups twice/week; mainly aerobic and weights (strength/resi</td><td>N=41

Control
(usual care; not restrict their exercise activities in any way)</td><td>6 months</td><td>Primary outcome: 6 minute walk distance</td><td>Grant from the Health Foundation, UK.</td></tr>
</table>

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
a seated exercise program to improve physical function and health status in frail patients [greater-than or equal to]70 years of age with heart failure. *American Journal of Cardiology* 95 (9):1120-1124, 2005. ID 1664	vs 22% control) • Power study (6 min walk)		NS differences at baseline	stance) Second phase (3-6 months) perform the exercises at home 2-3 times/week with weekly telephone liason with physiotherapist who gave new targets for daily walking activity.				

<table>
<tr><th>Reference</th><th>Study type/
Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td colspan="9">Effect Size
Outcomes
1. 6-minute walk distance (median % change from baseline):
Exercise: 4.4 (-3.1 to 11.8); control 3.2 (-6.0 to 12.4), p=0.84 (NS)
Exercise: Baseline 261 (117), 6 months 262 (110); control: baseline 240 (93), 6 months 246 (111)</td></tr>
<tr><td>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</td><td>RCT
(Single centre, Italy)
• No mention of allocation concealment
• No mention of blinding
• ITT analysis</td><td>N=99
Drop-outs: Exercise 4%, control 6%</td><td>Inclusion criteria: clinically stable 3 months before the study; HF (clinical symptoms and signs), LVEF ≤40% and sinus rhythm.
Exclusion criteria: unstable angina, recent acute MI, decompensated congestive HF, haemodynamically significant valvular heart disease, significant chronic pulmonary illness, uncontrolled hypertension, renal insufficiency, orthopaedic or neurological limitations.<table><tr><th>Baseline</th><th>Exercise (n=50)</th><th>Control (n=49)</th></tr><tr><td>Mean age (years)</td><td>56 (7)</td><td>53 (9)</td></tr><tr><td>Men/women</td><td>90% /10%</td><td>88%/12%</td></tr></table></td><td>N=50
2 phases of suoervised exercise training. Phase I: 3 times/week for 8 weeks, phase II: 12 month maintenance programme only 2 sessions/week. Each sessin 1 hour including 40 mons cycling on a cycle</td><td>N=49
Control
(no exercise)</td><td>14 months of training; plus 1214 days of follow-up (1639 days total – 4.5 years)</td><td>QoL (MLHFQ); mortality; Hospital readmission for HF</td><td>None mentioned</td></tr>
</table>

<table>
<tr><th>Reference</th><th>Study type/ Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>clinical outcome. [see comments.]. Circulation. 1999; 99(9):1173-1182.</td><td></td><td></td><td><table><tr><td>NYHA class</td><td></td><td></td></tr><tr><td>II</td><td>22</td><td>25</td></tr><tr><td>III</td><td>18</td><td>16</td></tr><tr><td>IV</td><td>10</td><td>9</td></tr></table>NS differences at baseline</td><td>ergometer.</td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="9">Effect Size
Outcomes
1. QoL (MLHFQ) - at 14 months
• Exercise: baseline 52 (22), 14 months 39 (20); control: baseline 50 (21), 14 months 52 (20); significant difference (-13, p<0.001) between the groups at 14 months
2. Hospital readmission for HF – at 4.4 years follow-up
• Significantly higher in control (RR 0.29, 95% CI 0.11 to 0.84, p=0.02) exercise: 5/50; control: 14/49
3. Mortality – at 4.4 years follow-up
• Significantly higher in control (RR 0.37, 95% CI 0.17 to 0.84, p=0.01): exercise: 9/50; control: 20/49</td></tr>
<tr><td>J. Austin, W. R. Williams, L. Ross, and S. Hutchison. Five-year</td><td>RCT
(Multicentre, UK)
• Allocation concealm</td><td>N=200 originally randomised; N=112 remained at 6</td><td>Inclusion criteria: patients >60 yrs with heart failure, NYHA class II-III and LVEF ≤40% confirmed by echo. The sources of recruitment reflected a diversity of healthcare so that results would be reflective of a</td><td>N=100 (N=57 at 5 years)
Rehabilitation (experimental regimen)
Standard care plus an 8 week</td><td>N=100 (N=55 at 5 years)
Standard care</td><td>5-year follow-up (original 24 week intervention)</td><td>Primary: 6 minute walking test, NYHA class, QoI (MLHFQ)</td><td>Chief medical officer's budget.</td></tr>
</table>

<table>
<tr><th>Reference</th><th>Study type/
Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>follow-up findings from a randomized controlled trial of cardiac rehabilitation for heart failure. European Journal of Cardiovascular Prevention & Rehabilitation 15 (2):162-167, 2008.

ID 4488</td><td>ent

• No mention of blinding

• Not ITT analysis for 5-year data

5-YEAR FOLLOW UP OF AUSTIN et al 2005 (ID 503): Randomised, allocation concealment, ITT</td><td>months for the 5-year follow-up.

Drop-outs between 0-5 years:
Rehab 43%,
Standard care 45%</td><td>conventional programme.

Exclusion criteria: patients with diastolic dysfunction, a significant co-morbidity either a terminal disease or an inability to exercise (severe musculoskeletal condition, unstable ischaemic heart disease, advanced valvular disease)

Patient Characteristics:<table><tr><th>Baseline</th><th>Standard care</th><th>Experimental</th></tr><tr><td>Mean Age (yrs) (SD)</td><td>71.8 (6.8)</td><td>71.9 (6.3)</td></tr><tr><td>Male</td><td>42 (64)</td><td>44 (67)</td></tr><tr><td>Source of recruitment</td><td></td><td></td></tr><tr><td>Outpatients</td><td>62</td><td>61</td></tr><tr><td>Ward</td><td>28</td><td>23</td></tr></table></td><td>cardiac rehabilitation programme co-ordinated by clinical nurse specialist. Patients attended classes twice weekly for 2.5 hrs. (Transport provided by hospital if unable to make their own way). After 8 weeks patients began a 16 week community based care regimen of weekly 1hr exercise sessions supervised by a British Association of Cardiac Rehabilitation exercise instructor.

Patients were encouraged to attend with their spouse or partner. Patients performed aerobic endurance training and low resistance training/high repetitive muscular strength work. Patients were issued with guidance to promote exercise for an additional 3 times/week at home.

During first 8 weeks patients also received additional education input in weekly group sessions on topics such as medication, diet and exercise</td><td>8 weekly monitoring of clinical status (functional performance, fluid status, cardiac rhythm, laboratory assessment) in the cardiology outpatients by the clinical nurse specialist. Participants also given an explanati</td><td></td><td>Secondary: all-cause mortality, HF hospitalisation</td><td></td></tr>
</table>

<table>
<tr><th>Reference</th><th>Study type/
Evidence level</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>General practice</td><td>10</td><td>16</td></tr>
<tr><td>LVEF ≤40-35%</td><td>18</td><td>15</td></tr>
<tr><td>LVEF <35-30%</td><td>41</td><td>49</td></tr>
<tr><td>LVEF <30%</td><td>41</td><td>36</td></tr>
<tr><td>NYHA class II</td><td>47</td><td>56</td></tr>
<tr><td>NYHA class III</td><td>53</td><td>44</td></tr>
</table>
NS differences at baseline
</td><td>from members of the MDT. If required patients also received individual counselling from the dietician, psychotherapist and occupational therapist.
N=57</td><td>on of HF and its treatment-self monitoring (fluid overload, dietary advice, patient health record containing list of drugs, weights, blood test results, hospital appointments and nurse specialist contact details)
N=55</td><td></td><td></td><td></td></tr>
<tr><td colspan="9"></td></tr>
</table>

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Effect Size **Outcomes (between 0-5 years)** 1. 6 min walking test (metres) **only for the N=112**: • Standard care: baseline: 293.2 (107.8); at 5 years: 260.4 (126.6) • Experimental group: baseline: 306.0 (85.9); at 5 years: 290.1 (114.2) 2. Qol: MLHFQ **only for the N=112**: • Standard care: baseline: 41.5 (21.7); 5 years: 37.1 (24.9) • Experimental group: baseline: 39.7(23.8); 5 years: 35.5 (21.7) 3. Change NYHA class (0-5 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% 4. All cause mortality (0-5 years) • Standard group: 38/100; experimental: 31/100 5. Total admissions/hospitalisation Standard group: n=38; experimental: n=53								

Appendix F– Forest Plots

DIAG: symptoms and signs vs gold standard

What is the diagnostic accuracy of a collection of symptoms and signs, including any scoring systems vs gold standard in the diagnosis of heart failure?

No forest plots

BNP1: natriuretic peptides vs gold standard

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

No forest plots

BNP2: natriuretic peptides vs echocardiography

What is the accuracy of echocardiography *vs* natriuretic peptides in the diagnosis of diastolic dysfunction?

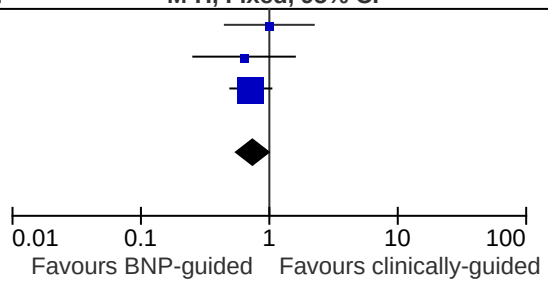
No forest plots

BNP3: natriuretic peptide monitoring (guided therapy) vs standard care

Does serial BNP monitoring (guided therapy) improve outcome compared to standard care in adults with chronic heart failure?

Study or Subgroup	BNP monitoring Events	Total	Clinically-guided Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BATTLESCARRED 2010	11	121	11	121	14.2%	1.00 [0.45, 2.22]
STARS-BNP 2007	7	110	11	110	14.2%	0.64 [0.26, 1.58]
TIME-CHF 2009	40	251	55	248	71.6%	0.72 [0.50, 1.04]
Total (95% CI)		**482**		**479**	**100.0%**	**0.75 [0.55, 1.02]**
Total events	58		77			

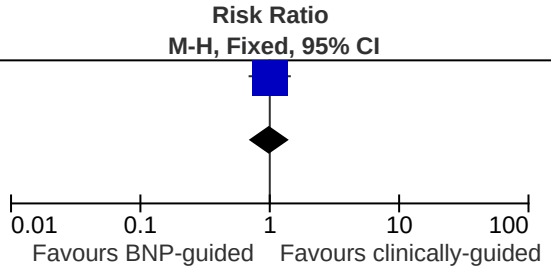
Heterogeneity: Chi² = 0.68, df = 2 (P = 0.71); I² = 0%
Test for overall effect: Z = 1.83 (P = 0.07)



1.1 Mortality (all causes) - range median 9.5 to 18 mths

Study or Subgroup	BNP-guided Events	Total	Clinically-guided Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BATTLESCARRED 2010	40	121	40	121	100.0%	1.00 [0.70, 1.43]
Total (95% CI)		**121**		**121**	**100.0%**	**1.00 [0.70, 1.43]**
Total events	40		40			

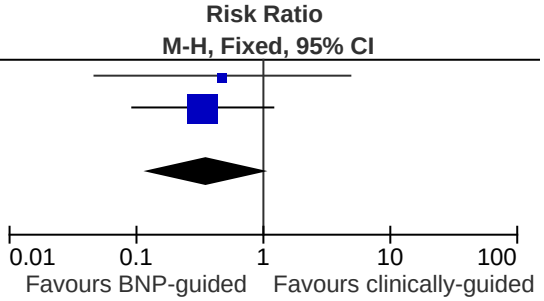
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



1.2 Mortality (all cause) - 3 yrs.

Study or Subgroup	BNP-guided Events	Total	Clinically-guided Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Beck-da-silva	1	21	2	20	18.5%	0.48 [0.05, 4.85]
STARS-BNP 2007	3	110	9	110	81.5%	0.33 [0.09, 1.20]
Total (95% CI)		**131**		**130**	**100.0%**	**0.36 [0.12, 1.10]**
Total events	4		11			

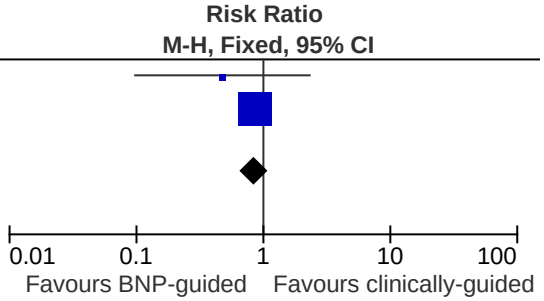
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%
Test for overall effect: Z = 1.79 (P = 0.07)



1.3 Mortality (HF) - range 3 to median 15 mths.

Study or Subgroup	BNP-guided Events	Total	Clinically-guided Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Beck-da-silva	2	21	4	20	6.4%	0.48 [0.10, 2.32]
STARS-BNP 2007	52	110	60	110	93.6%	0.87 [0.67, 1.12]
Total (95% CI)		**131**		**130**	**100.0%**	**0.84 [0.65, 1.09]**
Total events	54		64			

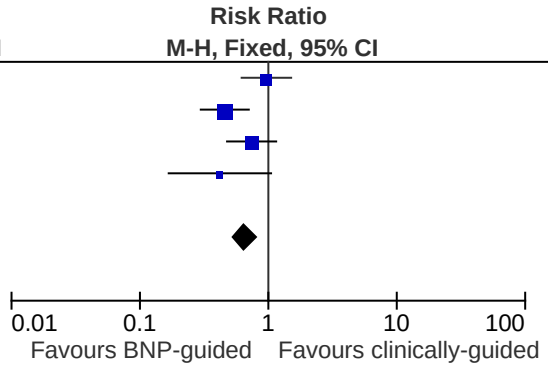
Heterogeneity: Chi² = 0.55, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 1.30 (P = 0.19)



1.4 Hospitalisation (all cause) (no. of patients) – range 3 to median 15 mths.

Study or Subgroup	BNP-guided Events	Total	Clinically-guided Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BATTLESCARRED 2010	29	121	30	121	23.0%	0.97 [0.62, 1.51]
STARS-BNP 2007	22	110	48	110	36.7%	0.46 [0.30, 0.70]
TIME-CHF 2009	30	251	40	248	30.8%	0.74 [0.48, 1.15]
Troughton 2000	5	33	13	36	9.5%	0.42 [0.17, 1.05]
Total (95% CI)		**515**		**515**	**100.0%**	**0.66 [0.52, 0.84]**
Total events	86		131			

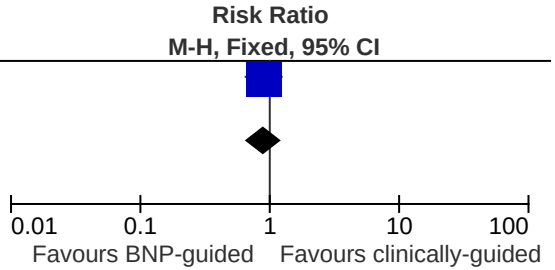
Heterogeneity: Chi² = 6.81, df = 3 (P = 0.08); I² = 56%
Test for overall effect: Z = 3.40 (P = 0.0007)



1.5 Heart failure hospitalisation (no. of patients) - range median 9.5 mths to 18 mths.

Study or Subgroup	BNP-guided Events	Total	Clinically-guided Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BATTLESCARRED 2010	44	121	49	121	100.0%	0.90 [0.65, 1.24]
Total (95% CI)		**121**		**121**	**100.0%**	**0.90 [0.65, 1.24]**
Total events	44		49			

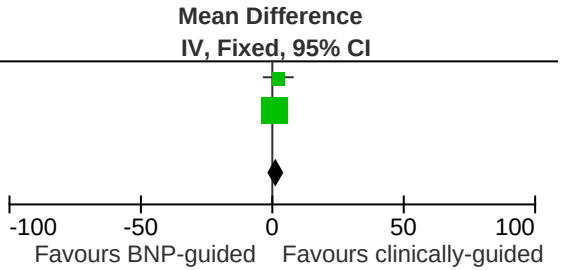
Heterogeneity: Not applicable
Test for overall effect: Z = 0.66 (P = 0.51)



1.6 Heart failure hospitalisation (no. of patients) - 3 yrs

Study or Subgroup	BNP-guided Mean	SD	Total	Clinically-guided Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
BATTLESCARRED 2010	28.8	21.6	121	26.5	22	121	28.3%	2.30 [-3.19, 7.79]
TIME-CHF 2009	28.2	17.6	251	27.3	21.5	248	71.7%	0.90 [-2.55, 4.35]
Total (95% CI)			**372**			**369**	**100.0%**	**1.30 [-1.63, 4.22]**

Heterogeneity: Chi² = 0.18, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.87 (P = 0.38)

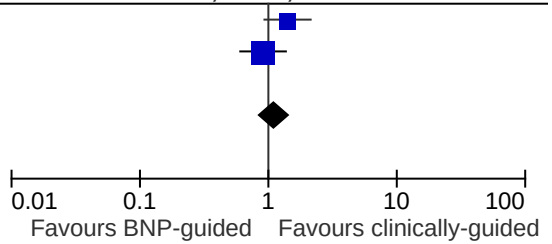


1.7 Quality of Life (range 12 to 18 months).

Sub-group analysis by age

Study or Subgroup	BNP-guided Events	Total	Clinically-guided Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BATTLESCARED 2010	31	63	23	66	38.0%	1.41 [0.93, 2.14]
TIME-CHF2009	33	143	37	146	62.0%	0.91 [0.61, 1.37]
Total (95% CI)		**206**		**212**	**100.0%**	**1.10 [0.82, 1.47]**
Total events	64		60			

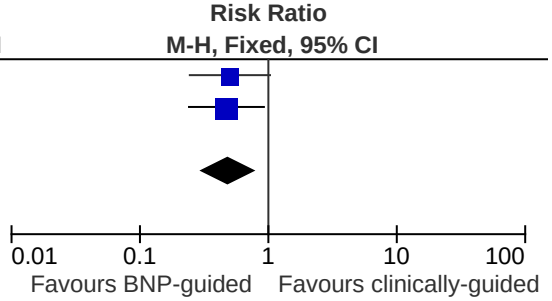
Heterogeneity: Chi² = 2.21, df = 1 (P = 0.14); I² = 55%
Test for overall effect: Z = 0.65 (P = 0.52)



1.1 Mortality 76 yrs or more - 18 mths to 3 yrs.

Study or Subgroup	BNP-guided Events	Total	Clinically-guided Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BATTLESCARED 2010	9	58	17	55	43.5%	0.50 [0.24, 1.03]
TIME-CHF2009	11	108	22	102	56.5%	0.47 [0.24, 0.92]
Total (95% CI)		**166**		**157**	**100.0%**	**0.49 [0.30, 0.79]**
Total events	20		39			

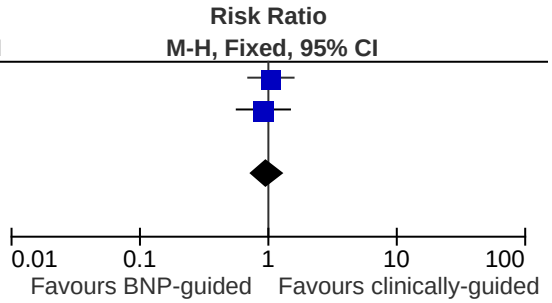
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.90); I² = 0%
Test for overall effect: Z = 2.89 (P = 0.004)



1.2 Mortality 75 yrs or less - 18 mths to 3 yrs.

Study or Subgroup	BNP-guided Events	Total	Clinically-guided Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BATTLESCARED 2010	27	63	27	66	47.9%	1.05 [0.70, 1.57]
TIME-CHF2009	26	143	29	146	52.1%	0.92 [0.57, 1.47]
Total (95% CI)		**206**		**212**	**100.0%**	**0.98 [0.72, 1.34]**
Total events	53		56			

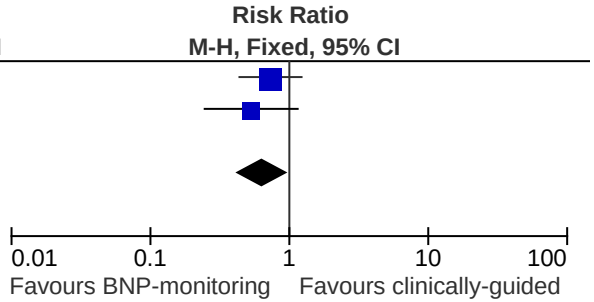
Heterogeneity: Chi² = 0.18, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.13 (P = 0.89)



1.3 HF hospitalisation 76 yrs or more - 18 mths to 3 yrs.

Study or Subgroup	BNP-guided Events	Total	Clinically-guided Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BATTLESCARED 2010	17	58	22	55	57.8%	0.73 [0.44, 1.23]
TIME-CHF2009	9	108	16	102	42.2%	0.53 [0.25, 1.15]
Total (95% CI)		**166**		**157**	**100.0%**	**0.65 [0.42, 1.00]**
Total events	26		38			

Heterogeneity: Chi² = 0.48, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 1.97 (P = 0.05)

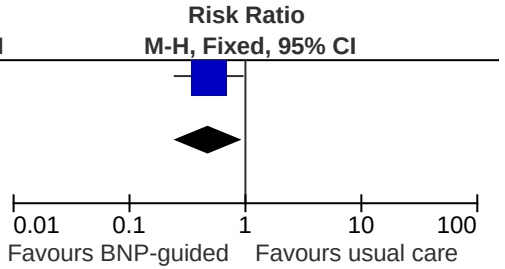


1.4 HF hospitalisation 75 yrs or less - 18 mths to 3 yrs.

BNP-guided compared with usual care

Study or Subgroup	BNP-guided Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BATTLESCARED 2010	11	121	23	122	100.0%	0.48 [0.25, 0.95]
Total (95% CI)		**121**		**122**	**100.0%**	**0.48 [0.25, 0.95]**
Total events	11		23			

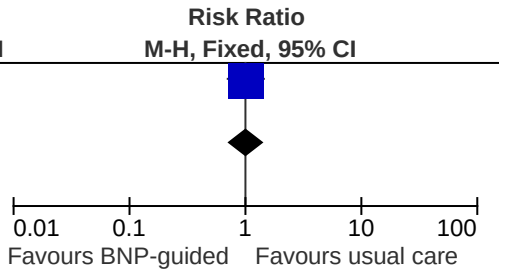
Heterogeneity: Not applicable
Test for overall effect: Z = 2.12 (P = 0.03)



1.1 Mortality (all cause) - one yr.

Study or Subgroup	BNP-guided Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BATTLESCARED 2010	40	121	40	122	100.0%	1.01 [0.70, 1.44]
Total (95% CI)		**121**		**122**	**100.0%**	**1.01 [0.70, 1.44]**
Total events	40		40			

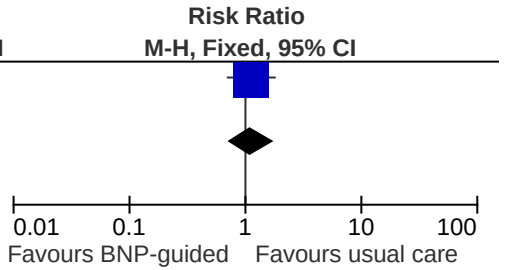
Heterogeneity: Not applicable
Test for overall effect: Z = 0.04 (P = 0.96)



1.2 Mortality (all cause) - three yrs.

Study or Subgroup	BNP-guided Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BATTLESCARED 2010	29	121	26	122	100.0%	1.12 [0.71, 1.79]
Total (95% CI)		**121**		**122**	**100.0%**	**1.12 [0.71, 1.79]**
Total events	29		26			

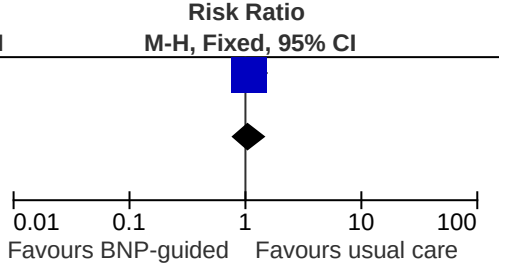
Heterogeneity: Not applicable
Test for overall effect: Z = 0.49 (P = 0.62)



1.3 Hospitalisation (HF) - one yr

Study or Subgroup	BNP-guided Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BATTLESCARED 2010	44	121	41	122	100.0%	1.08 [0.77, 1.53]
Total (95% CI)		**121**		**122**	**100.0%**	**1.08 [0.77, 1.53]**
Total events	44		41			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.45 (P = 0.65)

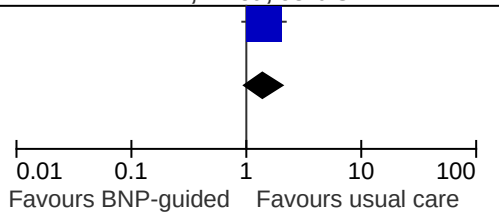


1.4 Hospitalisation (HF) - three yrs.

Sub-group analysis by age

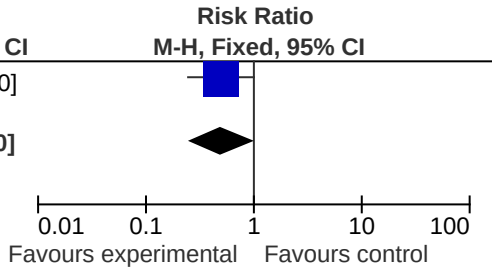
Forest plots

Study or Subgroup	BNP-guided monitoring Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BATTLESCARRED 2010	31	63	20	58	100.0%	1.43 [0.92, 2.20]
Total (95% CI)		**63**		**58**	**100.0%**	**1.43 [0.92, 2.20]**
Total events	31		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.60 (P = 0.11)						



76 yrs or more, outcome: 1.1 Mortality (all cause) - three years.

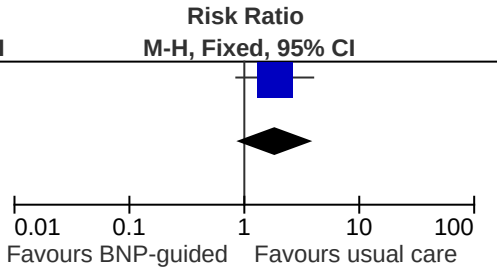
Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BATTLESCARRED 2010	9	58	20	64	100.0%	0.50 [0.25, 1.00]
Total (95% CI)		**58**		**64**	**100.0%**	**0.50 [0.25, 1.00]**
Total events	9		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.95 (P = 0.05)						



75 yrs or less, outcome: 1.2 Mortality (all cause) - three years.

Study or Subgroup	BNP-guided monitoring Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BATTLESCARRED 2010	16	63	8	58	100.0%	1.84 [0.85, 3.98]
Total (95% CI)		**63**		**58**	**100.0%**	**1.84 [0.85, 3.98]**
Total events	16		8			

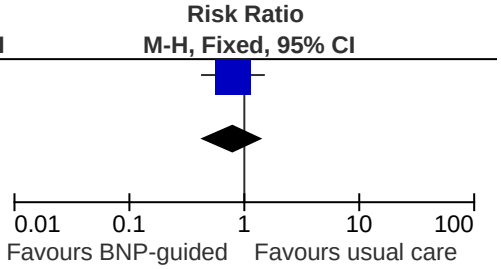
Heterogeneity: Not applicable
Test for overall effect: Z = 1.55 (P = 0.12)



76 yrs or more, outcome: 1.3 Hospitalisation (heart failure) - one year.

Study or Subgroup	BNP-guided monitoring Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BATTLESCARRED 2010	13	58	18	64	100.0%	0.80 [0.43, 1.48]
Total (95% CI)		**58**		**64**	**100.0%**	**0.80 [0.43, 1.48]**
Total events	13		18			

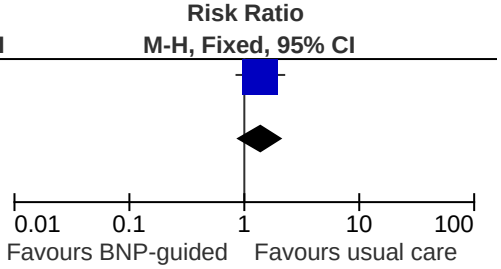
Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)



75 yrs or less, outcome: 1.4 Hospitalisation (heart failure) - one year.

Study or Subgroup	BNP-guided monitoring Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BATTLESCARRED 2010	27	63	18	58	100.0%	1.38 [0.86, 2.23]
Total (95% CI)		**63**		**58**	**100.0%**	**1.38 [0.86, 2.23]**
Total events	27		18			

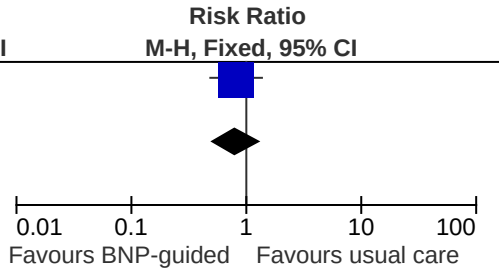
Heterogeneity: Not applicable
Test for overall effect: Z = 1.32 (P = 0.19)



76 yrs or more, outcome: 1.5 Hospitalisation (heart failure) - three years.

Study or Subgroup	BNP-guided monitoring Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BATTLESCARRED 2010	17	58	23	64	100.0%	0.82 [0.49, 1.37]
Total (95% CI)		**58**		**64**	**100.0%**	**0.82 [0.49, 1.37]**
Total events	17		23			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.77 (P = 0.44)

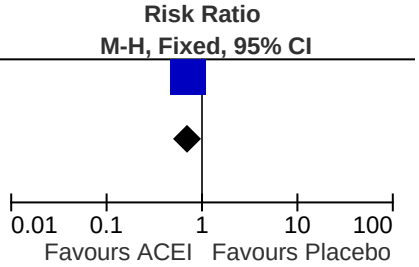


75 yrs or less, outcome: 1.6 Hospitalisation (heart failure) -three years.

ACE: Angiotensin converting enzyme inhibitors

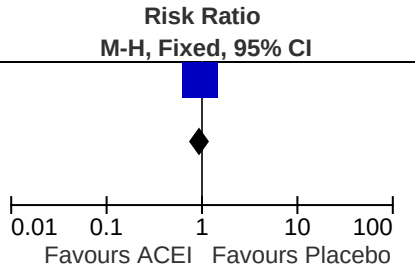
What is the efficacy and safety of ACE Inhibitors in people with heart failure and preserved left ventricular ejection fraction?

	ACEI		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
PEP-CHF 2006	46	420	65	426	100.0%	0.72 [0.50, 1.02]	
Total (95% CI)		**420**		**426**	**100.0%**	**0.72 [0.50, 1.02]**	
Total events	46		65				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.84 (P = 0.07)							



Forest plot of comparison: 1 ACE I vs. PLACEBO, outcome: 1.1 All cause mortality or unplanned hospitalisation (no. of patients) - one year

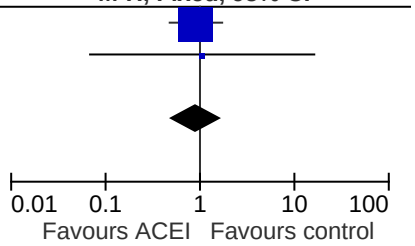
	ACEI		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
PEP-CHF 2006	100	420	107	426	100.0%	0.95 [0.75, 1.20]	
Total (95% CI)		**420**		**426**	**100.0%**	**0.95 [0.75, 1.20]**	
Total events	100		107				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.44 (P = 0.66)							



Forest plot of comparison: 1 ACE I vs. PLACEBO, outcome: 1.2 All cause mortality or unplanned hospitalisation (no. of patients) - 12 to 54 months.

Study or Subgroup	ACEI Events	ACEI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PEP-CHF 2006	17	420	19	426	95.1%	0.91 [0.48, 1.72]
ZI 2003	1	36	1	38	4.9%	1.06 [0.07, 16.25]
Total (95% CI)		**456**		**464**	**100.0%**	**0.91 [0.49, 1.71]**
Total events	18		20			

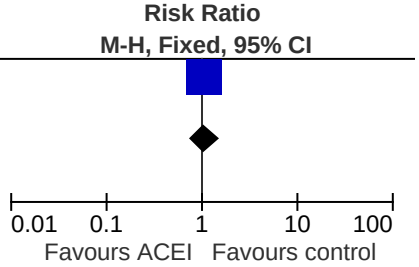
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.28 (P = 0.78)



Forest plot of comparison: 1 ACE I vs. PLACEBO, outcome: 1.5 All cause mortality (no. of patients) - 6 to 12 months.

Study or Subgroup	ACEI Events	ACEI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PEP-CHF 2006	56	1420	53	1426	100.0%	1.06 [0.73, 1.53]
Total (95% CI)		**1420**		**1426**	**100.0%**	**1.06 [0.73, 1.53]**
Total events	56		53			

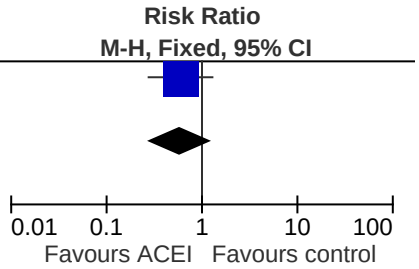
Heterogeneity: Not applicable
Test for overall effect: Z = 0.32 (P = 0.75)



Forest plot of comparison: 1 ACE I vs. PLACEBO, outcome: 1.6 All cause Mortality (no. of patients) -12 to 54 months.

Study or Subgroup	ACEI Events	ACEI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PEP-CHF 2006	10	420	17	426	100.0%	0.60 [0.28, 1.29]
Total (95% CI)		**420**		**426**	**100.0%**	**0.60 [0.28, 1.29]**
Total events	10		17			

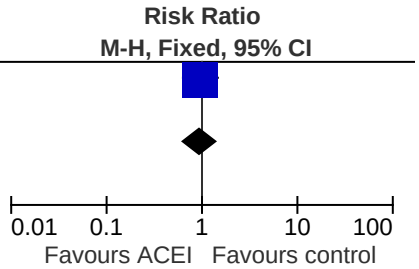
Heterogeneity: Not applicable
Test for overall effect: Z = 1.32 (P = 0.19)



Forest plot of comparison: 1 ACE I vs. PLACEBO, outcome: 1.7 CV mortality (no. of patients) - one year.

Study or Subgroup	ACEI Events	ACEI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PEP-CHF 2006	38	420	40	426	100.0%	0.96 [0.63, 1.47]
Total (95% CI)		**420**		**426**	**100.0%**	**0.96 [0.63, 1.47]**
Total events	38		40			

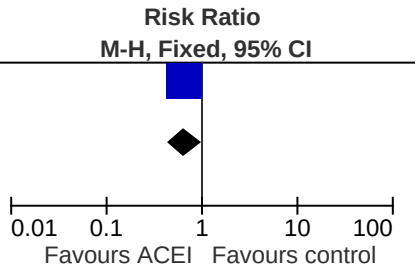
Heterogeneity: Not applicable
Test for overall effect: Z = 0.17 (P = 0.86)



Forest plot of comparison: 1 ACE I vs. PLACEBO, outcome: 1.8 CV mortality (no. of patients) -12 to 54 months

Study or Subgroup	ACEI Events	ACEI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PEP-CHF 2006	34	420	53	426	100.0%	0.65 [0.43, 0.98]
Total (95% CI)		**420**		**426**	**100.0%**	**0.65 [0.43, 0.98]**
Total events	34		53			

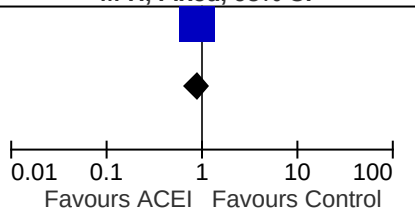
Heterogeneity: Not applicable
Test for overall effect: Z = 2.06 (P = 0.04)



Forest plot of comparison: 1 ACE I vs. PLACEBO, outcome: 1.9 HF hospitalization (no. of patients) -one year.

Study or Subgroup	ACEI Events	ACEI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PEP-CHF 2006	64	420	73	426	100.0%	0.89 [0.65, 1.21]
Total (95% CI)		**420**		**426**	**100.0%**	**0.89 [0.65, 1.21]**
Total events	64		73			

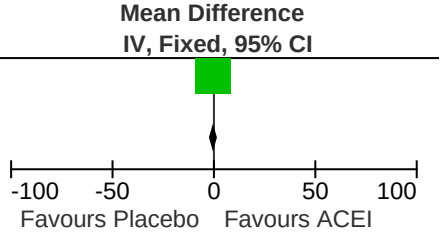
Heterogeneity: Not applicable
Test for overall effect: Z = 0.75 (P = 0.45)



Forest plot of comparison: 1 ACE I vs. PLACEBO, outcome: 1.10 HF hospitalisation (no. of patients) - 12 to 54 months.

Study or Subgroup	ACEI Mean	ACEI SD	ACEI Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
ZI 2003	12.9	3.1	36	13.1	4.7	38	100.0%	-0.20 [-2.01, 1.61]
Total (95% CI)			**36**			**38**	**100.0%**	**-0.20 [-2.01, 1.61]**

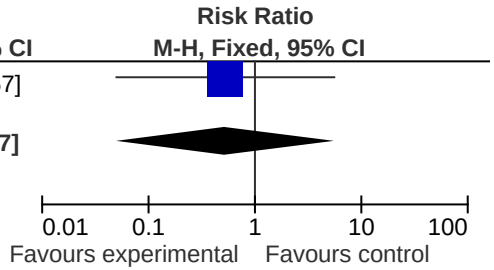
Heterogeneity: Not applicable
Test for overall effect: Z = 0.22 (P = 0.83)



Forest plot of comparison: 1 ACE I vs. PLACEBO, outcome: 1.11 Quality of life (McMaster) - 6 months.

Study or Subgroup	ACEI Events	ACEI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ZI 2003	1	36	2	38	100.0%	0.53 [0.05, 5.57]
Total (95% CI)		**36**		**38**	**100.0%**	**0.53 [0.05, 5.57]**
Total events	1		2			

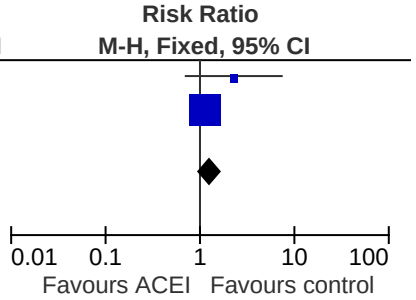
Heterogeneity: Not applicable
Test for overall effect: Z = 0.53 (P = 0.60)



Forest plot of comparison: 1 ACE I vs. PLACEBO, outcome: 1.12 Change in NYHA class (III to II) - 6 months.

Study or Subgroup	ACEI Events	ACEI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PEP-CHF 2006	9	420	4	426	12.7%	2.28 [0.71, 7.35]
ZI 2003	30	36	28	38	87.3%	1.13 [0.89, 1.44]
Total (95% CI)		**456**		**464**	**100.0%**	**1.28 [0.97, 1.69]**
Total events	39		32			

Heterogeneity: Chi² = 1.94, df = 1 (P = 0.16); I² = 48%
Test for overall effect: Z = 1.71 (P = 0.09)



Forest plot of comparison: 1 ACE I vs. PLACEBO, outcome: 1.14 Serious adverse events (no. of patients) - 12 to 54 months.

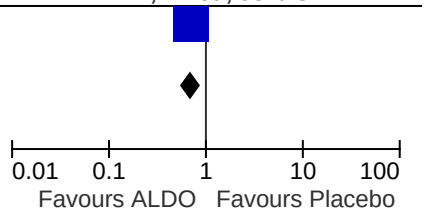
ALDO: Aldosterone antagonists + optimal medical management vs placebo + optimal medical management

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?

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

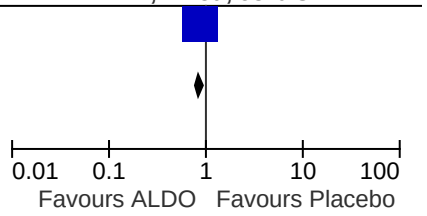
Forest plot of comparison: 1 Aldosterone vs Placebo, outcome: 1.1 Mortality all cause - 30 days.

	Aldosterone		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
PITT (EPHESUS) 2005	107	3319	153	3313	100.0%	0.70 [0.55, 0.89]	
Total (95% CI)		**3319**		**3313**	**100.0%**	**0.70 [0.55, 0.89]**	
Total events	107		153				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.91 (P = 0.004)							



Forest plot of comparison: 1 Aldosterone vs Placebo, outcome: 1.2 Mortality all cause - 16 mths.

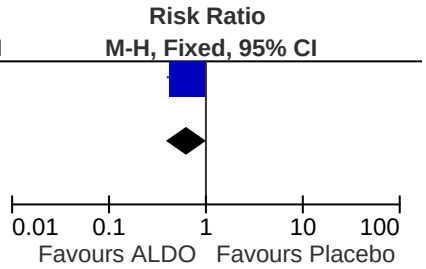
	Aldosterone		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
PITT (EPHESUS) 2003	478	3319	554	3313	100.0%	0.86 [0.77, 0.96]	
Total (95% CI)		**3319**		**3313**	**100.0%**	**0.86 [0.77, 0.96]**	
Total events	478		554				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.60 (P = 0.009)							



Forest plot of comparison: 1 Aldosterone vs Placebo, outcome: 1.3 Sudden death - 30 days.

Study or Subgroup	Aldosterone Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PITT (EPHESUS) 2005	30	3319	47	3313	100.0%	0.64 [0.40, 1.00]
Total (95% CI)		**3319**		**3313**	**100.0%**	**0.64 [0.40, 1.00]**
Total events	30		47			

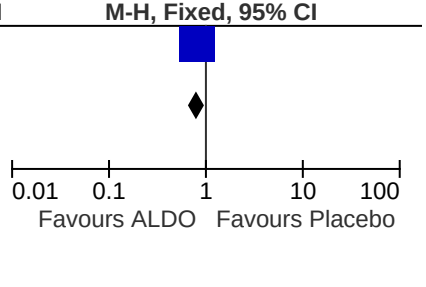
Heterogeneity: Not applicable
Test for overall effect: Z = 1.94 (P = 0.05)



Forest plot of comparison: 1 Aldosterone vs Placebo, outcome: 1.4 Sudden death - 16 mths.

Study or Subgroup	Aldosterone Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PITT (EPHESUS) 2003	162	3319	201	3313	100.0%	0.80 [0.66, 0.98]
Total (95% CI)		**3319**		**3313**	**100.0%**	**0.80 [0.66, 0.98]**
Total events	162		201			

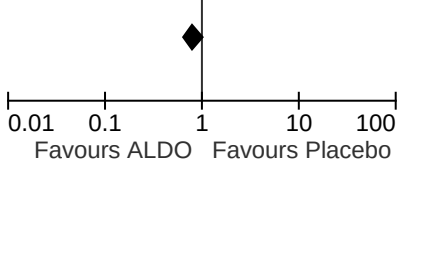
Heterogeneity: Not applicable
Test for overall effect: Z = 2.12 (P = 0.03)



Forest plot of comparison: 1 Aldosterone vs Placebo, outcome: 1.5 Hospitalisation HF - 30 days.

Study or Subgroup	Aldosterone Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PITT (EPHESUS) 2005	114	3319	138	3313	100.0%	0.82 [0.65, 1.05]
Total (95% CI)		**3319**		**3313**	**100.0%**	**0.82 [0.65, 1.05]**
Total events	114		138			

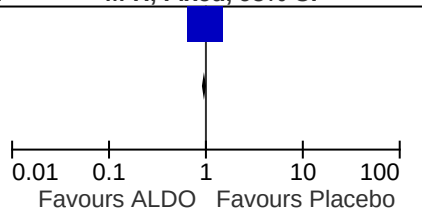
Heterogeneity: Not applicable
Test for overall effect: Z = 1.55 (P = 0.12)



Forest plot of comparison: 1 Aldosterone vs Placebo, outcome: 1.6 Hospitalisation all cause - 16 mths

Study or Subgroup	Aldosterone Events	Aldosterone Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PITT (EPHESUS) 2003	1493	3319	1526	3313	100.0%	0.98 [0.93, 1.03]
Total (95% CI)		**3319**		**3313**	**100.0%**	**0.98 [0.93, 1.03]**
Total events	1493		1526			

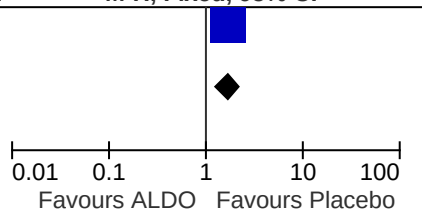
Heterogeneity: Not applicable
Test for overall effect: Z = 0.88 (P = 0.38)



Forest plot of comparison: 1 Aldosterone vs Placebo, outcome: 1.7 Hyperkalaemia.

Study or Subgroup	Aldosterone Events	Aldosterone Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PITT (EPHESUS) 2003	113	3307	66	3301	100.0%	1.71 [1.27, 2.31]
Total (95% CI)		**3307**		**3301**	**100.0%**	**1.71 [1.27, 2.31]**
Total events	113		66			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.50 (P = 0.0005)

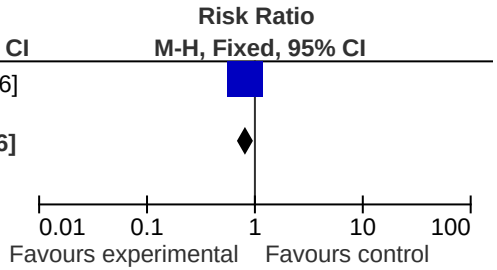


Severe HF LVEF < 30%

Forest plot of comparison: 2 Aldosterone vs Placebo - post MI severe HF < 35%, outcome: 2.1 Mortality all cause - 16 mths.

Study or Subgroup	Aldosterone Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PITT (EPHESUS) 2006	205	1048	254	1058	100.0%	0.81 [0.69, 0.96]
Total (95% CI)		**1048**		**1058**	**100.0%**	**0.81 [0.69, 0.96]**
Total events	205		254			

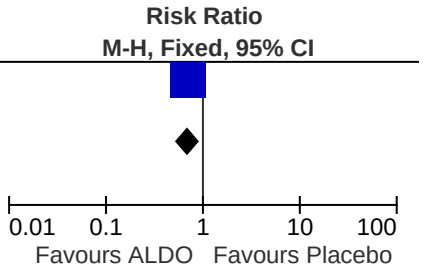
Heterogeneity: Not applicable
Test for overall effect: Z = 2.46 (P = 0.01)



Forest plot of comparison: 2 Aldosterone vs Placebo - post MI severe HF < 35%, outcome: 2.2 Sudden death - 16 mths

Study or Subgroup	Aldosterone Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PITT (EPHESUS) 2006	71	1048	103	1058	100.0%	0.70 [0.52, 0.93]
Total (95% CI)		**1048**		**1058**	**100.0%**	**0.70 [0.52, 0.93]**
Total events	71		103			

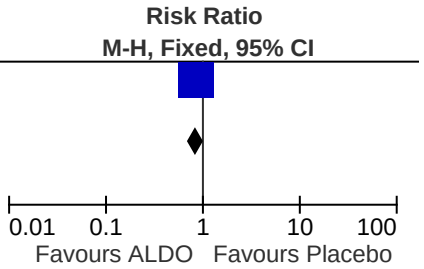
Heterogeneity: Not applicable
Test for overall effect: Z = 2.45 (P = 0.01)



Forest plot of comparison: 2 Aldosterone vs Placebo - post MI severe HF < 35%, outcome: 2.3 Hospitalisation non-fatal HF - 16 mths.

Study or Subgroup	Aldosterone Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PITT (EPHESUS) 2006	152	1048	181	1058	100.0%	0.85 [0.70, 1.03]
Total (95% CI)		**1048**		**1058**	**100.0%**	**0.85 [0.70, 1.03]**
Total events	152		181			

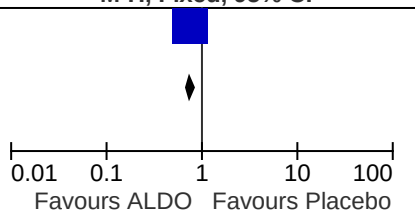
Heterogeneity: Not applicable
Test for overall effect: Z = 1.63 (P = 0.10)



Aldosterone antagonists plus optimal medical management with placebo plus optimal medical management in patients with severe chronic heart failure defined as LVEF <35%.

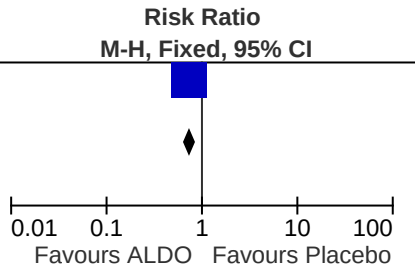
Forest plot of comparison: 3 Aldosterone vs Placebo - severe HF < 35%, outcome: 3.1 Mortality all cause - 24 mths.

	Aldosterone		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
PITT (RALES) 1999	284	822	386	841	100.0%	0.75 [0.67, 0.85]	
Total (95% CI)		**822**		**841**	**100.0%**	**0.75 [0.67, 0.85]**	
Total events	284		386				
Heterogeneity: Not applicable							
Test for overall effect: Z = 4.67 (P < 0.00001)							



Forest plot of comparison: 3 Aldosterone vs Placebo - severe HF < 35%, outcome: 3.2 Hospitalisation HF - 24 mths.

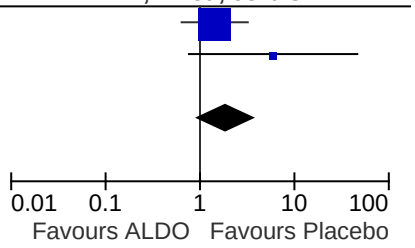
	Aldosterone		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
PITT (RALES) 1999	215	822	300	841	100.0%	0.73 [0.63, 0.85]	
Total (95% CI)		**822**		**841**	**100.0%**	**0.73 [0.63, 0.85]**	
Total events	215		300				
Heterogeneity: Not applicable							
Test for overall effect: Z = 4.15 (P < 0.0001)							



Forest plot of comparison: 3 Aldosterone vs Placebo - severe HF < 35%, outcome: 3.3 hyperkalaemia.

Study or Subgroup	Aldosterone Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PITT (RALES) 1999	14	822	10	841	90.1%	1.43 [0.64, 3.21]
RALES 1996	7	47	1	40	9.9%	5.96 [0.77, 46.39]
Total (95% CI)		**869**		**881**	**100.0%**	**1.88 [0.91, 3.90]**
Total events	21		11			

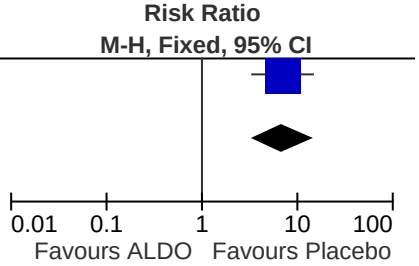
Heterogeneity: Chi² = 1.65, df = 1 (P = 0.20); I² = 39%
Test for overall effect: Z = 1.69 (P = 0.09)



Forest plot of comparison: 3 Aldosterone vs Placebo - severe HF < 35%, outcome: 3.4 Gynecomastia in men - 24 mths.

Study or Subgroup	Aldosterone Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PITT (RALES) 1999	55	603	8	614	100.0%	7.00 [3.36, 14.57]
Total (95% CI)		**603**		**614**	**100.0%**	**7.00 [3.36, 14.57]**
Total events	55		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 5.20 (P < 0.00001)

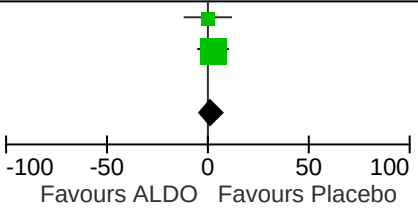


Aldosterone antagonists plus optimal medical management with placebo plus optimal medical management in patients with chronic heart failure.

Forest plot of comparison: 4 Aldosterone + optimal vs Optimal + placebo, outcome: 4.1 quality of life at 6 months (MLWHFQ).

	ALDO			Placebo				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
AGOSTONI 2005	27	15	15	27	17	15	28.9%	0.00 [-11.47, 11.47]	
MACDONALD 2004	18.8	18.6	43	16.2	15.9	43	71.1%	2.60 [-4.71, 9.91]	
Total (95% CI)			**58**			**58**	**100.0%**	**1.85 [-4.32, 8.02]**	

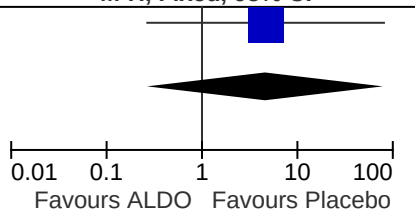
Heterogeneity: Chi² = 0.14, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.59 (P = 0.56)



Forest plot of comparison: 4 Aldosterone + optimal vs Optimal + placebo, outcome: 4.2 raised creatinine >300umol/L.

	ALDO		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
BARR 1995	4	28	0	14	100.0%	4.66 [0.27, 80.84]	
Total (95% CI)		**28**		**14**	**100.0%**	**4.66 [0.27, 80.84]**	
Total events	4		0				

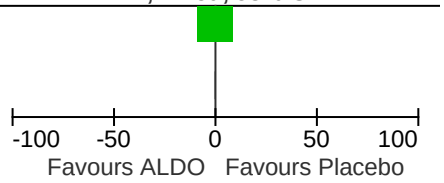
Heterogeneity: Not applicable
Test for overall effect: Z = 1.06 (P = 0.29)



Forest plot of comparison: 4 Aldosterone + optimal vs Optimal + placebo, outcome: 4.3 creatinine mean change.

Study or Subgroup	ALDO Mean	ALDO SD	ALDO Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
AGOSTONI 2005	0	0.22	15	0.03	0.3	15	100.0%	-0.03 [-0.22, 0.16]
Total (95% CI)			**15**			**15**	**100.0%**	**-0.03 [-0.22, 0.16]**

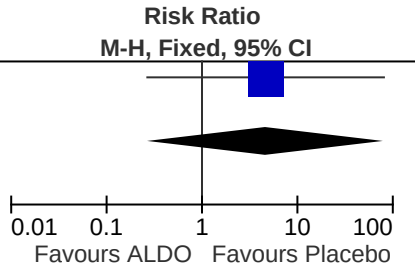
Heterogeneity: Not applicable
Test for overall effect: Z = 0.31 (P = 0.75)



Forest plot of comparison: 4 Aldosterone + optimal vs Optimal + placebo, outcome: 4.4 Hyperkalaemia.

Study or Subgroup	ALDO Events	ALDO Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BARR 1995	4	28	0	14	100.0%	4.66 [0.27, 80.84]
Total (95% CI)		**28**		**14**	**100.0%**	**4.66 [0.27, 80.84]**
Total events	4		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.06 (P = 0.29)



ARB1: angiotensin II receptor antagonists vs placebo

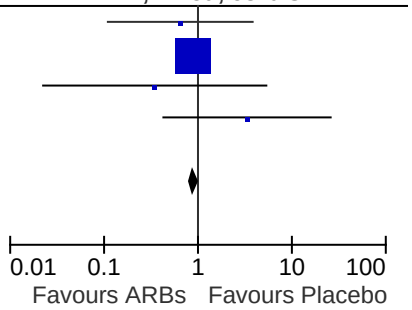
What is the efficacy and safety of angiotensin-II receptor antagonists (ARBS) in comparison to placebo in the medical management of adults with heart failure?

ARBs vs. placebo in heart failure with reduced left ventricular ejection fraction (LVEF).

	ARB		PLACEBO			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
ARCH-J	2	148	3	144	1.0%	0.65 [0.11, 3.83]	
CHARM-alternative	265	1013	296	1015	98.0%	0.90 [0.78, 1.03]	
Mazayez	1	75	1	26	0.5%	0.35 [0.02, 5.35]	
STRETCH	10	633	1	211	0.5%	3.33 [0.43, 25.89]	
Total (95% CI)		**1869**		**1396**	**100.0%**	**0.90 [0.79, 1.04]**	
Total events	278		301				

Heterogeneity: Chi² = 2.17, df = 3 (P = 0.54); I² = 0%

Test for overall effect: Z = 1.41 (P = 0.16)

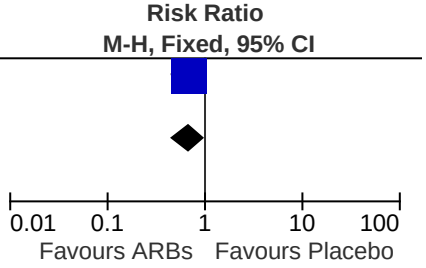


Forest plot of comparison: 1 ARB vs. placebo, outcome: all cause mortality

	ARB		PLACEBO			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
Val-HeFT (post-hoc)	32	185	46	181	100.0%	0.68 [0.46, 1.02]	
Total (95% CI)		**185**		**181**	**100.0%**	**0.68 [0.46, 1.02]**	
Total events	32		46				

Heterogeneity: Not applicable

Test for overall effect: Z = 1.88 (P = 0.06)

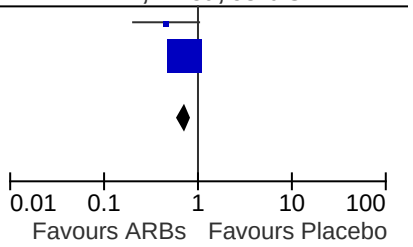


Forest plot of comparison: 1 ARB vs. placebo, outcome: All cause mortality - post hoc subgp (follow-up 24 months).

Study or Subgroup	ARB Events	ARB Total	PLACEBO Events	PLACEBO Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ARCH-J	8	148	17	144	5.7%	0.46 [0.20, 1.03]
CHARM-alternative	207	1013	286	1015	94.3%	0.73 [0.62, 0.85]
Total (95% CI)		**1161**		**1159**	**100.0%**	**0.71 [0.61, 0.83]**
Total events	215		303			

Heterogeneity: Chi² = 1.20, df = 1 (P = 0.27); I² = 17%

Test for overall effect: Z = 4.37 (P < 0.0001)

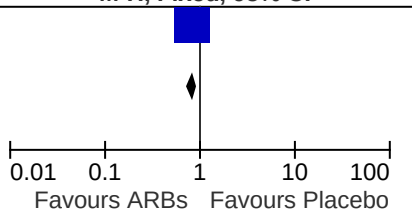


Forest plot of comparison: 1 ARB vs. placebo, outcome: HF hospitalization.

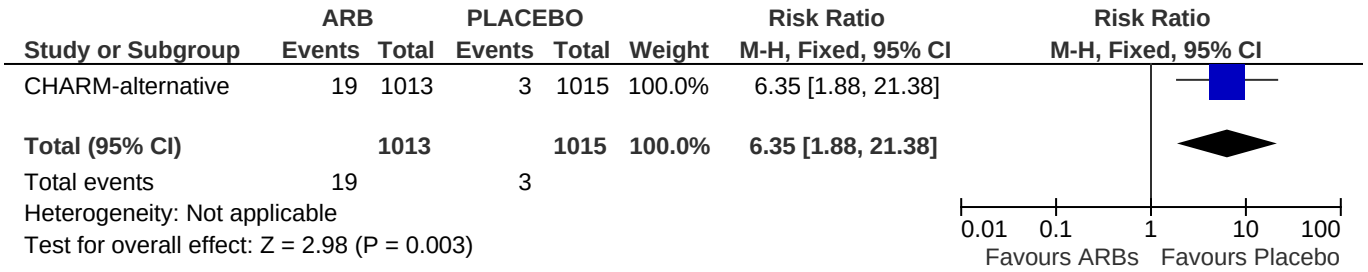
Study or Subgroup	ARB Events	ARB Total	PLACEBO Events	PLACEBO Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CHARM-alternative	334	1013	406	1015	100.0%	0.82 [0.73, 0.93]
Total (95% CI)		**1013**		**1015**	**100.0%**	**0.82 [0.73, 0.93]**
Total events	334		406			

Heterogeneity: Not applicable

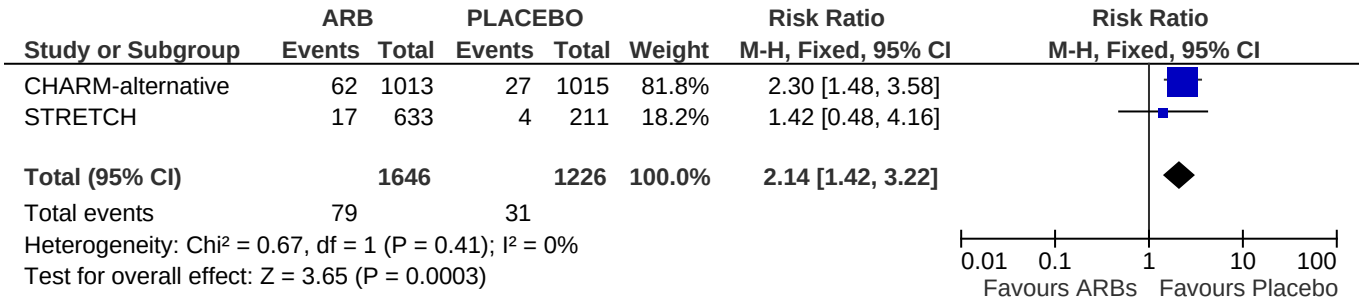
Test for overall effect: Z = 3.27 (P = 0.001)



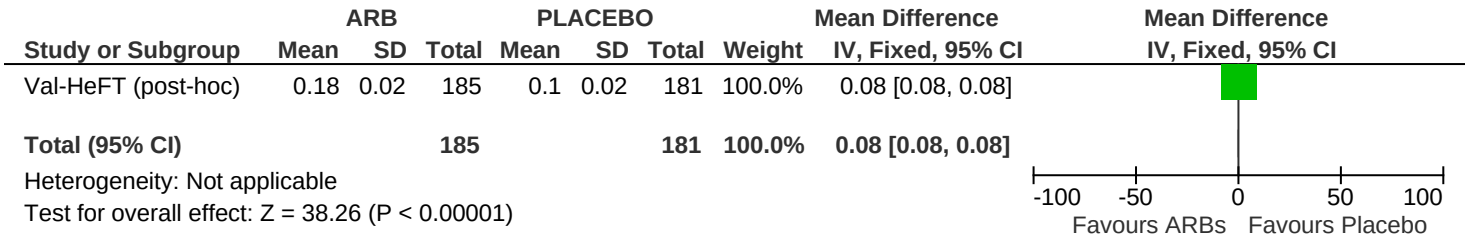
Forest plot of comparison: 1 ARB vs. placebo, outcome: Combined outcome.



Forest plot of comparison: 1 ARB vs. placebo, outcome: Hyperkalaemia (alternative).



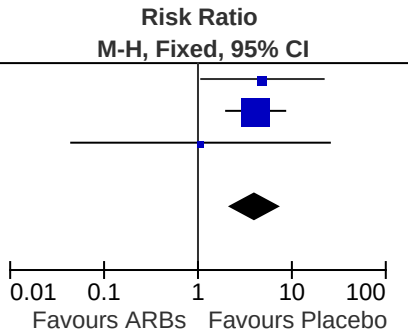
Forest plot of comparison: 1 ARB vs. placebo, outcome: Raised creatinine.



Forest plot of comparison: 1 ARB vs. placebo, outcome: Mean increase in creatinine (subgp).

Study or Subgroup	ARB Events	ARB Total	PLACEBO Events	PLACEBO Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ARCH-J	10	151	2	147	17.2%	4.87 [1.08, 21.84]
CHARM-alternative	37	1013	9	1015	76.5%	4.12 [2.00, 8.49]
Mazayez	1	75	0	26	6.3%	1.07 [0.04, 25.38]
Total (95% CI)		**1239**		**1188**	**100.0%**	**4.06 [2.15, 7.64]**
Total events	48		11			

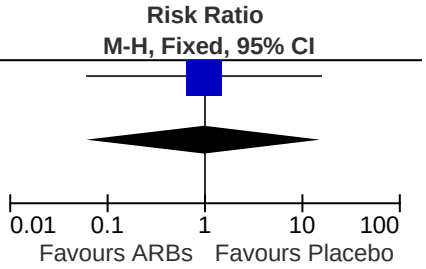
Heterogeneity: Chi² = 0.74, df = 2 (P = 0.69); I² = 0%
Test for overall effect: Z = 4.33 (P < 0.0001)



Forest plot of comparison: 1 ARB vs. placebo, outcome: 1.8 Hypotension.

Study or Subgroup	ARB Events	ARB Total	PLACEBO Events	PLACEBO Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Val-HeFT (post-hoc)	1	185	1	181	100.0%	0.98 [0.06, 15.52]
Total (95% CI)		**185**		**181**	**100.0%**	**0.98 [0.06, 15.52]**
Total events	1		1			

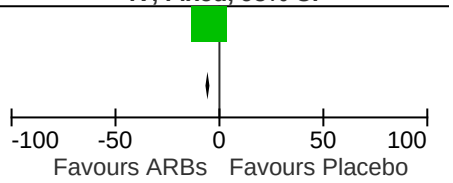
Heterogeneity: Not applicable
Test for overall effect: Z = 0.02 (P = 0.99)



Forest plot of comparison: 1 ARB vs. placebo, outcome: Hypotension (subgp).

Study or Subgroup	ARB Mean	ARB SD	ARB Total	PLACEBO Mean	PLACEBO SD	PLACEBO Total	Weight	Mean Difference IV, Fixed, 95% CI
Val-HeFT (post-hoc)	-4.15	1.78	86	1.01	2.11	73	100.0%	-5.16 [-5.77, -4.55]
Total (95% CI)			**86**			**73**	**100.0%**	**-5.16 [-5.77, -4.55]**

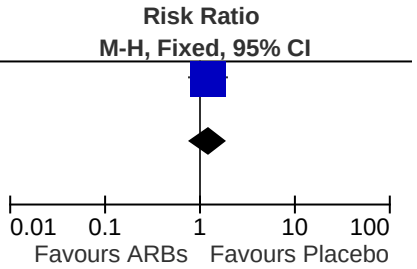
Heterogeneity: Not applicable
Test for overall effect: Z = 16.50 (P < 0.00001)



Forest plot of comparison: 1 ARB vs. placebo, outcome: Quality of Life (MLWHFQ).

Study or Subgroup	ARB Events	ARB Total	PLACEBO Events	PLACEBO Total	Weight	Risk Ratio M-H, Fixed, 95% CI
STRETCH	34	201	28	201	100.0%	1.21 [0.77, 1.92]
Total (95% CI)		**201**		**201**	**100.0%**	**1.21 [0.77, 1.92]**
Total events	34		28			

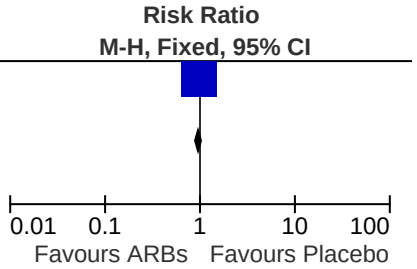
Heterogeneity: Not applicable
Test for overall effect: Z = 0.83 (P = 0.41)



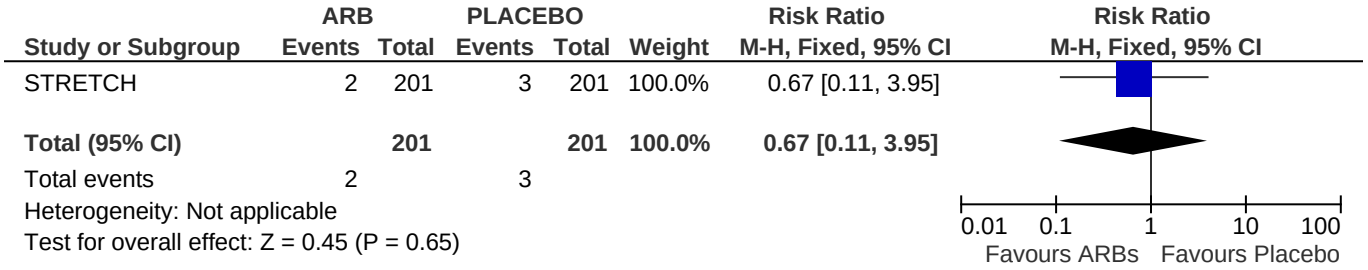
Forest plot of comparison: 1 ARB vs. placebo, outcome: NYHA class improvement.

Study or Subgroup	ARB Events	ARB Total	PLACEBO Events	PLACEBO Total	Weight	Risk Ratio M-H, Fixed, 95% CI
STRETCH	165	201	170	201	100.0%	0.97 [0.89, 1.06]
Total (95% CI)		**201**		**201**	**100.0%**	**0.97 [0.89, 1.06]**
Total events	165		170			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.50)

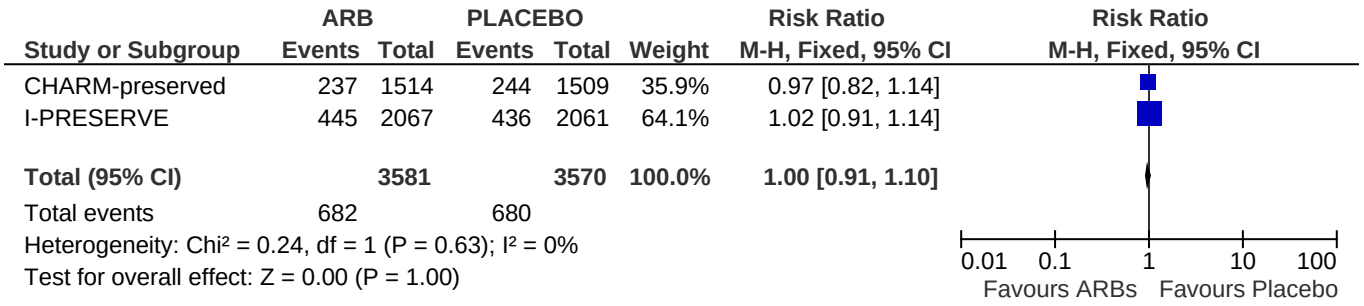


Forest plot of comparison: 1 ARB vs. placebo, outcome: NYHA class no change.

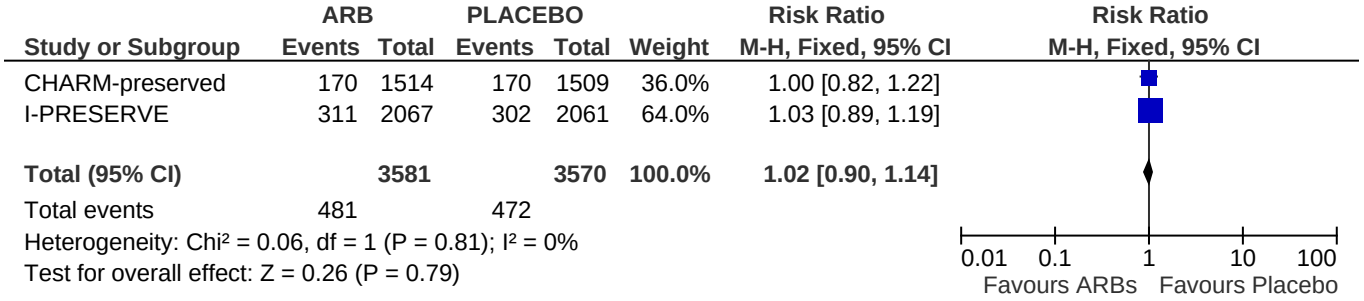


Forest plot of comparison: 1 ARB vs. placebo, outcome: NYHA class deterioration.

ARBs vs. placebo in heart failure with preserved EF.



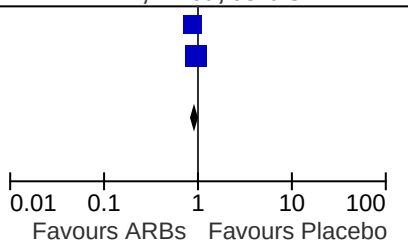
Forest plot of comparison: 1 ARB vs. placebo, outcome: All cause mortality (PLVEF).



Forest plot of comparison: 1 ARB vs. placebo, outcome: CV mortality (PLVEF).

Study or Subgroup	ARB Events	ARB Total	PLACEBO Events	PLACEBO Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CHARM-preserved	241	1514	276	1509	45.1%	0.87 [0.74, 1.02]
I-PRESERVE	325	2067	336	2061	54.9%	0.96 [0.84, 1.11]
Total (95% CI)		**3581**		**3570**	**100.0%**	**0.92 [0.83, 1.02]**
Total events	566		612			

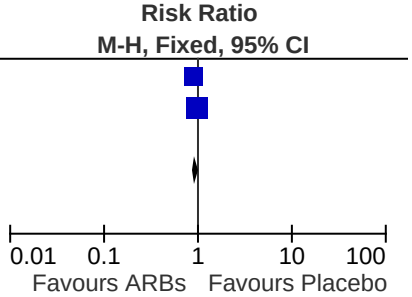
Heterogeneity: Chi² = 0.91, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 1.52 (P = 0.13)



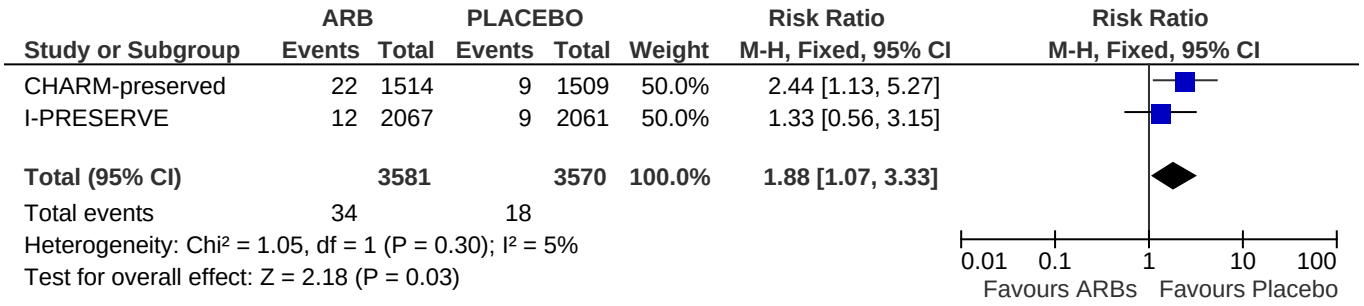
Forest plot of comparison: 1 ARB vs. placebo, outcome: 1.2 HF hospitalization (PLVEF).

Study or Subgroup	ARB Events	ARB Total	PLACEBO Events	PLACEBO Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CHARM-preserved	333	1514	366	1509	45.5%	0.91 [0.80, 1.03]
I-PRESERVE	428	2067	438	2061	54.5%	0.97 [0.87, 1.10]
Total (95% CI)		**3581**		**3570**	**100.0%**	**0.94 [0.86, 1.03]**
Total events	761		804			

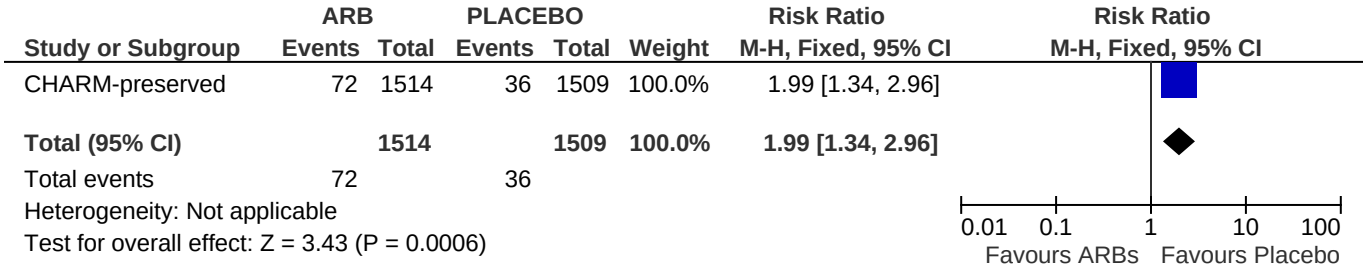
Heterogeneity: Chi² = 0.64, df = 1 (P = 0.42); I² = 0%
Test for overall effect: Z = 1.30 (P = 0.19)



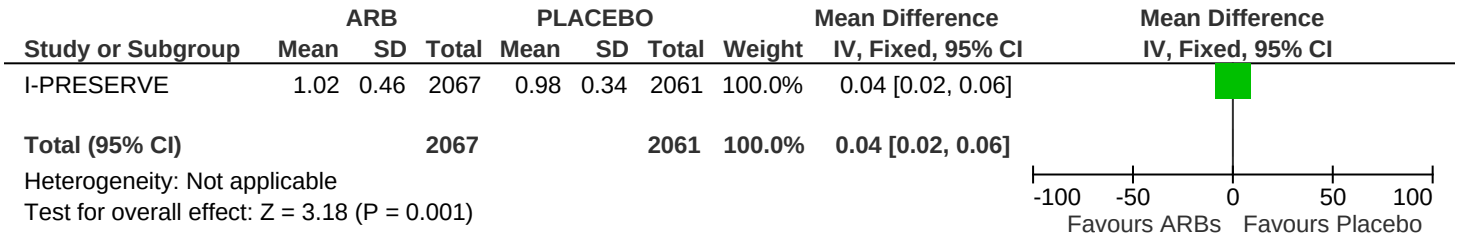
Forest plot of comparison: 1 ARB vs. placebo, outcome: Combined outcome (CV death + HF hospitalisation) (PLVEF).



Forest plot of comparison: 1 ARB vs. placebo, outcome: Hyperkalaemia (PLVEF).



Forest plot of comparison: 1 ARB vs. placebo, outcome: Raised creatinine (PLVEF).

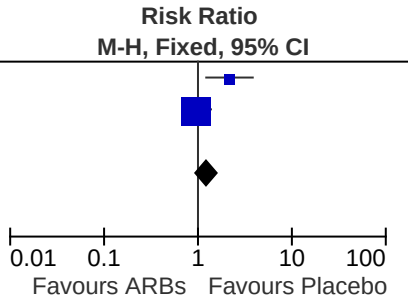


Forest plot of comparison: 1 ARB vs. placebo, outcome: Mean creatinine (PLVEF).

Study or Subgroup	ARB Events	ARB Total	PLACEBO Events	PLACEBO Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CHARM-preserved	37	1514	17	1509	21.5%	2.17 [1.23, 3.84]
I-PRESERVE	60	2067	62	2061	78.5%	0.96 [0.68, 1.37]
Total (95% CI)		**3581**		**3570**	**100.0%**	**1.22 [0.91, 1.64]**
Total events	97		79			

Heterogeneity: Chi² = 5.65, df = 1 (P = 0.02); I² = 82%

Test for overall effect: Z = 1.35 (P = 0.18)



Forest plot of comparison: 1 ARB vs. placebo, outcome: 1.5 Hypotension (PLVEF).

ARB2: a) angiotensin-II receptor antagonists + angiotensin converting enzyme inhibitor vs placebo + angiotensin converting enzyme inhibitor

b) angiotensin-II receptor antagonists + angiotensin converting enzyme inhibitor + beta blocker vs placebo + angiotensin converting enzyme inhibitor + beta blocker in chronic heart failure

c) angiotensin-II receptor antagonists + angiotensin converting enzyme inhibitor + beta blocker vs placebo + angiotensin converting enzyme inhibitor + beta blocker in chronic heart failure post MI

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

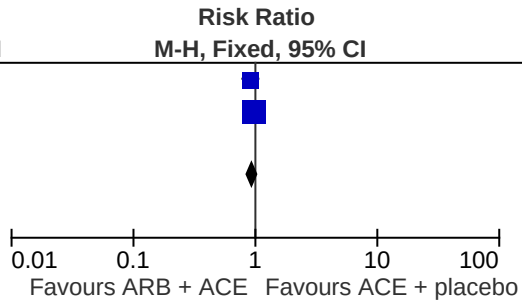
a) angiotensin-II receptor antagonists + angiotensin converting enzyme inhibitor vs placebo + angiotensin converting enzyme inhibitor

Forest plot of comparison: 2 ARB + ACE vs ACE + placebo (no BB), outcome: 2.1 Mortality.

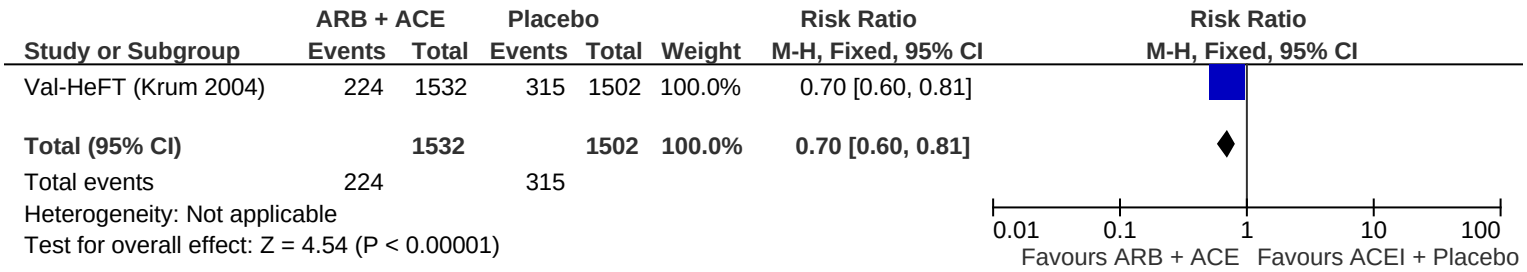
	ARB + ACE		Placebo			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
CHARM-added (McMurray)	202	574	217	561	39.1%	0.91 [0.78, 1.06]
Val-HeFT (Krum 2004)	334	1532	338	1502	60.9%	0.97 [0.85, 1.11]
Total (95% CI)		**2106**		**2063**	**100.0%**	**0.95 [0.85, 1.05]**
Total events	536		555			

Heterogeneity: Chi² = 0.37, df = 1 (P = 0.54); I² = 0%

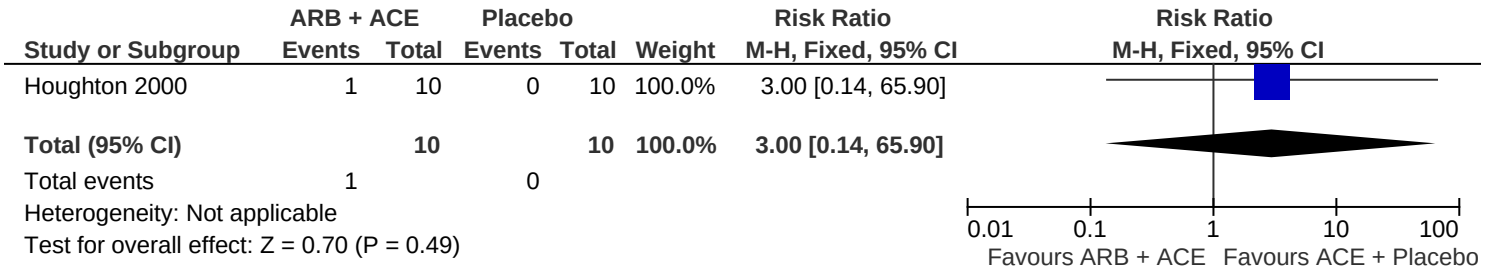
Test for overall effect: Z = 1.08 (P = 0.28)



Forest plot of comparison: 2 ARB + ACE vs ACE + placebo (no BB), outcome: 2.2 First Hospitalisation.



Forest plot of comparison: 2 ARB + ACE vs ACE + placebo (no BB), outcome: 2.3 Hyperkalaemia.

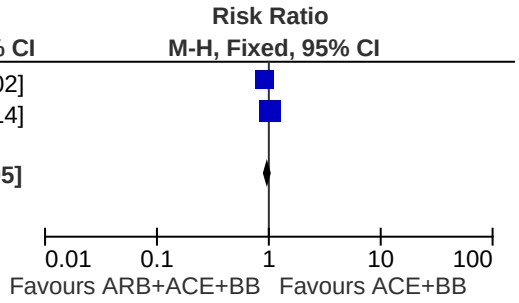


b) angiotensin-II receptor antagonists + angiotensin converting enzyme inhibitor + beta blocker vs placebo + angiotensin converting enzyme inhibitor + beta blockerin CHF

Forest plot of comparison: 1 ARB + ACE + BB vs Placebo + ACE + BB, outcome: 1.1 All cause mortality.

Study or Subgroup	ARB + ACE Events	Total	ACE + placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CHARM-added (McMurray)	377	1276	412	1272	46.0%	0.91 [0.81, 1.02]
Val-HeFT (Cohn 2001)	495	2511	484	2499	54.0%	1.02 [0.91, 1.14]
Total (95% CI)		**3787**		**3771**	**100.0%**	**0.97 [0.89, 1.05]**
Total events	872		896			

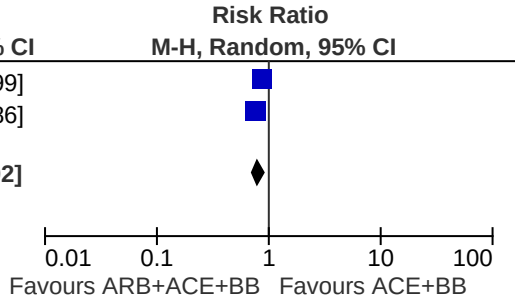
Heterogeneity: Chi² = 1.78, df = 1 (P = 0.18); I² = 44%
Test for overall effect: Z = 0.76 (P = 0.45)



Forest plot of comparison: 1 ARB + ACE + BB vs Placebo + ACE + BB, outcome: 1.2 HF Hospitalisation (no. of patients).

Study or Subgroup	ARB + ACE Events	Total	ACE + placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
CHARM-added (McMurray)	309	1276	356	1272	49.5%	0.87 [0.76, 0.99]
Val-HeFT (Cohn 2001)	346	2511	455	2499	50.5%	0.76 [0.67, 0.86]
Total (95% CI)		**3787**		**3771**	**100.0%**	**0.81 [0.71, 0.92]**
Total events	655		811			

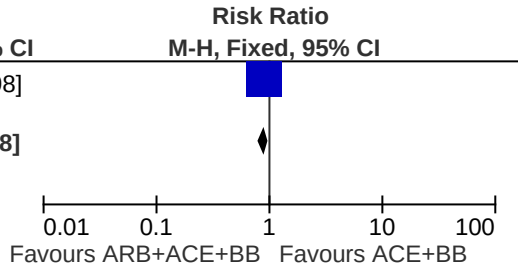
Heterogeneity: Tau² = 0.00; Chi² = 2.06, df = 1 (P = 0.15); I² = 51%
Test for overall effect: Z = 3.16 (P = 0.002)



Forest plot of comparison: 1 ARB + ACE + BB vs Placebo + ACE + BB, outcome: 1.5 Combined outcome: CV Death or hospital admission for CHF.

Study or Subgroup	ARB + ACE Events	Total	ACE + placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CHARM-added (McMurray)	483	1276	538	1272	100.0%	0.89 [0.81, 0.98]
Total (95% CI)		**1276**		**1272**	**100.0%**	**0.89 [0.81, 0.98]**
Total events	483		538			

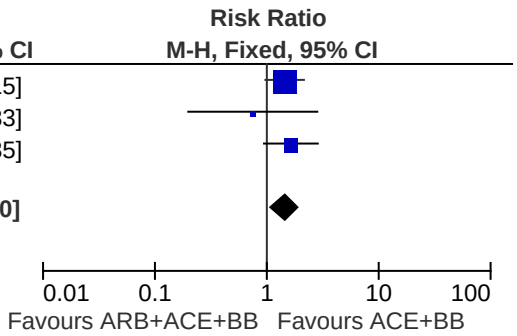
Heterogeneity: Not applicable
Test for overall effect: Z = 2.28 (P = 0.02)



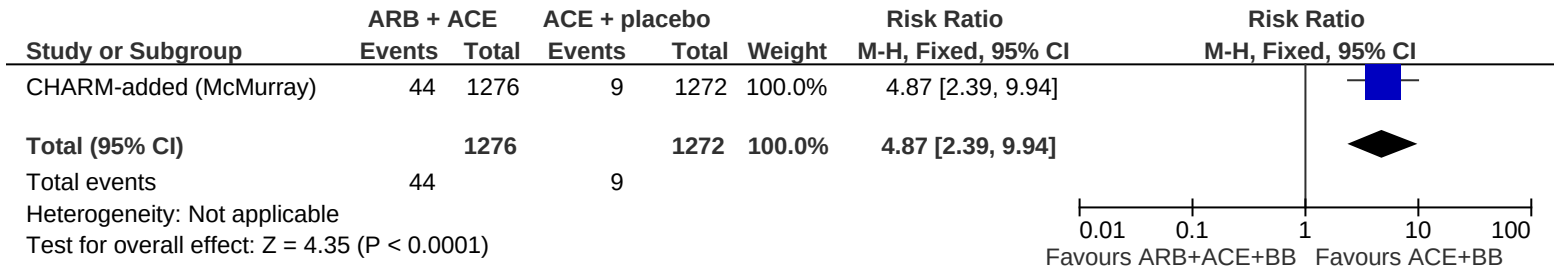
Forest plot of comparison: 1 ARB + ACE + BB vs Placebo + ACE + BB, outcome: 1.3 Hypotension (no. of patients).

Study or Subgroup	ARB + ACE Events	Total	ACE + placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CHARM-added (McMurray)	58	1276	40	1272	62.5%	1.45 [0.97, 2.15]
Cocco 2002	3	16	4	16	6.2%	0.75 [0.20, 2.83]
Val-HeFT (Cohn 2001)	33	2511	20	2499	31.3%	1.64 [0.94, 2.85]
Total (95% CI)		**3803**		**3787**	**100.0%**	**1.46 [1.07, 2.00]**
Total events	94		64			

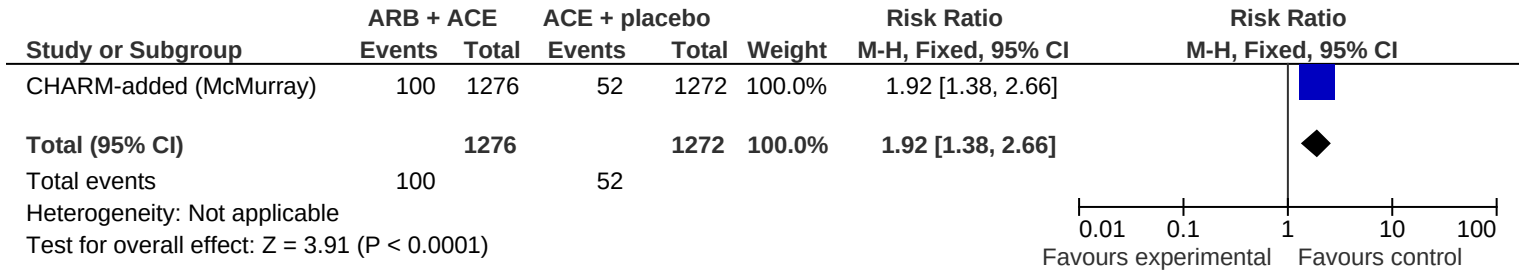
Heterogeneity: Chi² = 1.15, df = 2 (P = 0.56); I² = 0%
Test for overall effect: Z = 2.39 (P = 0.02)



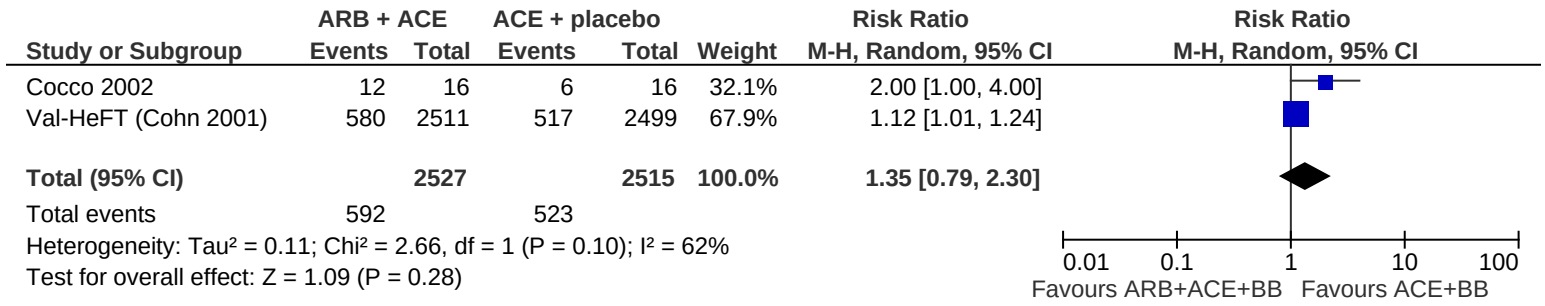
Forest plot of comparison: 1 ARB + ACE + BB vs Placebo + ACE + BB, outcome: 1.4 Hyperkalaemia (no. of patients).



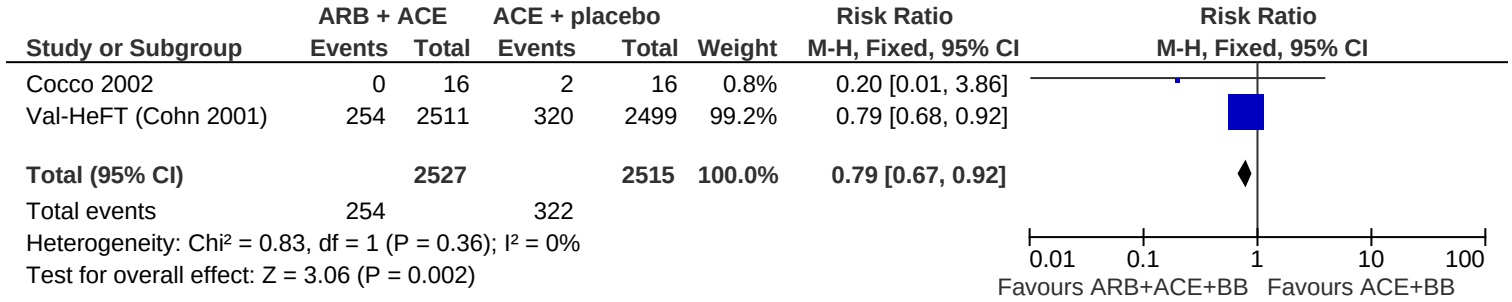
Forest plot of comparison: 1 ARB + ACE + BB vs Placebo + ACE + BB, outcome: 1.6 Increased serum creatinine (number of patients).



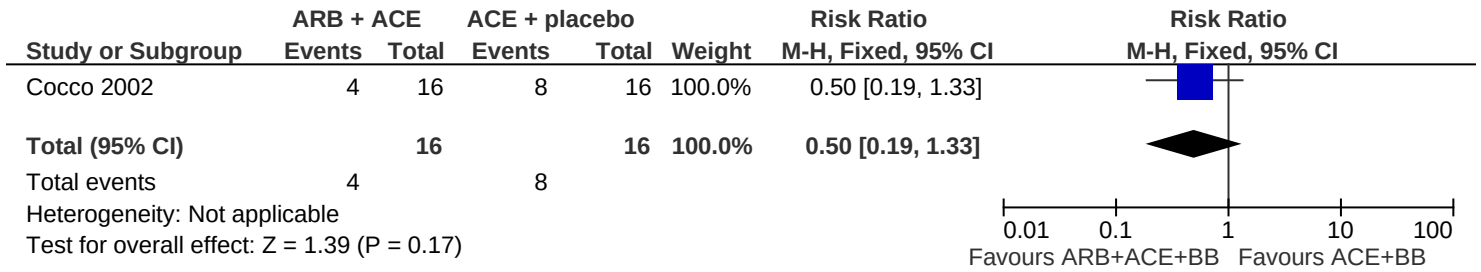
Forest plot of comparison: 1 ARB + ACE + BB vs Placebo + ACE + BB, outcome: 1.7 Improved NYHA class



Forest plot of comparison: 1 ARB + ACE + BB vs Placebo + ACE + BB, outcome: 1.8 Worsened NYHA class.

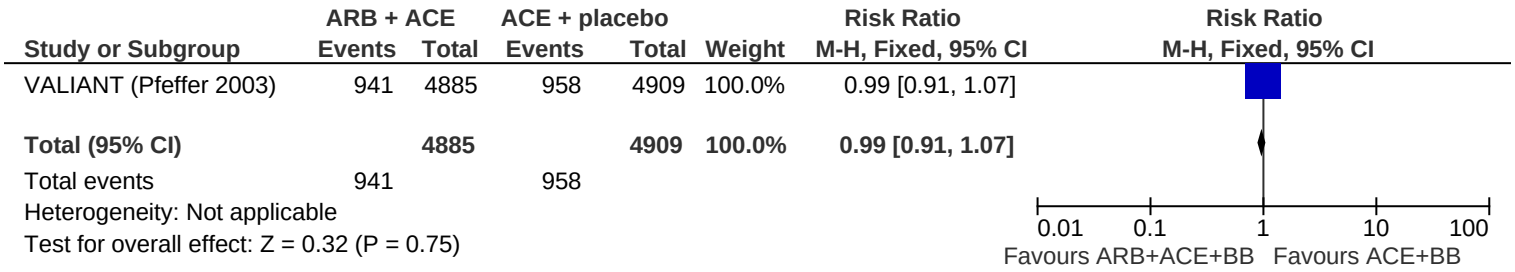


Forest plot of comparison: 1 ARB + ACE + BB vs Placebo + ACE + BB, outcome: 1.9 Unchanged NYHA class.

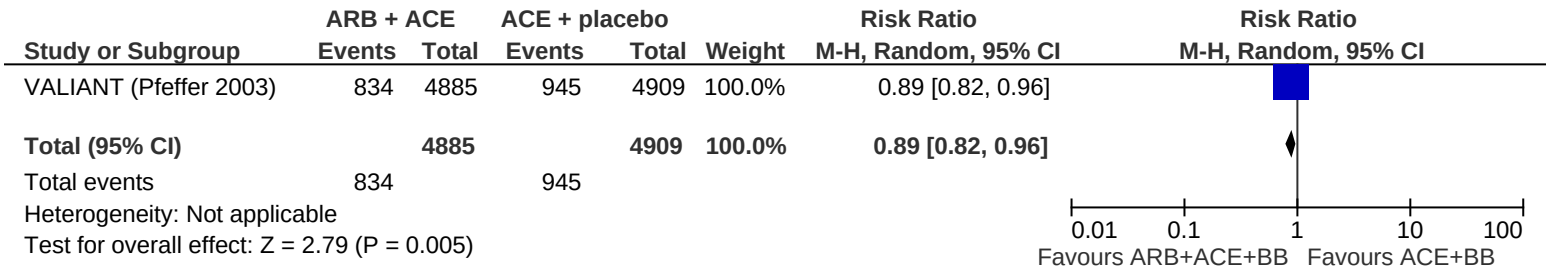


c) angiotensin-II receptor antagonists + angiotensin converting enzyme inhibitor + beta blocker vs placebo + angiotensin converting enzyme inhibitor + beta blocker in chronic heart failure post MI

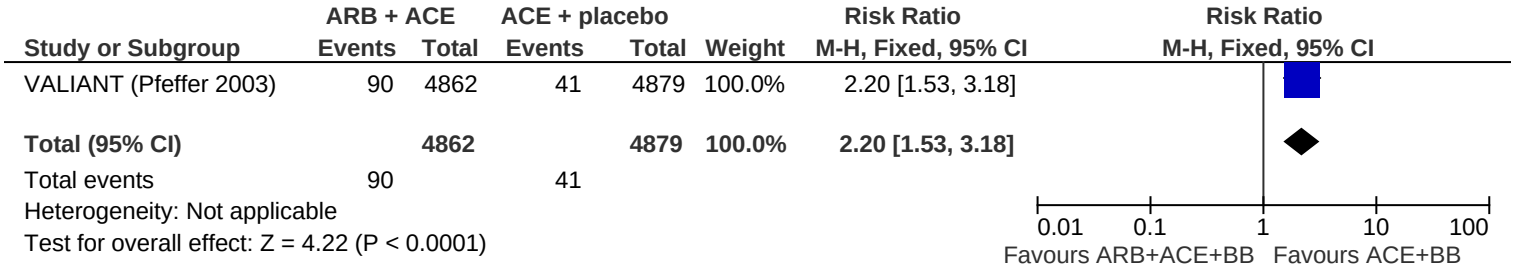
Forest plot of comparison: 1 ARB + ACE + BB vs Placebo + ACE + BB, outcome: 1.1 All cause mortality.



Forest plot of comparison: 1 ARB + ACE + BB vs Placebo + ACE + BB, outcome: 1.2 HF Hospitalisation (no. of patients).



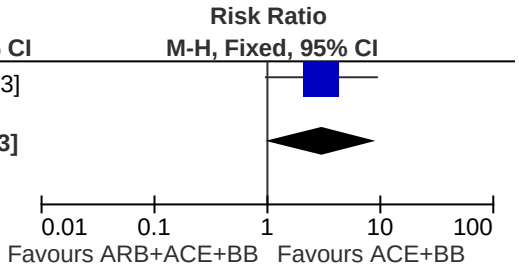
Forest plot of comparison: 1 ARB + ACE + BB vs Placebo + ACE + BB, outcome: 1.3 Hypotension (no. of patients).



Forest plot of comparison: 1 ARB + ACE + BB vs Placebo + ACE + BB, outcome: 1.4 Hyperkalaemia (no. of patients).

Study or Subgroup	ARB + ACE Events	Total	ACE + placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
VALIANT (Pfeffer 2003)	12	4862	4	4879	100.0%	3.01 [0.97, 9.33]
Total (95% CI)		**4862**		**4879**	**100.0%**	**3.01 [0.97, 9.33]**
Total events	12		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.91 (P = 0.06)



BB: beta blockers vs placebo, optimal medical management or other beta blockers

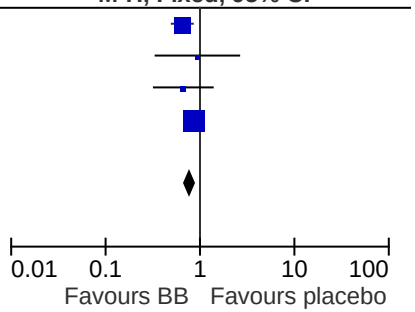
What is the efficacy and safety of beta blockers in comparison to placebo, optimal medical management or other beta blockers in people with chronic heart failure?

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

	BB		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
Deedwania 2004	87	990	134	992	38.4%	0.65 [0.50, 0.84]	
Edes 2005	7	134	7	126	2.1%	0.94 [0.34, 2.61]	
Erdmann 2001	10	61	15	61	4.3%	0.67 [0.33, 1.37]	
Flather 2005	169	1067	192	1061	55.2%	0.88 [0.72, 1.06]	
Total (95% CI)		**2252**		**2240**	**100.0%**	**0.78 [0.67, 0.90]**	
Total events	273		348				

Heterogeneity: Chi² = 3.69, df = 3 (P = 0.30); I² = 19%

Test for overall effect: Z = 3.30 (P = 0.0010)

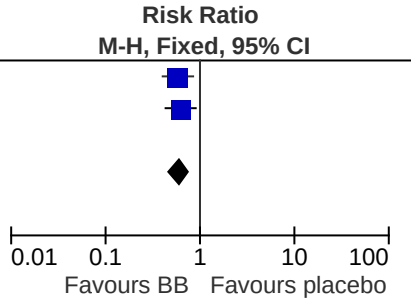


Forest plot of comparison: 1 BB vs Placebo, outcome: Mortality.

	BB		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
Deedwania 2004	42	990	72	992	50.6%	0.58 [0.40, 0.85]	
Flather 2005	44	1067	70	1061	49.4%	0.63 [0.43, 0.90]	
Total (95% CI)		**2057**		**2053**	**100.0%**	**0.60 [0.47, 0.78]**	
Total events	86		142				

Heterogeneity: Chi² = 0.06, df = 1 (P = 0.80); I² = 0%

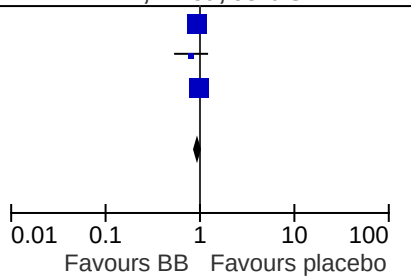
Test for overall effect: Z = 3.78 (P = 0.0002)



Forest plot of comparison: 1 BB vs Placebo, outcome: Sudden death

Study or Subgroup	BB Events	BB Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Deedwania 2004	345	990	368	992	48.1%	0.94 [0.84, 1.06]
Erdmann 2001	25	61	31	61	4.1%	0.81 [0.55, 1.19]
Flather 2005	359	1067	364	1061	47.8%	0.98 [0.87, 1.10]
Total (95% CI)		**2118**		**2114**	**100.0%**	**0.95 [0.88, 1.03]**
Total events	729		763			

Heterogeneity: Chi² = 0.99, df = 2 (P = 0.61); I² = 0%
Test for overall effect: Z = 1.14 (P = 0.26)



Forest plot of comparison: 1 BB vs Placebo, outcome: hospitalisation – all cause

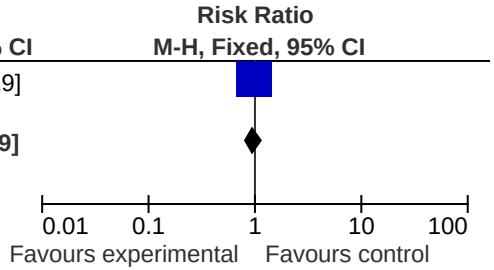
Study or Subgroup	BB Mean	BB SD	BB Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Edes 2005	-9.13	13.78	134	-11.01	14.66	126	100.0%	1.88 [-1.58, 5.34]
Total (95% CI)			**134**			**126**	**100.0%**	**1.88 [-1.58, 5.34]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.06 (P = 0.29)

Forest plot of comparison: 1 BB vs Placebo, outcome: 1.4 Quality of Life (MLHF)

Study or Subgroup	BB Events	BB Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Edes 2005	81	134	78	126	100.0%	0.98 [0.80, 1.19]
Total (95% CI)		**134**		**126**	**100.0%**	**0.98 [0.80, 1.19]**
Total events	81		78			

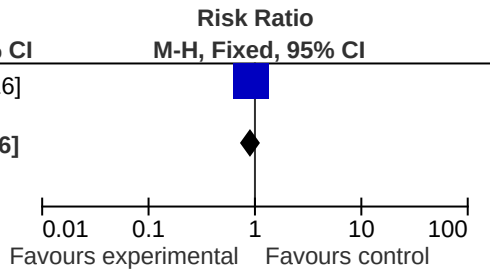
Heterogeneity: Not applicable
Test for overall effect: Z = 0.24 (P = 0.81)



Forest plot of comparison: 1 BB vs Placebo, outcome: 1.7 Adverse events - no. of patients reporting.

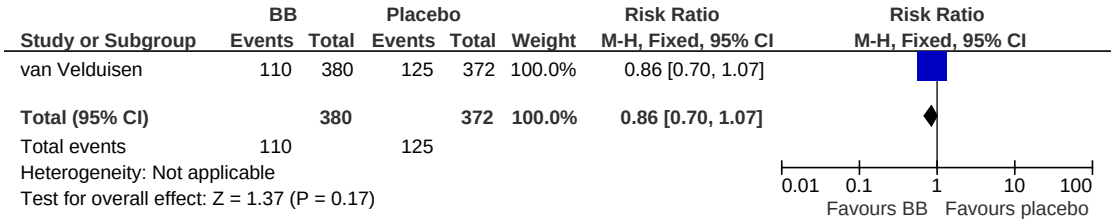
Study or Subgroup	BB Events	BB Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Deedwania 2004	121	990	132	992	100.0%	0.92 [0.73, 1.16]
Total (95% CI)		**990**		**992**	**100.0%**	**0.92 [0.73, 1.16]**
Total events	121		132			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)

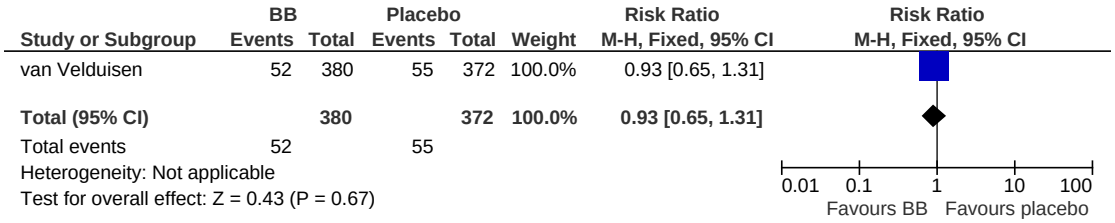


Forest plot of comparison: 1 BB vs Placebo, outcome: 1.5 Adverse events - no. of patients

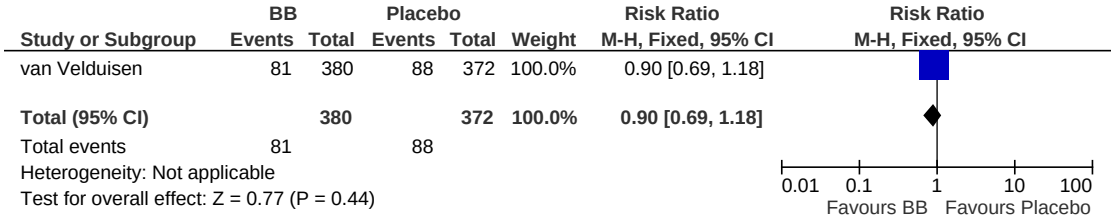
2.0 Evidence profile: Beta blockers versus placebo for patients with preserved left ventricular systolic dysfunction



BB vs Placebo - preserved LVEF, All cause mortality or CV hospitalisation.



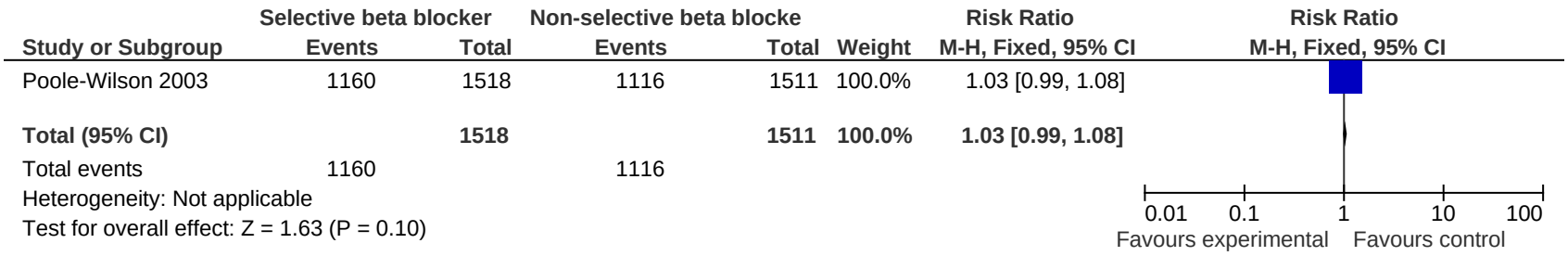
BB vs Placebo - preserved LVEF, outcome: All-cause mortality.



BB vs Placebo - preserved LVEF, outcome: All cause mortality or HF hospitalisation

BB vs Placebo - preserved LVEF, outcome: All cause hospitalisation.

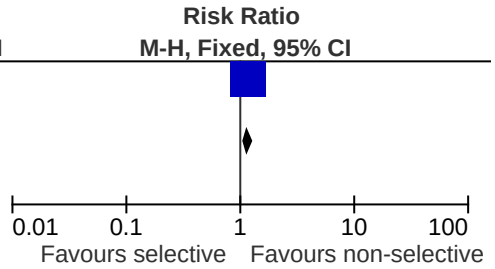
3.0 Evidence profile: Selective vs non-selective beta blockers



Forest plot of comparison: 2 Selective vs non-selective beta blockers, outcome: 2.2 All cause death and all cause admission.

Study or Subgroup	Selective beta blocker Events	Total	Non-selective beta blocke Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Poole-Wilson 2003	600	1518	512	1511	100.0%	1.17 [1.06, 1.28]
Total (95% CI)		**1518**		**1511**	**100.0%**	**1.17 [1.06, 1.28]**
Total events	600		512			

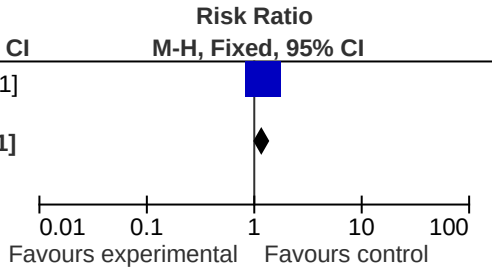
Heterogeneity: Not applicable
Test for overall effect: Z = 3.21 (P = 0.001)



Forest plot of comparison: 2 Selective vs non-selective beta blockers, outcome: 2.1 Mortality - all cause.

Study or Subgroup	Selective beta blocker Events	Total	Non-selective beta blocke Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Poole-Wilson 2003	262	1518	218	1511	100.0%	1.20 [1.01, 1.41]
Total (95% CI)		**1518**		**1511**	**100.0%**	**1.20 [1.01, 1.41]**
Total events	262		218			

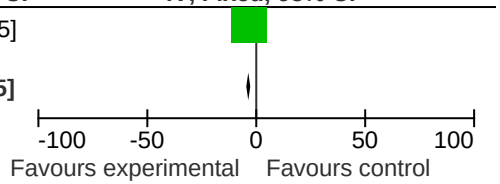
Heterogeneity: Not applicable
Test for overall effect: Z = 2.13 (P = 0.03)



Forest plot of comparison: 2 Selective vs non-selective beta blockers, outcome: 2.4 Sudden death.

Study or Subgroup	Selective beta blocker Mean	SD	Total	Non-selective beta blocke Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Sanderson 1999	4.8	1.4	26	8.1	2	25	100.0%	-3.30 [-4.25, -2.35]
Total (95% CI)			**26**			**25**	**100.0%**	**-3.30 [-4.25, -2.35]**

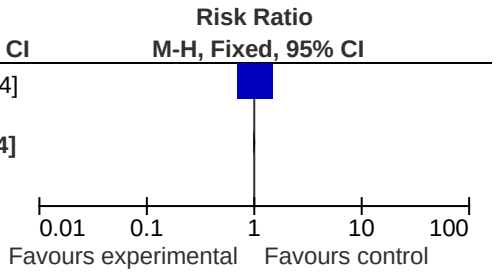
Heterogeneity: Not applicable
Test for overall effect: Z = 6.80 (P < 0.00001)



Forest plot of comparison: 2 Selective vs non-selective beta blockers, outcome: 2.5 Quality of Life ((MLHF).

Study or Subgroup	Selective beta blocker Events	Total	Non-selective beta blocke Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Poole-Wilson 2003	1457	1518	1420	1511	100.0%	1.02 [1.00, 1.04]
Total (95% CI)		**1518**		**1511**	**100.0%**	**1.02 [1.00, 1.04]**
Total events	1457		1420			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.52 (P = 0.01)

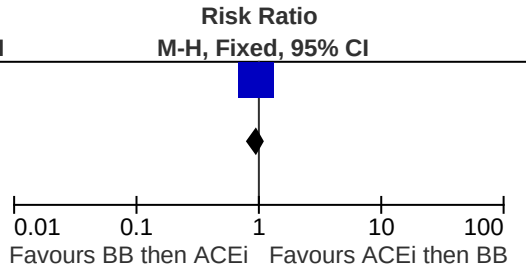


Forest plot of comparison: 2 Selective vs non-selective beta blockers, outcome: 2.3 Adverse events.

4.0 Evidence profile: Beta blockers then ACEI vs ACEI then beta blockers

Study or Subgroup	BB then ACEI Events	Total	ACEI then BB Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Willenheimer 2005	178	505	186	505	100.0%	0.96 [0.81, 1.13]
Total (95% CI)		**505**		**505**	**100.0%**	**0.96 [0.81, 1.13]**
Total events	178		186			

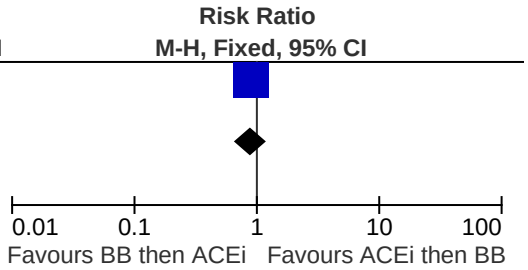
Heterogeneity: Not applicable
Test for overall effect: Z = 0.52 (P = 0.60)



Forest plot of comparison: 3 BB then ACEI vs ACEI then BB, outcome: 3.1 All cause mortality or hospitalisation.

Study or Subgroup	BB then ACEI Events	Total	ACEI then BB Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Willenheimer 2005	65	505	73	505	100.0%	0.89 [0.65, 1.21]
Total (95% CI)		**505**		**505**	**100.0%**	**0.89 [0.65, 1.21]**
Total events	65		73			

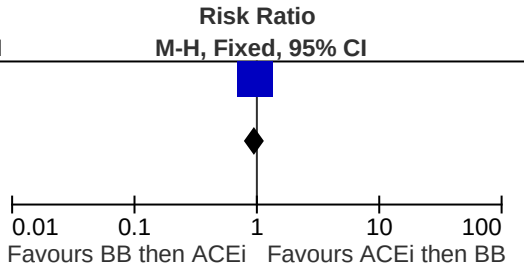
Heterogeneity: Not applicable
Test for overall effect: Z = 0.73 (P = 0.46)



Forest plot of comparison: 3 BB then ACEI vs ACEI then BB, outcome: 3.2 Mortality - all cause.

Study or Subgroup	BB then ACEI Events	Total	ACEI then BB Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Willenheimer 2005	151	505	157	505	100.0%	0.96 [0.80, 1.16]
Total (95% CI)		**505**		**505**	**100.0%**	**0.96 [0.80, 1.16]**
Total events	151		157			

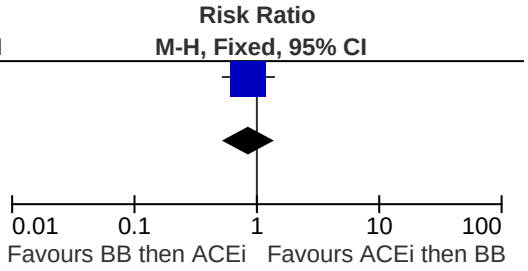
Heterogeneity: Not applicable
Test for overall effect: Z = 0.41 (P = 0.68)



Forest plot of comparison: 3 BB then ACEI vs ACEI then BB, outcome: 3.3 Hospitalisation - all cause.

Study or Subgroup	BB then ACEI Events	Total	ACEI then BB Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Willenheimer 2005	29	505	34	505	100.0%	0.85 [0.53, 1.38]
Total (95% CI)		**505**		**505**	**100.0%**	**0.85 [0.53, 1.38]**
Total events	29		34			

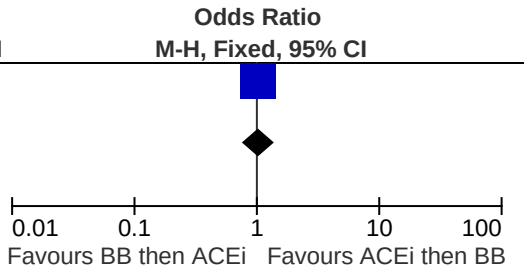
Heterogeneity: Not applicable
Test for overall effect: Z = 0.65 (P = 0.52)



Forest plot of comparison: 3 BB then ACEI vs ACEI then BB, outcome: 3.4 Sudden death

Study or Subgroup	BB then ACEI Events	Total	ACEI then BB Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Willenheimer 2005	113	505	111	505	100.0%	1.02 [0.76, 1.38]
Total (95% CI)		**505**		**505**	**100.0%**	**1.02 [0.76, 1.38]**
Total events	113		111			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.15 (P = 0.88)



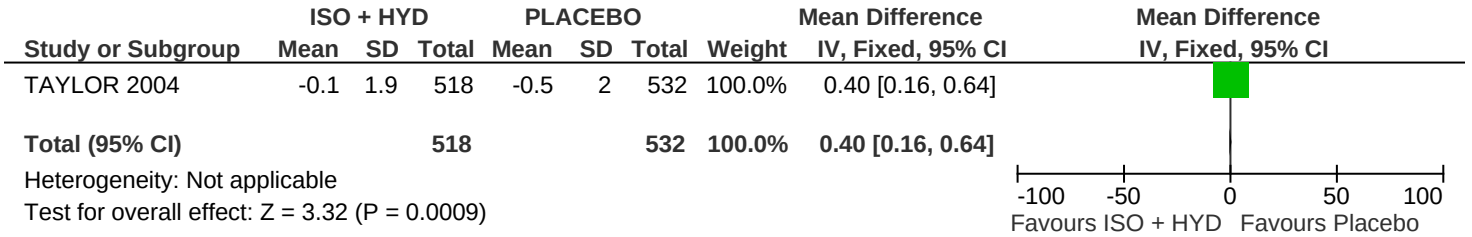
Forest plot of comparison: 3 BB then ACEI vs ACEI then BB, outcome: 3.5 Serious adverse event.

ISO: isosorbide/hydralazine vs placebo or ACE or placebo+optimal medical treatment

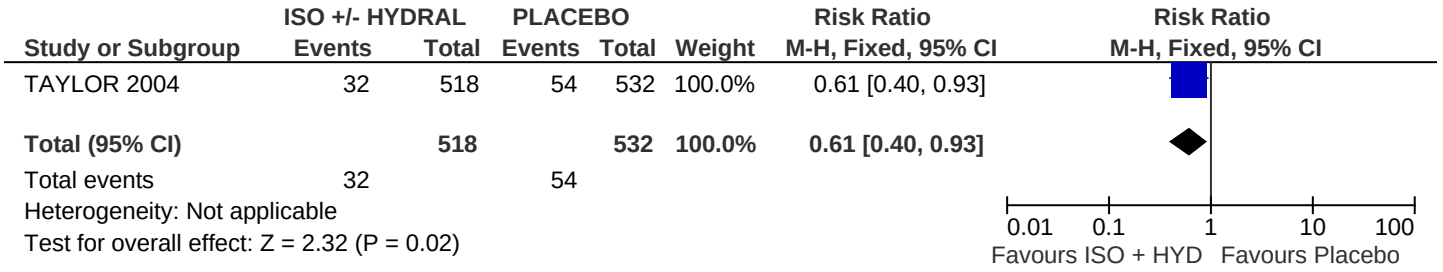
What is the efficacy and safety of isosorbide/hydralazine combination in comparison to a) Placebo, b) ACEI c) placebo + optimal medical treatment in the medical management of adults with heart failure?

ISO a) isosorbide +/- hydralazine vs. placebo + optimal medical management in the black population

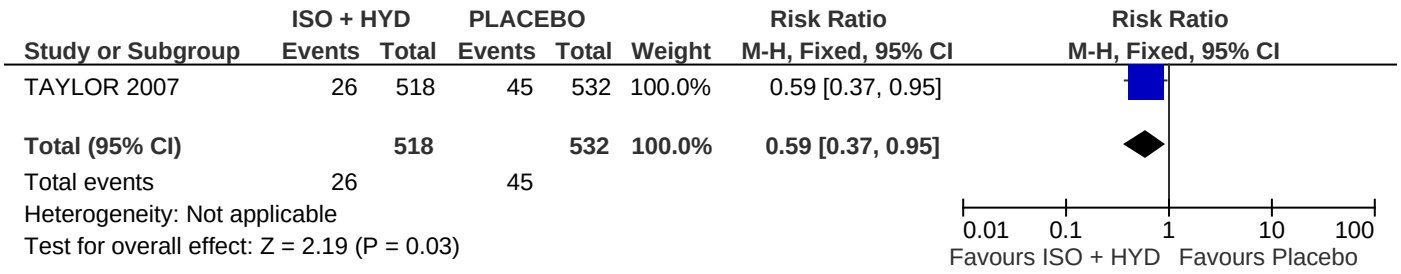
TAYLOR



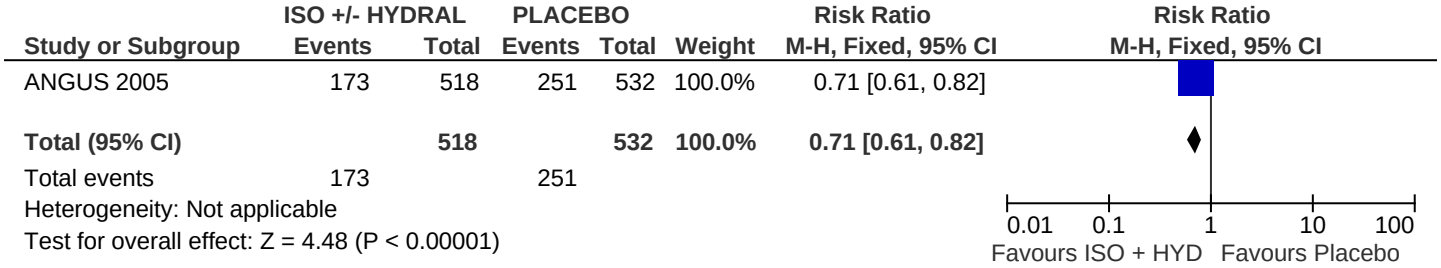
Forest plot of comparison: 1 ISOSRBIDE +/-HYDRALAZINE vs. PLACEBO, outcome: 1.1 Composite score - 0 to 18 mths.



All cause mortality



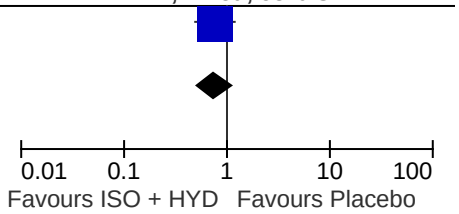
Forest plot of comparison: 1 ISOSRBIDE +/-HYDRALAZINE vs. PLACEBO, outcome: 1.3 Cardiovascular death



Forest plot of comparison: 1 ISOSRBIDE +/-HYDRALAZINE vs. PLACEBO, outcome: 1.4 Hospitalization for HF

Study or Subgroup	ISO + HYD Events	Total	PLACEBO Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ANGUS 2005	32	518	43	532	100.0%	0.76 [0.49, 1.19]
Total (95% CI)		**518**		**532**	**100.0%**	**0.76 [0.49, 1.19]**
Total events	32		43			

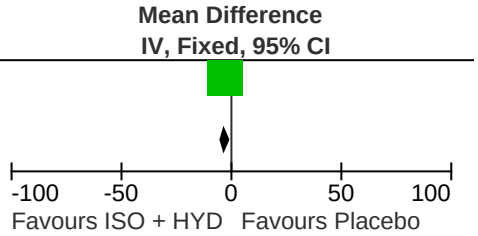
Heterogeneity: Not applicable
Test for overall effect: Z = 1.19 (P = 0.23)



Forest plot of comparison: 1 ISOSRBIDE +/-HYDRALAZINE vs. PLACEBO, outcome: 1.5 Total no. of ER and unscheduled hospital visits (HF related) - mean 12.8 mths.

Study or Subgroup	ISO + HYD Mean	SD	Total	PLACEBO Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
TAYLOR 2004	-5.6	20.6	518	-2.7	21.2	532	100.0%	-2.90 [-5.43, -0.37]
Total (95% CI)			**518**			**532**	**100.0%**	**-2.90 [-5.43, -0.37]**

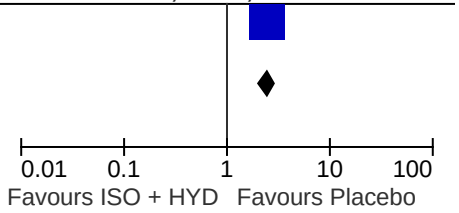
Heterogeneity: Not applicable
Test for overall effect: Z = 2.25 (P = 0.02)



Forest plot of comparison: 1 ISOSRBIDE +/-HYDRALAZINE vs. PLACEBO, outcome: 1.6 Quality of life (change from baseline

Study or Subgroup	ISO + HYD Events	Total	PLACEBO Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
TAYLOR 2004	243	518	102	532	100.0%	2.45 [2.01, 2.98]
Total (95% CI)		**518**		**532**	**100.0%**	**2.45 [2.01, 2.98]**
Total events	243		102			

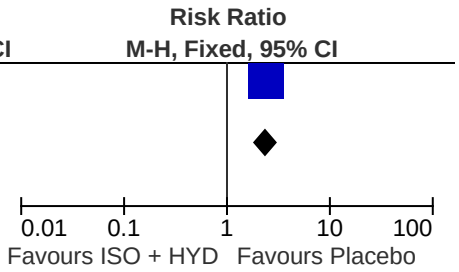
Heterogeneity: Not applicable
Test for overall effect: Z = 8.90 (P < 0.00001)



Forest plot of comparison: 1 ISOSRBIDE +/-HYDRALAZINE vs. PLACEBO, outcome: 1.7 Adverse events (headache)

Study or Subgroup	ISO + HYD Events	Total	PLACEBO Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
TAYLOR 2004	152	518	65	532	100.0%	2.40 [1.84, 3.13]
Total (95% CI)		**518**		**532**	**100.0%**	**2.40 [1.84, 3.13]**
Total events	152		65			

Heterogeneity: Not applicable
Test for overall effect: Z = 6.50 (P < 0.00001)

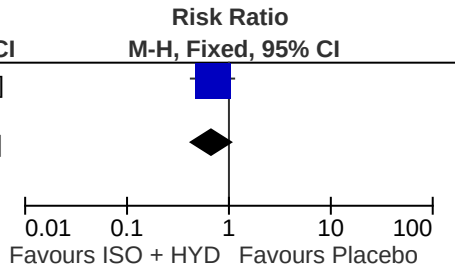


Forest plot of comparison: 1 ISOSRBIDE +/-HYDRALAZINE vs. PLACEBO, outcome: 1.8 Adverse events (dizziness).

CARSON

Study or Subgroup	ISO +/- HYDRAL Events	Total	PLACEBO Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CARSON 1999	15	49	35	79	100.0%	0.69 [0.42, 1.13]
Total (95% CI)		**49**		**79**	**100.0%**	**0.69 [0.42, 1.13]**
Total events	15		35			

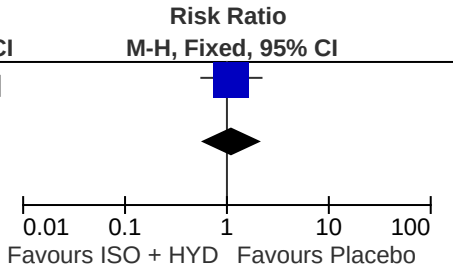
Heterogeneity: Not applicable
Test for overall effect: Z = 1.48 (P = 0.14)



Forest plot of comparison: 1 ISOSRBIDE +/-HYDRALAZINE vs. PLACEBO, outcome: 1.2 All cause mortality

Study or Subgroup	ISO +/- HYDRAL Events	Total	PLACEBO Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CARSON 1999	11	49	16	79	100.0%	1.11 [0.56, 2.19]
Total (95% CI)		**49**		**79**	**100.0%**	**1.11 [0.56, 2.19]**
Total events	11		16			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.30 (P = 0.77)

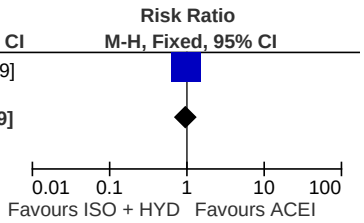


Forest plot of comparison: 1 ISOSRBIDE +/-HYDRALAZINE vs. PLACEBO, outcome: 1.4 Hospitalization for HF

ISO +/- HYDRALAZINE vs ACEI

Study or Subgroup	ISO + HYD Events	Total	ACEI Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CARSON 1999	39	109	39	106	100.0%	0.97 [0.68, 1.39]
Total (95% CI)		**109**		**106**	**100.0%**	**0.97 [0.68, 1.39]**
Total events	39		39			

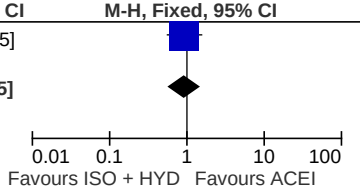
Heterogeneity: Not applicable
Test for overall effect: Z = 0.15 (P = 0.88)



Forest plot of comparison: 2 ISO + HYD vs ACEI, outcome: 2.1 All cause mortality - 0 to 66 mths.

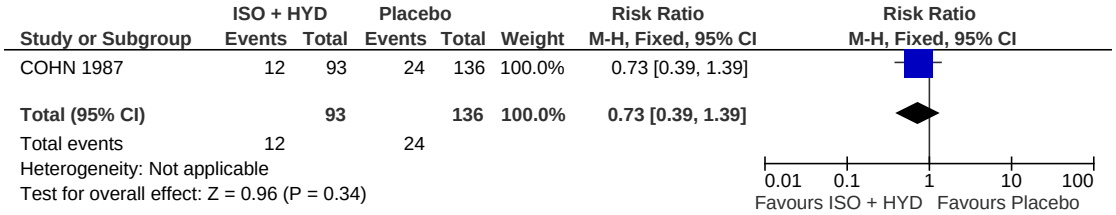
Study or Subgroup	ISO + HYD Events	Total	ACEI Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CARSON 1999	23	109	24	106	100.0%	0.93 [0.56, 1.55]
Total (95% CI)		**109**		**106**	**100.0%**	**0.93 [0.56, 1.55]**
Total events	23		24			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.27 (P = 0.78)

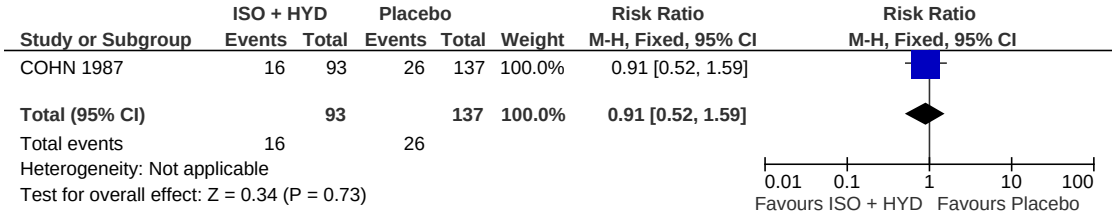


Forest plot of comparison: 2 ISO + HYD vs ACEI, outcome: 2.2 Hospitalisation for HF - 0 to 66 mths.

Vs PLACEBO Age groups

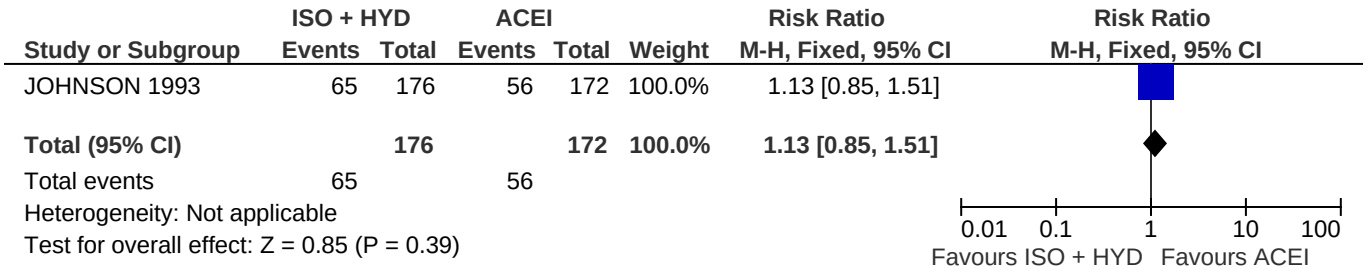


Forest plot of comparison: 3 ISO + HYD vs Placebo - age groups, outcome: 3.1 All cause mortality rate < 60 yrs (per annum).



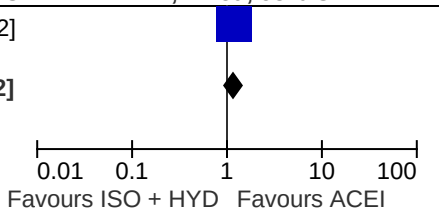
Forest plot of comparison: 3 ISO + HYD vs Placebo - age groups, outcome: 3.2 All cause mortality 60 yrs or older (per annum).

Isosorbide plus hydralazine vs. ACE I in different age groups



Forest plot of comparison: 4 ISO + HYD vs ACEI - age groups, outcome: 4.1 All cause mortality < 60 yrs - 2 yrs.

	ISO + HYD		ACEI			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
JOHNSON 1993	88	225	76	231	100.0%	1.19 [0.93, 1.52]	
Total (95% CI)		**225**		**231**	**100.0%**	**1.19 [0.93, 1.52]**	
Total events	88		76				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.38 (P = 0.17)							



Forest plot of comparison: 4 ISO + HYD vs ACEI - age groups, outcome: 4.2 All cause mortality 60 yrs or older - 2 yrs.

MONIT: patient telemonitoring vs out patient monitoring

What is the efficacy and safety of patient telemonitoring in comparison to outpatient monitoring for adults with chronic heart failure?

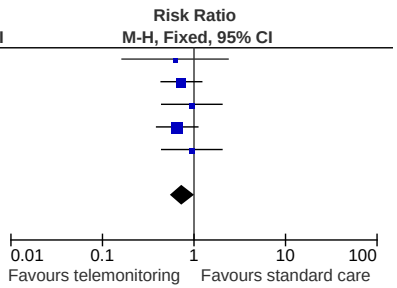
TELEMONITORING VS STANDARD CARE

Telemonitoring – Forest plot

Forest plot of comparison: 1 Telemonitoring vs standard care, outcome: 1.1 All cause mortality.

Study or Subgroup	Telemonitoring Events	Total	Standard care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Antonicelli 2008	3	28	5	29	5.8%	0.62 [0.16, 2.36]
Cleland 2005	28	163	20	85	31.0%	0.73 [0.44, 1.22]
Dansky 2008	10	47	11	49	12.7%	0.95 [0.44, 2.02]
Giordano 2009	21	230	32	230	37.8%	0.66 [0.39, 1.10]
Wakefield 2008	10	47	11	49	12.7%	0.95 [0.44, 2.02]
Total (95% CI)		**515**		**442**	**100.0%**	**0.75 [0.56, 1.01]**
Total events	72		79			

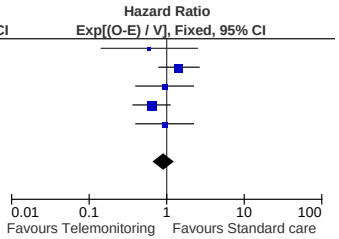
Heterogeneity: Chi² = 1.07, df = 4 (P = 0.90); I² = 0%
Test for overall effect: Z = 1.91 (P = 0.06)



Forest plot of comparison: 1 Telemonitoring vs standard care, outcome: 1.10 HR All cause mortality (8 to 12 mths).

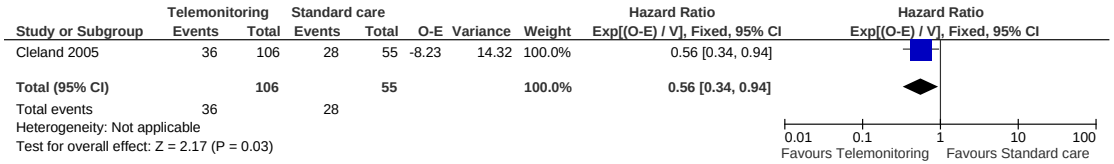
Study or Subgroup	Telemonitoring Events	Total	Standard care Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Antonicelli 2008	3	28	5	29	-0.97	1.88	5.2%	0.60 [0.14, 2.49]
Cleland 2005	28	163	20	85	3.95	10.81	30.2%	1.44 [0.79, 2.62]
Dansky 2008	10	47	11	49	-0.32	5.24	14.6%	0.94 [0.40, 2.21]
Giordano 2009	21	230	32	230	-5.69	12.68	35.4%	0.64 [0.37, 1.11]
Wakefield 2008	10	47	11	49	-0.32	5.24	14.6%	0.94 [0.40, 2.21]
Total (95% CI)		**515**		**442**			**100.0%**	**0.91 [0.66, 1.26]**
Total events	72		79					

Heterogeneity: Chi² = 4.22, df = 4 (P = 0.38); I² = 5%
Test for overall effect: Z = 0.56 (P = 0.58)

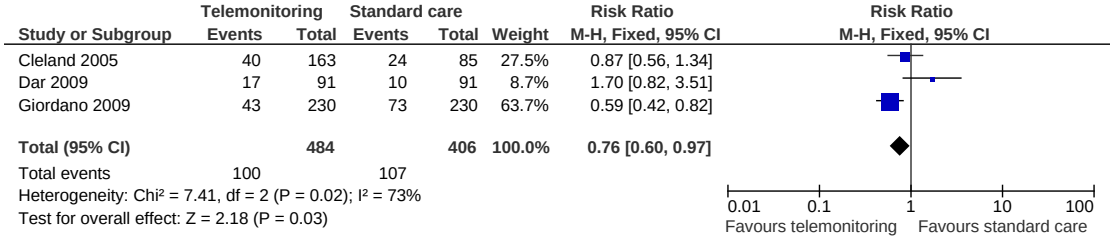


Forest plot of comparison: 1 Telemonitoring vs standard care, outcome: 1.6 all cause mortality (450 days follow-up).

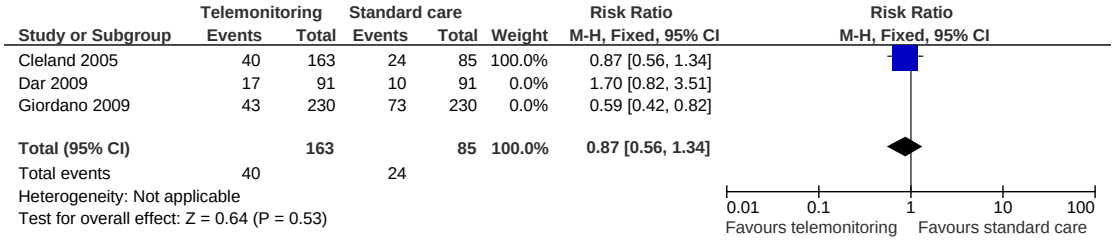
Forest plot of comparison: 1 Telemonitoring vs standard care, outcome: 1.11 HR all cause mortality (450 days).

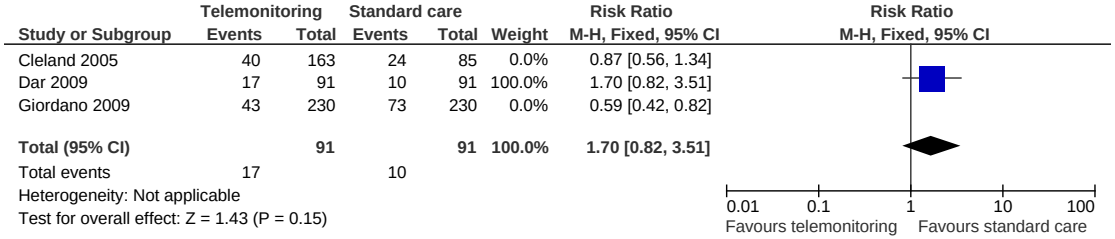


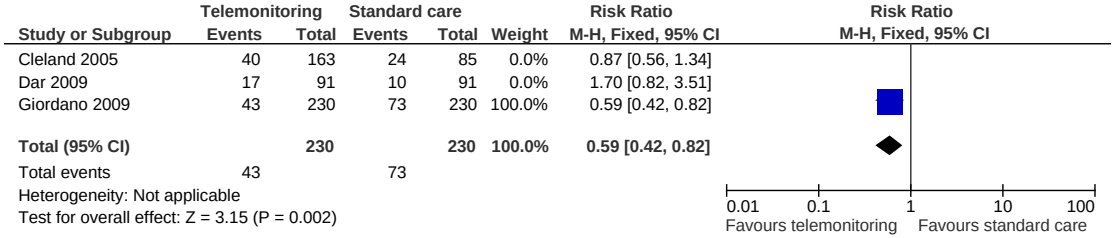
Forest plot of comparison: 1 Telemonitoring vs standard care, outcome: 1.4 Heart failure hospitalisations (no. of patients).



Heart failure hospitalisation – reported study by study



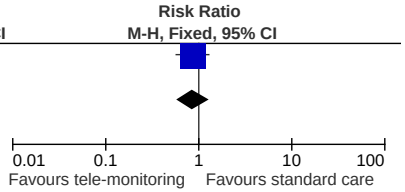




Forest plot of comparison: 1 Telemonitoring vs standard care, outcome: 1.9 Heart failure hospitalisation (no. of patients), 450 days.

Study or Subgroup	Telemonitoring Events	Total	Standard care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cleland 2005	38	106	23	55	100.0%	0.86 [0.57, 1.28]
Total (95% CI)		**106**		**55**	**100.0%**	**0.86 [0.57, 1.28]**
Total events	38		23			

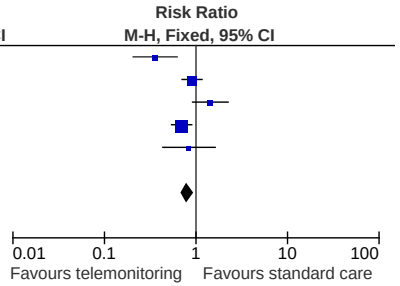
Heterogeneity: Not applicable
Test for overall effect: Z = 0.75 (P = 0.45)



Forest plot of comparison: 1 Telemonitoring vs standard care, outcome: 1.2 All cause hospitalisations (no. of patients).

Study or Subgroup	Telemonitoring Events	Total	Standard care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Antonicelli 2008	9	28	26	29	11.7%	0.36 [0.21, 0.62]
Cleland 2005	80	163	46	85	27.7%	0.91 [0.71, 1.17]
Dar 2009	33	91	23	91	10.5%	1.43 [0.92, 2.24]
Giordano 2009	67	230	96	230	43.9%	0.70 [0.54, 0.90]
Schwarz 2008	12	44	13	40	6.2%	0.84 [0.43, 1.62]
Total (95% CI)		**556**		**475**	**100.0%**	**0.80 [0.69, 0.94]**
Total events	201		204			

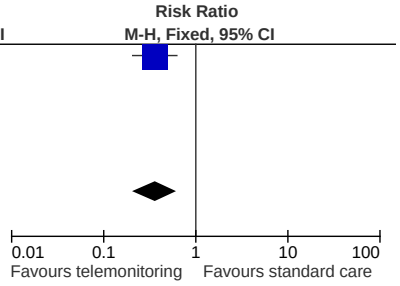
Heterogeneity: Chi² = 16.80, df = 4 (P = 0.002); I² = 76%
Test for overall effect: Z = 2.80 (P = 0.005)



All cause hospitalisation (no. of patients) by study

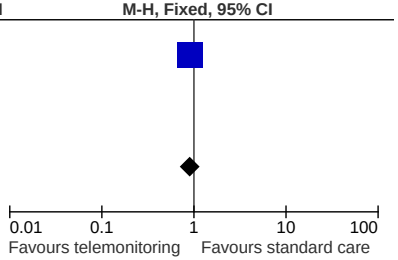
Study or Subgroup	Telemonitoring Events	Total	Standard care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Antonicelli 2008	9	28	26	29	100.0%	0.36 [0.21, 0.62]
Cleland 2005	80	163	46	85	0.0%	0.91 [0.71, 1.17]
Dar 2009	33	91	23	91	0.0%	1.43 [0.92, 2.24]
Giordano 2009	67	230	96	230	0.0%	0.70 [0.54, 0.90]
Schwarz 2008	12	44	13	40	0.0%	0.84 [0.43, 1.62]
Total (95% CI)		**28**		**29**	**100.0%**	**0.36 [0.21, 0.62]**
Total events	9		26			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.64 (P = 0.0003)



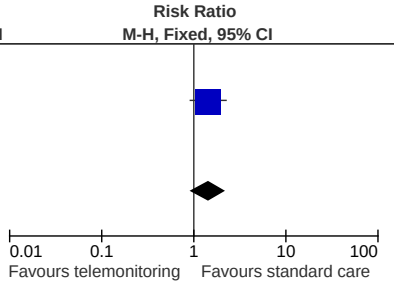
Study or Subgroup	Telemonitoring Events	Total	Standard care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Antonicelli 2008	9	28	26	29	0.0%	0.36 [0.21, 0.62]
Cleland 2005	80	163	46	85	100.0%	0.91 [0.71, 1.17]
Dar 2009	33	91	23	91	0.0%	1.43 [0.92, 2.24]
Giordano 2009	67	230	96	230	0.0%	0.70 [0.54, 0.90]
Schwarz 2008	12	44	13	40	0.0%	0.84 [0.43, 1.62]
Total (95% CI)		**163**		**85**	**100.0%**	**0.91 [0.71, 1.17]**
Total events	80		46			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.76 (P = 0.44)



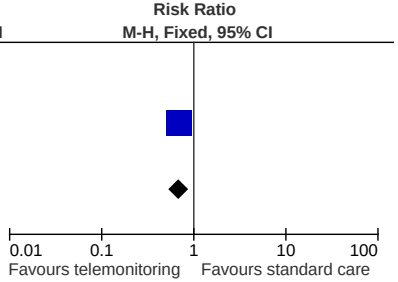
Study or Subgroup	Telemonitoring Events	Total	Standard care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Antonicelli 2008	9	28	26	29	0.0%	0.36 [0.21, 0.62]
Cleland 2005	80	163	46	85	0.0%	0.91 [0.71, 1.17]
Dar 2009	33	91	23	91	100.0%	1.43 [0.92, 2.24]
Giordano 2009	67	230	96	230	0.0%	0.70 [0.54, 0.90]
Schwarz 2008	12	44	13	40	0.0%	0.84 [0.43, 1.62]
Total (95% CI)		**91**		**91**	**100.0%**	**1.43 [0.92, 2.24]**
Total events	33		23			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.59 (P = 0.11)



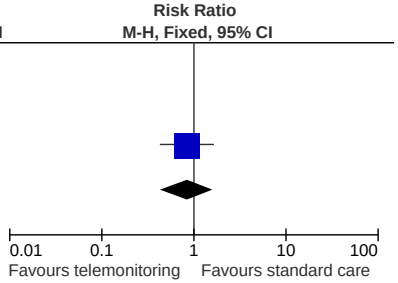
Study or Subgroup	Telemonitoring Events	Total	Standard care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Antonicelli 2008	9	28	26	29	0.0%	0.36 [0.21, 0.62]
Cleland 2005	80	163	46	85	0.0%	0.91 [0.71, 1.17]
Dar 2009	33	91	23	91	0.0%	1.43 [0.92, 2.24]
Giordano 2009	67	230	96	230	100.0%	0.70 [0.54, 0.90]
Schwarz 2008	12	44	13	40	0.0%	0.84 [0.43, 1.62]
Total (95% CI)		**230**		**230**	**100.0%**	**0.70 [0.54, 0.90]**
Total events	67		96			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.79 (P = 0.005)



Study or Subgroup	Telemonitoring Events	Total	Standard care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Antonicelli 2008	9	28	26	29	0.0%	0.36 [0.21, 0.62]
Cleland 2005	80	163	46	85	0.0%	0.91 [0.71, 1.17]
Dar 2009	33	91	23	91	0.0%	1.43 [0.92, 2.24]
Giordano 2009	67	230	96	230	0.0%	0.70 [0.54, 0.90]
Schwarz 2008	12	44	13	40	100.0%	0.84 [0.43, 1.62]
Total (95% CI)		**44**		**40**	**100.0%**	**0.84 [0.43, 1.62]**
Total events	12		13			

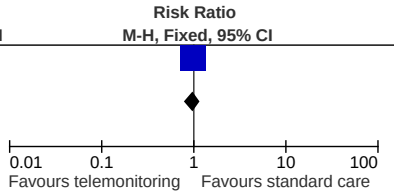
Heterogeneity: Not applicable
Test for overall effect: Z = 0.52 (P = 0.60)



Forest plot of comparison: 1 Telemonitoring vs standard care, outcome: 1.8 All cause hospitalisations (no. of patients) 450 days.

Study or Subgroup	Telemonitoring Events	Total	Standard care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cleland 2005	75	106	40	55	100.0%	0.97 [0.79, 1.19]
Total (95% CI)		**106**		**55**	**100.0%**	**0.97 [0.79, 1.19]**
Total events	75		40			

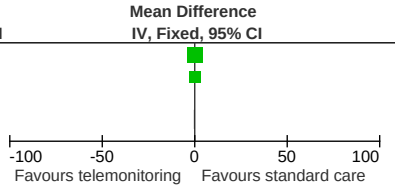
Heterogeneity: Not applicable
Test for overall effect: Z = 0.27 (P = 0.79)



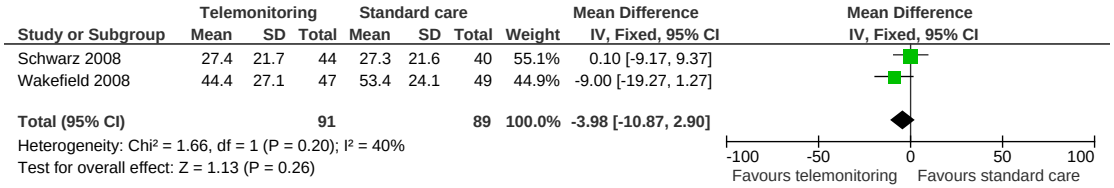
Forest plot of comparison: 1 Telemonitoring vs standard care, outcome: 1.3 All cause hospitalisation (no. of events).

Study or Subgroup	Telemonitoring Mean	SD	Total	Standard care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Dansky 2008	0.54	0.78	126	0.6	0.91	110	58.2%	-0.06 [-0.28, 0.16]
Schwarz 2008	0.32	0.6	44	0.33	0.6	40	41.8%	-0.01 [-0.27, 0.25]
Total (95% CI)			**170**			**150**	**100.0%**	**-0.04 [-0.21, 0.13]**

Heterogeneity: Chi² = 0.08, df = 1 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.46 (P = 0.64)

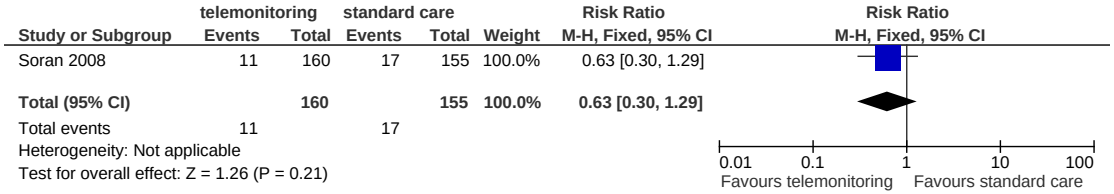


Forest plot of comparison: 1 Telemonitoring vs standard care, outcome: 1.5 Quality of life (MLHF).

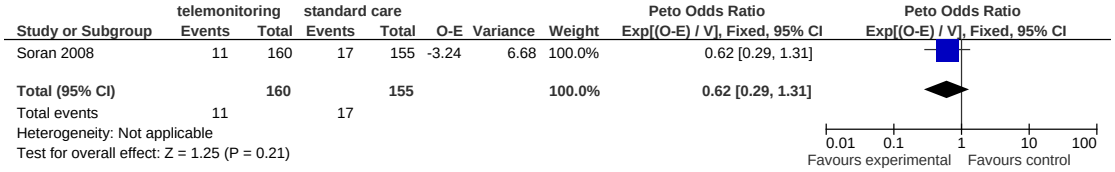


Women and older adults

Forest plot of comparison: 1 Telemonitoring vs standard care, outcome: 1.1 all cause mortality (mean follow-up 6 months).



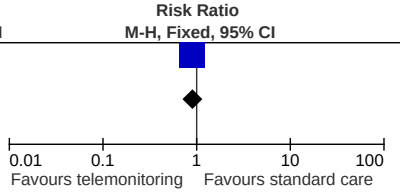
Forest plot of comparison: 1 Telemonitoring vs standard care, outcome: 1.3 HR all cause mortality (mean follow-up 6 months).



Forest plot of comparison: 1 Telemonitoring vs standard care, outcome: 1.2 all cause hospitalisation (mean follow=up 6 months).

Study or Subgroup	telemonitoring Events	Total	standard care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Soran 2008	68	160	73	155	100.0%	0.90 [0.71, 1.15]
Total (95% CI)		**160**		**155**	**100.0%**	**0.90 [0.71, 1.15]**
Total events	68		73			

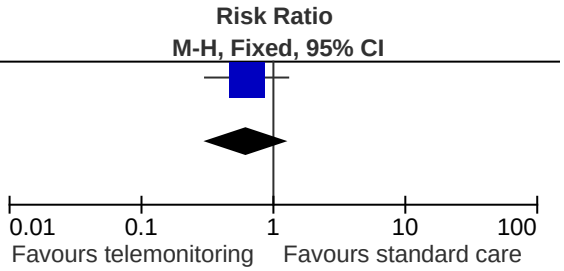
Heterogeneity: Not applicable
Test for overall effect: Z = 0.82 (P = 0.41)



Women and non-Caucasian males

Study or Subgroup	telemonitoring Events	Total	standard care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Soran 2008	11	160	17	155	100.0%	0.63 [0.30, 1.29]
Total (95% CI)		**160**		**155**	**100.0%**	**0.63 [0.30, 1.29]**
Total events	11		17			

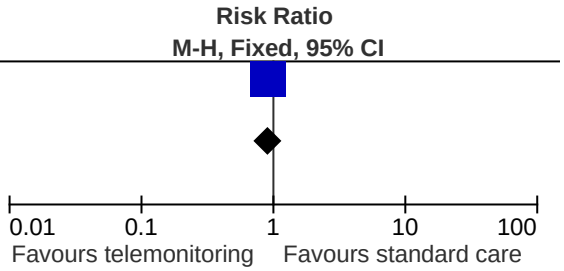
Heterogeneity: Not applicable
Test for overall effect: Z = 1.26 (P = 0.21)



Forest plot of comparison: 1 Telemonitoring vs standard care, outcome: 1.1 all cause mortality (mean follow-up 6 months).

Study or Subgroup	telemonitoring Events	Total	standard care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Soran 2008	68	160	73	155	100.0%	0.90 [0.71, 1.15]
Total (95% CI)		**160**		**155**	**100.0%**	**0.90 [0.71, 1.15]**
Total events	68		73			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.82 (P = 0.41)



Forest plot of comparison: 1 Telemonitoring vs standard care, outcome: 1.2 all cause hospitalisation (mean follow=up 6 months).

REHAB: exercise based cardiac rehabilitation

What is the safety and efficacy of exercise based cardiac rehabilitation in adults with chronic heart failure?

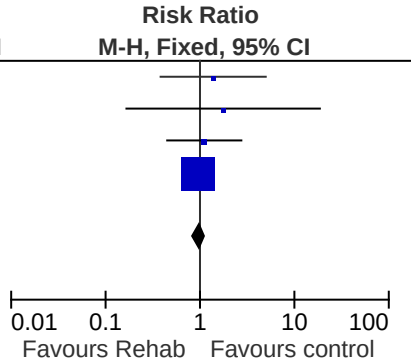
Exercise based cardiac rehabilitation vs. standard care.

Forest plot of comparison: 1 rehab vs. standard care, outcome: 1.1 All cause mortality up to 30 months.

Study or Subgroup	Rehab Events	Rehab Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AUSTIN 2005	5	85	4	94	1.8%	1.38 [0.38, 4.98]
CORVERA 2004	2	42	1	37	0.5%	1.76 [0.17, 18.65]
DRACUP2007	9	87	8	86	3.8%	1.11 [0.45, 2.75]
O'CONNOR 2009	189	1159	198	1172	93.8%	0.97 [0.80, 1.16]
Total (95% CI)		**1373**		**1389**	**100.0%**	**0.98 [0.82, 1.17]**
Total events	205		211			

Heterogeneity: Chi² = 0.62, df = 3 (P = 0.89); I² = 0%

Test for overall effect: Z = 0.20 (P = 0.84)

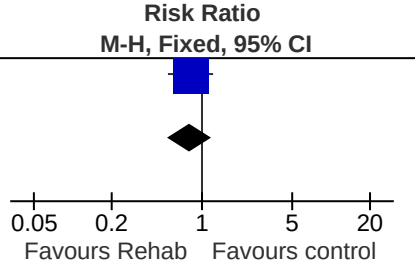


Forest plot of comparison: 1 rehab vs. standard care, outcome: 1.2 all cause death 5 yr follow-up.

Study or Subgroup	Rehab Events	Rehab Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AUSTIN 2008 FU	31	100	38	100	100.0%	0.82 [0.56, 1.20]
Total (95% CI)		**100**		**100**	**100.0%**	**0.82 [0.56, 1.20]**
Total events	31		38			

Heterogeneity: Not applicable

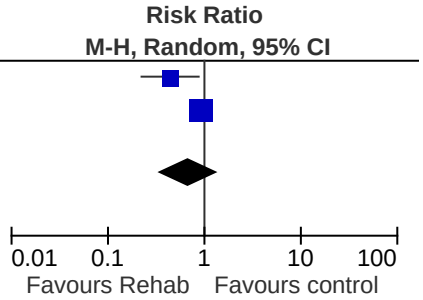
Test for overall effect: Z = 1.04 (P = 0.30)



Forest plot of comparison: 1 rehab vs. standard care, outcome: 1.4 CV death up to 4.4 years.

Study or Subgroup	Rehab Events	Rehab Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
BELARDINELLI 1999 (OG)	9	50	20	49	40.2%	0.44 [0.22, 0.87]
O'CONNOR 2009	131	1159	143	1172	59.8%	0.93 [0.74, 1.16]
Total (95% CI)		**1209**		**1221**	**100.0%**	**0.69 [0.34, 1.40]**
Total events	140		163			

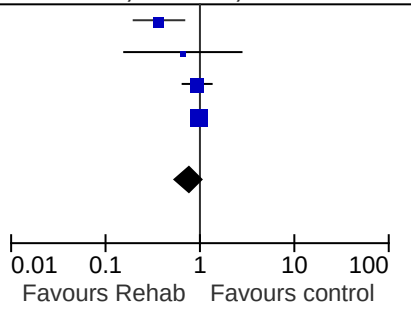
Heterogeneity: Tau² = 0.21; Chi² = 4.12, df = 1 (P = 0.04); I² = 76%
Test for overall effect: Z = 1.03 (P = 0.30)



Forest plot of comparison: 1 rehab vs. standard care, outcome: 1.3 All cause hospitalization up to 30 months.

Study or Subgroup	Rehab Events	Rehab Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
AUSTIN 2005	11	85	33	94	19.9%	0.37 [0.20, 0.68]
CORVERA 2004	3	42	4	37	5.9%	0.66 [0.16, 2.76]
DRACUP2007	35	87	37	86	31.3%	0.94 [0.66, 1.33]
O'CONNOR 2009	729	1159	760	1172	42.9%	0.97 [0.91, 1.03]
Total (95% CI)		**1373**		**1389**	**100.0%**	**0.77 [0.53, 1.12]**
Total events	778		834			

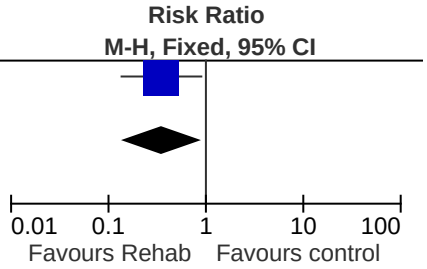
Heterogeneity: Tau² = 0.08; Chi² = 9.95, df = 3 (P = 0.02); I² = 70%
Test for overall effect: Z = 1.35 (P = 0.18)



Forest plot of comparison: 1 rehab vs. standard care, outcome: 1.6 HF hospitalization up to 4.4 years.

Study or Subgroup	Rehab Events	Rehab Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BELARDINELLI 1999 (OG)	5	50	14	49	100.0%	0.35 [0.14, 0.90]
Total (95% CI)		**50**		**49**	**100.0%**	**0.35 [0.14, 0.90]**
Total events	5		14			

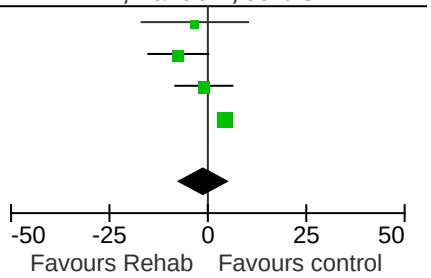
Heterogeneity: Not applicable
Test for overall effect: Z = 2.18 (P = 0.03)



Forest plot of comparison: 1 rehab vs. standard care, outcome: 1.7 Mean QoL score up to 6 months.

Study or Subgroup	Rehab Mean	Rehab SD	Rehab Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
CIDER 2003	24.5	16.9	15	27.8	16.9	10	14.0%	-3.30 [-16.82, 10.22]
DRACUP2007	35.7	23.7	86	43.2	27.3	87	24.3%	-7.50 [-15.12, 0.12]
NILSSON 2008	22	12	40	23	20	40	25.2%	-1.00 [-8.23, 6.23]
SARULLO 2006	35.5	1.9	30	31.2	2.6	30	36.6%	4.30 [3.15, 5.45]
Total (95% CI)			**171**			**167**	**100.0%**	**-0.96 [-7.36, 5.44]**

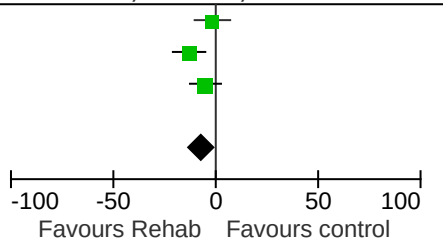
Heterogeneity: Tau² = 28.80; Chi² = 11.92, df = 3 (P = 0.008); I² = 75%
Test for overall effect: Z = 0.29 (P = 0.77)



Forest plot of comparison: 1 rehab vs. standard care, outcome: 1.8 Mean QoL score 5 year follow-up.

Study or Subgroup	Rehab Mean	Rehab SD	Rehab Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
AUSTIN 2008 FU	35.5	21.7	57	37.1	24.9	55	30.8%	-1.60 [-10.26, 7.06]
BELARDINELLI 1999 (OG)	39	20	50	52	20	49	33.9%	-13.00 [-20.88, -5.12]
NILSSON 2008 FU	23	14	40	28	20	40	35.3%	-5.00 [-12.57, 2.57]
Total (95% CI)			**147**			**144**	**100.0%**	**-6.67 [-13.20, -0.14]**

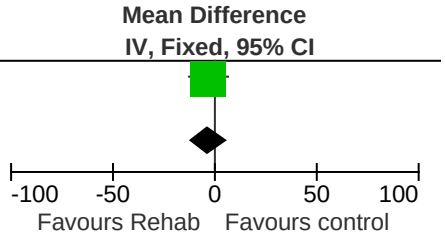
Heterogeneity: Tau² = 16.58; Chi² = 3.98, df = 2 (P = 0.14); I² = 50%
Test for overall effect: Z = 2.00 (P = 0.05)



Forest plot of comparison: 1 rehab vs. standard care, outcome: 1.9 Mean change in QoL score up to 3 months.

Study or Subgroup	Rehab Mean	Rehab SD	Rehab Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
COLLINS 2004	-3.2	13.7	15	-0.1	13.4	16	100.0%	-3.10 [-12.65, 6.45]
Total (95% CI)			**15**			**16**	**100.0%**	**-3.10 [-12.65, 6.45]**

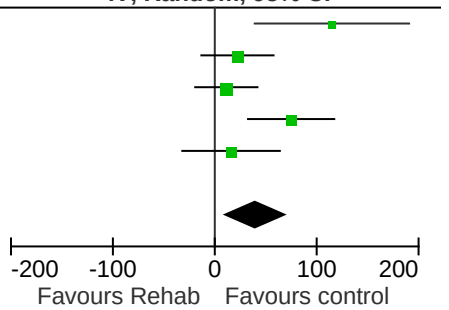
Heterogeneity: Not applicable
Test for overall effect: Z = 0.64 (P = 0.52)



Forest plot of comparison: 1 rehab vs. standard care, outcome: 1.10 Mean 6MWT up to 6 months.

Study or Subgroup	Rehab Mean	Rehab SD	Rehab Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
CIDER 2003	450	94	15	335	95	10	11.5%	115.00 [39.30, 190.70]
CORVERA 2004	407.55	82.97	42	385.24	77.57	37	23.4%	22.31 [-13.11, 57.73]
DRACUP2007	433.7	108	86	422.3	96.7	87	25.3%	11.40 [-19.16, 41.96]
NILSSON 2008	515	93	40	440	100	40	20.8%	75.00 [32.68, 117.32]
WITHAM 2005	262	110	41	246	111	41	18.9%	16.00 [-31.83, 63.83]
Total (95% CI)			**224**			**215**	**100.0%**	**40.04 [8.12, 71.95]**

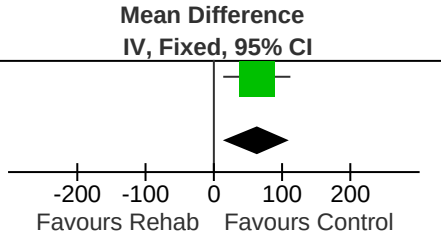
Heterogeneity: $Tau^2 = 805.70$; $Chi^2 = 11.04$, df = 4 (P = 0.03); $I^2 = 64\%$
Test for overall effect: Z = 2.46 (P = 0.01)



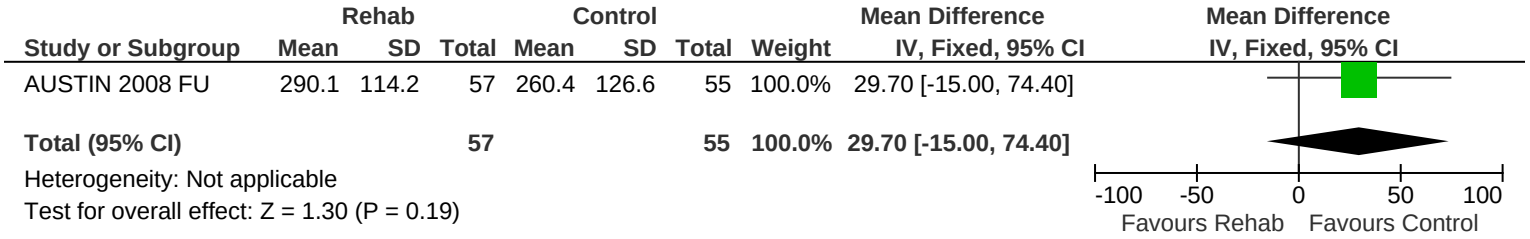
Forest plot of comparison: 1 rehab vs. standard care, outcome: 1.11 Mean 6MWT up to 12 months.

Study or Subgroup	Rehab Mean	Rehab SD	Rehab Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
NILSSON 2008 FU	498	100	40	435	117	40	100.0%	63.00 [15.30, 110.70]
Total (95% CI)			**40**			**40**	**100.0%**	**63.00 [15.30, 110.70]**

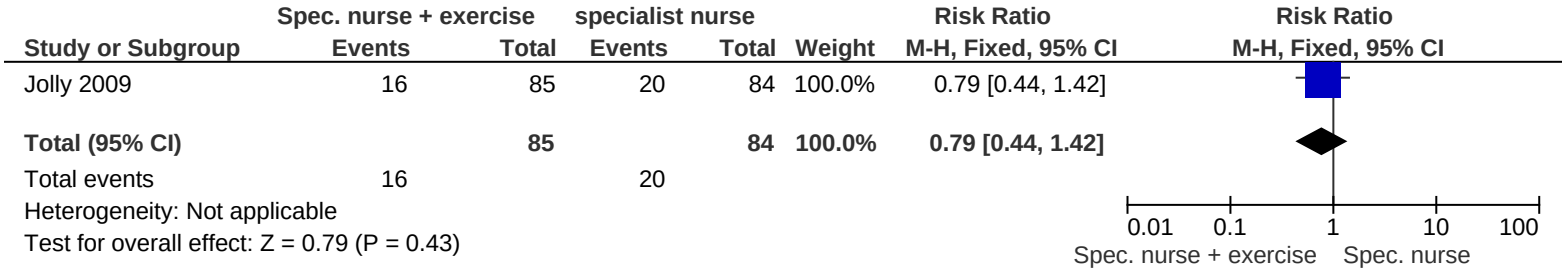
Heterogeneity: Not applicable
Test for overall effect: Z = 2.59 (P = 0.010)



Forest plot of comparison: 1 rehab vs. standard care, outcome: 1.12 Mean 6MWT 5 year follow-up.



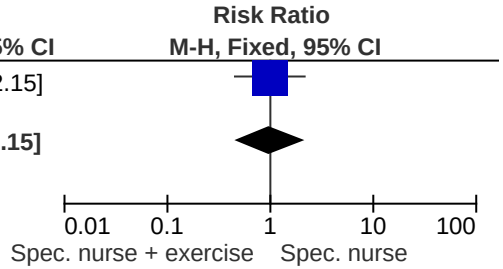
Specialist nurse care plus exercise compared with specialist nurse care only



Forest plot of comparison: 1 Specialist care plus exercise vs specialist care, outcome: 1.1 All cause hospitalisation.

Study or Subgroup	Spec. nurse + exercise Events	Total	specialist nurse Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jolly 2009	11	85	11	84	100.0%	0.99 [0.45, 2.15]
Total (95% CI)		**85**		**84**	**100.0%**	**0.99 [0.45, 2.15]**
Total events	11		11			

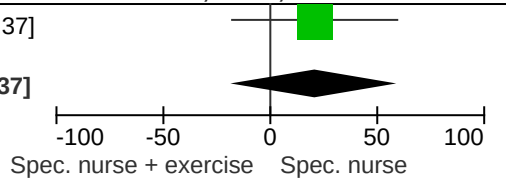
Heterogeneity: Not applicable
Test for overall effect: Z = 0.03 (P = 0.98)



Forest plot of comparison: 1 Specialist care plus exercise vs specialist care, outcome: 1.2 Hospitalisation (cardiac).

Study or Subgroup	Spec. nurse + exercise Mean	SD	Total	specialist nurse Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Jolly 2009	226.95	120.3	85	206.18	135.2	84	100.0%	20.77 [-17.83, 59.37]
Total (95% CI)			**85**			**84**	**100.0%**	**20.77 [-17.83, 59.37]**

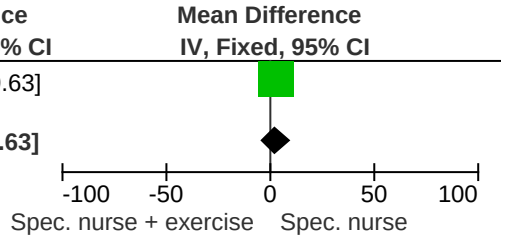
Heterogeneity: Not applicable
Test for overall effect: Z = 1.05 (P = 0.29)



Forest plot of comparison: 1 Specialist care plus exercise vs specialist care, outcome: 1.3 ISWT/m.

Study or Subgroup	Spec. nurse + exercise Mean	SD	Total	specialist nurse Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Jolly 2009	37.61	20.97	85	34.91	24.8	84	100.0%	2.70 [-4.23, 9.63]
Total (95% CI)			**85**			**84**	**100.0%**	**2.70 [-4.23, 9.63]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.76 (P = 0.44)



Forest plot of comparison: 1 Specialist care plus exercise vs specialist care, outcome: 1.4 MLHF.

Appendix G Health Economics Evidence Tables

Diagnostics questions

J. Mant, J. A. Doust, A. K. Roalfe, and P. Barton. Systematic Review and Individual Patient Data meta-Analysis of Diagnosis of Heart Failure, with Modelling of Implications of Different Diagnostic strategies in Primary Care. 2009.				
Study details	**Population & interventions**	**Health outcomes**	**Costs**	**Cost effectiveness**
Economic analysis: Cost-effectiveness analysis **Study design:** Decision-analytic model (based on a meta-analysis) **WTP threshold calculation** Calculation of WTP for interpretation of results from a UK perspective (1) WTP calculation not considering QALY gained • Considered the cost associated to misdiagnosed cases (diagnosed 6 months later): o additional hospitalisation cost o drug cost avoided • Calculated WTP value = £270 per misdiagnosed case	**Population:** Patients with suspected chronic heart failure in primary care Patients were stratified in sub-group by MICE score **Intervention 1:** 'Do nothing' (no more test post sign and symptom evaluation using MICE scoring system) **Intervention 2:** 'BNP' (post sign and symptom, perform BNP and	**Health outcomes incorporated:** Sensitivity and specificity of BNP at specific cut-points (Tables 20 to 24 in publication) Sensibility of echo + specialist assessment: 100% Survival raise as result of early diagnosis • 0.163 (3 years) • 0.247 (5 years) • 0.390 (10 years) QALY gained as result of early diagnosis • 0.106 (3 years) • 0.247 (5 years) • 0.390 (10 years) **Probabilities within the**	**Cost components incorporated:** Cost for echo: £100 per investigation Cost for BNP: £15 per investigation **Costs used to calculate WTP for misdiagnosed cases:** • Hospitalisation cost (additional for late diagnosis) • Drug cost (additional for early diagnosis) **Cost used for WTP calculation** (1) Avoided cost on treatment for late diagnosis (6-month delay): • Beta-blocker (carvedilol) £12.30 per month (for 34% of patients) = £25 per	**ICER calculation (all scenarios):** ICERs were calculated in term of cost per additional case found. ICERs were calculated by subgroups of patients (according to MICE score). 3 ICERs were calculated per subgroups ('do nothing' versus 'BNP', 'BNP' versus 'echo', and 'do nothing' versus 'echo'). **Base case analysis:** Cost-effectiveness analysis Reported cost per additional case found 6-month time horizon WTP of £270 (not considering QALY gained) Results (Table 20 in publication): • MICE score 0,2,3: No test • MICE score 5,6,7,8: BNP then echo • MICE score 9,10,11: Echo BNP threshold for referring to echo • MICE score 5 – refer if BNP > 149pg/ml • MICE score 6 – refer if BNP > 117pg/ml

(represents cost incurred for a 6-month delay in diagnosis) (2) WTP calculation considering QALY gained (using NICE threshold of £20k per QALY gained) • QALY gain * £20k (NICE threshold) + £270 (see above) o £2,370 to detect a case (3-year time horizon) o £3,470 (5 years) o £5,370 (10 years) **Perspective:** UK NHS Primary care **Time horizon:** 6 months (base-case analysis) 3 years (secondary analysis) 5, 10 years (sensitivity analysis) **Discounting:** No discounting for cost (there is no cost incurred after 1 year). QALYs after 1 year were not discounted.	then echo depending upon the result of the BNP test, using decision cut-points for BNP) **Intervention 3:** 'Echo' (post sign and symptom, proceed straight to echo)	**analysis** • 6-month probability of hospital admission if patient treated (0.413); if patient untreated (0.645) • Probability for a patient of having CHF according to MICE score (Tables 20 to 24 in publication)	patient • ACE inhibitor (lisinopril) £2.41 per month (69% of patients) = £10 per patient • ARB (losartan) £18.09 per month (16% of patients) = £17 per patient (2) Additional hospitalisation cost (for late diagnosis) • 23% extra admissions within 6 months • £1400 per admission (NHS reference cost [18 Sept 2007]) • £320 ('cost per patient' – 0.23*£1400) **Sensitivity analysis** • Cost of echo (£50 - £150) • Cost of BNP testing (£10 - £20) **Currency & cost year:** GBP, year not specified (probably 2007)	• MICE score 7 – refer if BNP > 92pg/ml • MICE score 8 – refer if BNP > 72pg/ml **Secondary analysis** Cost-effectiveness analysis Reported cost per additional case found 3-year time horizon WTP of £2,370 (considering QALY gained) Results (Table 21 in publication): • MICE score 0: BNP then echo (refer if BNP > 38pg/ml • MICE score 5,6,7,8, 9,10,11: Echo **Sensitivity analysis** 1- Base case analysis a) Varying cost of investigation ('extreme cases' - low cost echo and expensive BNP / high cost echo and cheap BNP) i) Cost of echo £50; cost of BNP £20 Results (Table 22 in publication): • MICE score 0,2: No test • MICE score 3,5,6,7,8, 9,10,11: Echo ii) Cost of echo £150; cost of BNP £10 Results (Table 23 in publication): • MICE score 0,2,3: No test • MICE score 5,6,7,8, 9,10,11: BNP then echo • MICE score 13,14,16: Echo BNP thresholds for referring to echo • MICE score 5 – refer if BNP > 313pg/ml • MICE score 6 – refer if BNP > 247pg/ml

				• MICE score 7 – refer if BNP > 194pg/ml • MICE score 8 – refer if BNP > 153pg/ml • MICE score 9 – refer if BNP > 120pg/ml • MICE score 10 – refer if BNP > 95pg/ml • MICE score 11 – refer if BNP > 75pg/ml 2- Secondary analysis a) Cost of echo £150; cost of BNP £10; 5-year time horizon; WTP £2,370 Results (Table 24 in publication) • MICE score 0,2,3: BNP then echo (cut-off 58, 36, 28 pg/ml) • MICE score 5,6,...: Echo b) Cost of echo £150; cost of BNP £10; 5-year time horizon; WTP £3,470 Results (Table 24 in publication) • MICE score 0,2: BNP then echo (cut-off 58, 36, pg/ml) • MICE score 3,5,6,...: Echo c)) Cost of echo £150; cost of BNP £10; 10-year time horizon; WTP £5,370 Results (Table 24 in publication) • MICE score 0: BNP then echo (cut-off 58 pg/ml) • MICE score 2,3,5,6,...: Echo 3- Use NT-proBNP instead of BNP in the base-case analysis Do not affect results
Data sources				
Health outcomes:				

Specificity and sensibility estimates were taken from the meta-analysis presented in the HTA

Life-year gain:
Survival curves were generated using the Framingham study[1]; risk ratios for effect on survival of ACEi and BB from meta-analyses[2, 3].

[1] Ho KKL, Anderson KM, Kannel WB et al. Survival after the onset of congestive heart failure in Framingham Heart Study Subjects. Circulation 1993; 88:.107-15
[2] Shibata MC, Flather MD, Wang D. Systematic review of the impact of beta blockers on mortality and hospital admissions in heart failure. European Journal of Heart Failure 2001; 3: 351-357
[3] Flather MD, Yusuf S, Kober L et al for the ACE-Inhibitor Myocardial Infarction Collaborative Group. Long term ACE-inhibitor therapy in patients with heart failure or left ventricular dysfunction: a systematic overview of data from individual patients. Lancet 2000; 355:1575-81

Quality-of-life weights:
Calvert 2005 = EQ-5D score of 0.6 for patients with significant heart failure; assume 0.65 for all patients with CHF for use in the analysis

Cost sources:
Drug cost: BNF online accessed 18 September 2007
Intervention cost (echo and BNP): Not referred
Hospitalisation cost: NHS reference cost, assessed 18 September 2007

Comments

Source of funding:
Not reported

Limitations:
It was assumed that if a patient with CHF was misdiagnosed, then the diagnosis would be made after an average delay of 6 months. There is no data on which to base this assumption.

Waiting lists for echo were not considered (the model assumed there was sufficient capacity). A limited supply of echo and a delay for the investigation could affect the results of the analysis.

Life-year gain estimates used to calculate QALYs (using a fixed utility score) have not been discounted after one year.

Overall quality*: *Minor limitations*	**Overall applicability**: *Directly applicable***	

Abbreviations: ICER = incremental cost-effectiveness ratio; Echo = echocardiography; WTP = willingness to pay; MICE = Male (2pts) / Infarction (6pts) / Crepitations (5pts) / Edema (3pts); QALY = cost per quality-adjusted life-years; NHS = National Health Service.
*Very serious limitations/Potentially serious limitations/Minor limitations; **Directly applicable/Partially applicable/Not applicable

Beta-blockers

G. Yao, N. Freemantle, M. Flather, P. Tharmanathan, A. Coats, Wilson PA Poole, and Investigators SENIORS. Long-term cost-effectiveness analysis of nebivolol compared with standard care in elderly patients with heart failure: an individual patient-based simulation model. Pharmacoeconomics 26 (10):879-889, 2008.				
Study details	**Population & interventions**	**Health outcomes**	**Costs**	**Cost effectiveness**
Economic analysis: Cost-effectiveness analysis, reporting cost per QALY gained **Study design:** - Individual patient-simulation model based on a Markov modelling framework - Based on the SENIORS trial **Perspective:** UK NHS **Time horizon:** Lifetime horizon **Discounting:** Future costs and	**Population:** - Elderly patients (≥ 70 years) with heart failure and reduced LVEF - N total = 2128; 1067 in nebivolol group; 1061 in standard care group. - Mean age of 76.1 years (SD 4.8) in nebivolol group; 76.1 years (SD 4.6) in standard care group - 82.1% on ACEi - 6.6% on ARB - 27.6% on aldosterone antagonist - 39.3 on glycosides - 42.2% on aspirin - 82.1% on diuretics **Intervention 1:** - Nebivolol + standard	**Health outcomes:** **(1) Probabilities incorporated to the model:** - Hospitalisation for cardiovascular event (SENIORS) - Cardiac death (SENIORS) - Sudden death (SENIORS) - Death due to other causes (derived from UK population based on age- and sex-specific mortality excluding cardiac related deaths; sex based on SENIORS; assume every patient started at 70 years old) **(2) Health-Utility scores** - For each NYHA class - Based on reported	**Cost components incorporated:** - Drugs o Nebivolol (based on maximum dosage that each patient maintained during SENIOR trial; 1.25mg/day in 7.2%; 2.5 in 7.6%; 5 in 13.3%; 10 in 71.9%) o Other relevant cardiac drugs used (based on SENIOR trial) - GP visits (assumptions) o Nebivolol group: each month for 3 months, then every 3 months o Standard care group: every 3 months - Outpatient specialist visits (assumption) o Cardiovascular hospitalisations were followed by 2 outpatient attendances - Cardiovascular hospitalisations (SENIOR) - Subgroups for cardiovascular	**Cost-effectiveness result (ICER):** - €3066 per life-year gained - €3926 per QALY gained **Sensitivity analysis:** One-way sensitivity analysis: - Age at start treatment (60, 65, 75, 80, instead of 70 for the base-case analysis) - Discount rate: 0% and 5% (instead of 3.5%) - Number of outpatient visits after cardiovascular hospitalisations: 3 instead of 2. Probabilistic sensitivity analysis: - Key values were varied using their respective distribution **Sensitivity analysis results (one-way):** - Age at start of treatment: ICERs (per QALY gained) varied from €3348 for 60 y.o. to €5291 for 80 y.o. - Discount rate: €4187 and €3657 per QALY

benefits were discounted at 3.5% per annum.	care - Nebivolol was up-titrated during a period of 16 weeks: initial dosage of 1.25mg once daily, if tolerated increase to 2.5 and then 5mg every 1-2 weeks, reaching a target of 10mg once daily over a maximum of 16 weeks. **Intervention 2:** Placebo + standard care	results of CARE-HF trial - NYHA class I, II, III, IV: respectively 0.815, 0.72, 0.59, 0.508 - When a patient was hospitalised, a disutility score of -0.1 was applied	hospitalisations for o Worsening heart failure (captured the cost of treatment for severe adverse events) o MI o Stroke o Rates of these events from SENIOR - Cardiovascular deaths (involved hospital stay cost and intravenous drug cost) **Currency & cost year:** - Euro 2006 - Exchange rate used: £1 = €1.478	gained for 0% and 5% respectively - Number of outpatient visits after cardiovascular hospitalisations (3 instead of 2 in the base-case analysis): €3923 cost per QALY gained
Data sources				
Health outcomes: See 'Health Outcomes' section **Cost sources:** - Drug cost: *BNF No. 52* - GP and outpatient visit cost: *Costs and Health Social Care 2006* - Cardiovascular hospitalisation cost: *National schedule of reference cost 2006*				
Comments				
Source of funding: Menarini Research SpA **Limitations:** - Several potentially important economic outcomes were not collected in SENIOR and assumptions where necessary (GP and outpatient attendances) - Quality of life estimates were not collected in SENIOR and data used were from another source (CARE-HF trial) - Same cost of hospitalisation used regardless of severity of heart failure				
Overall quality*: *Minor limitations*	**Overall applicability**: *Directly applicable***			

Abbreviations: ICER = incremental cost-effectiveness ratio; NHS = National Health Service; BB = Beta-blockers; ACEi = Angiotensin-converting enzyme inhibitors; MI = Myocardial Infarction; SD = Standard Deviation; NYHA = New York Heart Association Classification; SENIORS = Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure; LVEF = Left Ventricular Ejection Fraction; CARE-HF = Cardiac Resynchronisation – Heart Failure trial.
*Very serious limitations/Potentially serious limitations/Minor limitations; **Directly applicable/Partially applicable/Not applicable

Aldosterone antagonists

<table>
<tr><th colspan="5">M. Duerden and M. Tabberer. A budget impact model for a drug in heart failure: Eplerenone. British Journal of Cardiology 15 (2):101-105, 2008.</th></tr>
<tr><th>Study details</th><th>Population & interventions</th><th>Health outcomes</th><th>Costs</th><th>Cost effectiveness</th></tr>
<tr>
<td>Economic analysis:
- Cost impact analysis
- Cost effectiveness analysis

Study design:
- Base-case cohort (no eplerenone): resource use + cost and survival from UK-based statistical data
- Treatment cohort (eplerenone): difference in resource and survival based on the EPHESUS trial

Perspective:
UK NHS

Time horizon:
3 years

Discounting:
Future costs and benefits</td>
<td>Population:
Patients with acute myocardial infarction (MI) complicated by left ventricular dysfunction and heart failure

Intervention 1:
Eplerenone + optimal medical treatment (including ACEi and BB)

Intervention 2:
Placebo + optimal medical treatment</td>
<td>Health outcomes incorporated:
(1) Base-case cohort
- Incidence of hospitalised MI: 433/250,000 in England; 524/250,000 in Scotland (from population data from the ‘Office of National statistic and NHS data’ in England [2005-2006] and Scotland [2006])
- Cost and hospital length of stay for MI and heart failure patients (from England 2005-2006 NHS reference cost database)
- 20% of hospitalised MI patient shows signs of heart failure (NICE); 87 patients in England (7 per month)
- Survival probabilities were</td>
<td>Cost components incorporated:
- Hospitalisation cost (£1,492 per bed day; from England 2005-2006 NHS reference cost database)
- Eplerenone cost (£555 per annum; from Haymarket Publishing, eMIMs)

Currency & cost year:
2006 GBP</td>
<td>Cost-effectiveness result (ICER):
£6,730 per life year saved

Cost-impact analysis result:
In a primary care trust with a population of 250,000, eplerenone treatment results in a reduction of:
- 46 bed days for re-hospitalisations due to heart failure (£1,469 per bed day) = £67,574 (as reported in the abstract)
- 47 bed days for re-hospitalisations due to heart failure (£1,492 per bed day) = £70,124 (as reported in the text)

Sensitivity analysis:
Base-case cohort: increase mortality rate by 10%, 15%, and 20%

Sensitivity analysis results :

<table>
<tr><th colspan="4">Sensitivity analysis for year 3</th></tr>
<tr><th>Reduction in mortality over</th><th>10%</th><th>15%</th><th>20%</th></tr>
</table>
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<tr>
<td>were discounted at 3.5% per annum.</td>
<td></td>
<td>derived from an epidemiologic study of all-cause heart failure carried out in West London up to 18 months (Cowie 2000); extrapolated to 36 months. The extrapolation predicted a 48% 3-year survival.
(2) Treatment cohort:
- Reduction in overall mortality taken from the EPHESUS study (up to 16 months)
- Post EPHESUS study mortality: survival curve runs parallel to base-case cohort mortality curve up to 36 months.
- Rate of hospitalisation from the EPHESUS study (rates of re-admission and length of stay)</td>
<td></td>
<td>
<table>
<tr><td>baseline</td><td></td><td></td><td></td></tr>
<tr><td>Cost per life-years saved</td><td>£2,771</td><td>£2,180</td><td>£1,812</td></tr>
<tr><td>Bed days avoided with eplerenone</td><td>32</td><td>25</td><td>18</td></tr>
<tr><td>Cost per bed day avoided (total cost avoided)</td><td>£2,359 (£75,488)</td><td>£3,177 (£79,425)</td><td>£4,634 (£83,412)</td></tr>
</table>
</td>
</tr>
<tr><td colspan="5">Data sources</td></tr>
<tr><td colspan="5">Health outcomes:
Base-case cohort
- Incidence of hospitalised MI: Population data from the 'Office of National statistic and NHS data' in England [2005-2006] and Scotland [2006].
- Probability of hospitalised MI patients with heart failure: NICE. Costing report NICE clinical guideline 48. MI: secondary prevention. London, May 2007.
- Survival probabilities: Cowie MR, Wood DA, Coasts AJ et al. Survival of patients with a new diagnosis of heart failure: a population based study. Heart 2000; 83:505-10.
Treatment cohort
- EPHESUS study

Cost sources:</td></tr>
</table>

- Hospitalisation cost: England 2005-2006 NHS reference cost database;
- Eplerenone cost: Haymarket Publishing, eMIMs.
- Difference in resource use and survival for the treatment cohort based on the EPHESUS trial.

Comments

Source of funding:
Pfizer Ltd

Limitations:
- The analysis assumed a 100% adherence and compliance for patients on eplerenone treatment.
- Extrapolation of survival
- Short time horizon (3 years)
- Difference in survival and resource use from the EPHESUS trial, a multi-centre and multi-national study. Result applied to a UK context.

Overall quality*: *Potentially serious limitations*	Overall applicability**: *Directly applicable*	

Abbreviations: ICER = incremental cost-effectiveness ratio; NHS = National Health Service; BB = Beta-blockers; ACEi = Angiotensin-converting enzyme inhibitors; EPHESUS = Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; MI = Myocardial Infarction.
*Very serious limitations/Potentially serious limitations/Minor limitations; **Directly applicable/Partially applicable/Not applicable

L. Tilson, B. McGowan, M. Ryan, and M. Barry. Cost-effectiveness of spironolactone in patients with severe heart failure. *Irish Journal of Medical Science* 172 (2):70-72, 2003.

Study details	Population & interventions	Health outcomes	Costs	Cost effectiveness
Economic analysis: - Cost effectiveness analysis - Reporting cost per life-year gained **Study design:** - Based on the RALES study - Developed using a Markov Model o 3 health states: (1) severe	**Population:** - Patients with severe chronic heart failure - NYHA class III & IV and LVEF ≤35 - Mean age of 65 years **Intervention 1:** Spironolactone added to optimal medical	**Health outcomes incorporated:** - 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 difference in probabilities of death and	**Cost components incorporated:** - Spironolactone treatment cost (*Irish Monthly Index of Medical Specialties*, July 2002) - Hospitalisation cost for severe heart failure (McGowan B. et al.	**Cost-effectiveness result:** Analysis: Base-case analysis (pDeath = 0.18; pHosp = 0.25; 1 additional outpatient visit for spironolactone cohort; hosp cost = €3,019) Result: €466/LYG

CHF; (2) severe CHF + hospitalisation; (3) death o 1-year period before possible transition from one state to another. **Perspective:** Irish public healthcare system **Time horizon:** 10 years **Discounting:** Future costs and outcomes were discounted at 5% and 1.5% respectively.	management **Intervention 2:** Optimal medical management (might include diuretics, ACEi, digoxin, BB, or a combination of these)	hospitalisation for the treatment cohort were taken from RALES - Assumed no difference in death and hospitalisation rates between cohorts after the 2-year mean duration of RALES	Cost of treating heart failure in an Irish teaching hospital. *Ir Med Sci* 2001; 169:241-44) - Hospital outpatient visit cost (McGowan B. The clinical and economic aspects of the present management of heart failure in an Irish teaching hospital. MSc thesis, Trinity College Dublin 2001). **Currency & cost year:** Euro 2002	Two-way sensitivity analysis – variation of probabilities of death (0.16, 0.21) and hospitalisation (0.21, 0.29)	from € 309/LYG to €624/LYG
				One-way sensitivity analysis – additional outpatient visit required to initiate medication for spironolactone group (1, 2, 4)	from €466/LYG to €1,136/LYG
				One-way sensitivity analysis – cost of hospitalisation varied (€1,060; €9,319)	from €728/LYG to spironolactone cohort dominates placebo cohort (adding spironolactone to standard treatment is more effective and less costly)
Data sources					
Health outcomes: See above **Cost sources:** See above					
Comments					
Source of funding:					

NR **Limitations:** - The study did not incorporated a quality of life measure - The mean age of the population of patients in RALES study was lower than the Irish population of patient with chronic heart failure (65 vs 76 years) - Some cost data were taken from published studies and not from Government sources, which can affect their relevance
Overall quality*: *Potentially serious limitations* **Overall applicability**: *Partially applicable***

Abbreviations: RALES = Randomised Aldactone Evaluation Study; NYHA = New York Heart Association Classification; CHF = Chronic Heart Failure; BB = Beta-blockers; ACEi = Angiotensin-converting enzyme inhibitors.

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

Isosorbide/hydralazine combination

D. C. Angus, Zwirble WT Linde, S. W. Tam, J. K. Ghali, M. L. Sabolinski, V. G. Villagra, W. C. Winkelmayer, M. Worcel, and American Heart Failure Trial African. Cost-effectiveness of fixed-dose combination of isosorbide dinitrate and hydralazine therapy for blacks with heart failure. Circulation 112 (24):3745-3753, 2005.				
Study details	**Population & interventions**	**Health outcomes**	**Costs**	**Cost effectiveness**
Economic analysis: Cost-effectiveness analysis **Study design:** Decision-analytic model (based on the A-HeFT study) **Perspective:** - US perspective - Included direct healthcare costs and excluded indirect and non-healthcare costs **Time horizon:** - 18 months (A-HeFT follow-	**Population:** - Black people with moderate to severe heart failure - Mean age: 56.8 years - 100 % black people - 40% women - 94.9% NYHA class III heart failure - 93% were on ACEi or ARB - 87% were on BB - Treatment N=518; control N=532 - Baseline characteristics	**Health outcomes incorporated:** Data from A-HeFT RCT (18-month follow-up): - Mortality (treatment vs placebo): 6.2% vs 10.2%; p=0.016 - Survival time: 403 vs 380 days; p=0.01 **Post trial survival:** - Use 5-year follow-up data for NYHA class III patients reported by Bardy 2005 - Assumed that survival	**Cost components incorporated:** - Hospitalisation (including physician cost); - ER visits; - Unscheduled physician visits; - Scheduled physician visits; - ISDN/HYD therapy; - Concomitant medication; - Other cares.	**ICER:** Reported cost per life-year gained. Results reported using 2 total cost estimates: - Heart failure-related cost; - All healthcare-related cost **Cost-effectiveness within the A-HeFT study period (18 months):** - ISDN/HYD therapy is dominant (improved survival and saved cost) using both heart failure-related cost ($9144-$8611=$553) and all healthcare-related cost ($19728-$17998=$1730). Bootstrap simulation sampling :

up) - Lifetime **Discounting:** Future costs and survival were discounted at 3% per annum.	were similar across arms **Intervention 1:** Standard therapy (BB, ACEi or ARB, aldosterone antagonist, digoxin and diuretics as appropriate) **Intervention 2:** Standard therapy + ISDN/HYD therapy (20mg / 37.5mg); starting with 1 tablet 3 times daily and titrating to 2 tablets 3 times daily as tolerated. Average dose: 4.2 tablets per day. 68% took full doses of 6 tablets per day at some time. Failure of adherence (treatment vs placebo): 3.2% vs 10.2%; p=0.016. Mean follow-up: 12.8 months.	curves of treatment and control arms decayed at the same rate. - Zero survival at 10 years.	Resource use as collected from the A-HeFT trial. **Currency & cost year:** 2004 US dollars **Resource use results from A-HeFT:** - 43% of hospitalisations were related to heart failure - 30% fewer heart failure-related hospitalisations for treatment group - One-day reduction in the average LOS for each heart failure-related hospitalisations for the treatment group - All-cause hospitalisations, unscheduled office visits, ER visits, and use of concomitant medications: not significantly different between groups - All-cause hospitalisation LOS shorter for treatment group	- Heart-failure related cost : 49% dominant; 66% better than $10 000/life-year gained - All health costs : 71% dominant; 82% better than $10 000/life-year gained **Lifetime horizon:** - Using the assumption that there were no additional benefits of ISDN/HYD therapy beyond the trial period (survival and resource use – except drug cost for treatment arm); ICER = $41 800 per life-year gained (hearth failure-related costs); $44 400 (all medical costs) - When considering that ISDN/HYD therapy had benefit beyond the trial, considering one additional year of effect, the lifetime ICER was estimated to be $22 900 per life-year gained (hearth failure-related cost); $32 900 (all medical costs). **Sensitivity analysis:** Were varied: - Hospital cost and ISDN/HYD therapy cost ± 50%; - Cost of concomitant medication, unscheduled office visits, ER visits, and other usual medical care from +100% to -50%. - Other hospitalisation costs were used. **Sensitivity analysis results :** The incremental cost was most sensitive to hospital cost and treatment cost (ISDN/HYD therapy) variations.

				Using an alternative hospitalisation cost (Medicare heart failure-related hospitalisation cost unadjusted for race, gender, and LOS [adjusted for the main analysis]) : - ISDN/HYD therapy no longer dominant - Using hearth failure-related costs; ICER = $10 335 per life-year gained; 24% of simulations dominant; 49% of simulations less than $10 000/life-year gain - Using all medical costs; ICER = $1546 per life-year gained; 46% of simulations dominant; 66% of simulations less than $10 000/life-year gained
Data sources				
Health outcomes: - First 18-month survival from the A-HeFT study. - Survival curves post-trial: was used 5-year follow-up data for NYHA class III patients reported by Bardy 2005[1]. [1] Gust H. Bardy, M.D., Kerry L. Lee, Ph.D., Daniel B. Mark, M.D., Jeanne E. Poole, M.D., Douglas L. Packer, M.D., Robin Boineau, M.D., Michael Domanski, M.D., Charles Troutman, R.N., Jill Anderson, R.N., George Johnson, B.S.E.E., Steven E. McNulty, M.S., Nancy Clapp-Channing, R.N., M.P.H., Linda D. Davidson-Ray, M.A., Elizabeth S. Fraulo, R.N., Daniel P. Fishbein, M.D., Richard M. Luceri, M.D., John H. Ip, M.D., for the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators.Amiodarone or an Implantable Cardioverter–Defibrillator for Congestive Heart Failure. N Engl J Med 2005;352:225-237. **Cost sources:** - Hospitalisation cost: 2003 Medicare Hospital Discharge Database. Washington, DC. Data adjusted to years 2004. Increased this cost by 17% to account for physician fees (published method). - Cost for ER and unscheduled physician visits; cost for scheduled physician visits; and cost for other cares: Medicare Utilisation for Part B (supplementary Medical Insurance SMI). Baltimore, Md: Centres for Medicare and Medicaid Services; 2004. - Concomitant medication: 2004 Red book. - ISDN/HYD therapy: Manufacturer's (NitroMed Inc) announced price.				
Comments				

Source of funding: NitroMed Inc **Limitations:** This study did not use QALYs as health outcome (assessed in A-HeFT trial using the 'Minnesota Living With Heart Failure' survey, for which no validated approach to generate utility scores exist). To note that patients in the treatment arm reported better quality of life.		
Overall quality*: *Minor limitations*	**Overall applicability**: *Partially applicable***	

Abbreviations: ICER = incremental cost-effectiveness ratio; NHS = National Health Service; A-HeFT = African-American Heart Failure Trial; ISDN/HYD = Fixed-dose combination of isosorbide dinitrate and hydralazine; BB = Beta-blockers; ACEi = Angiotensin-converting enzyme inhibitors; ARB = Angiotensin receptor blockers; RCT = Randomised controlled trial; LOS = Length of stay; NYHA = New York Heart Association.

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

Angiotensin-II receptor antagonist

J. J. McMurray, F. L. Andersson, S. Stewart, K. Svensson, A. C. Solal, R. Dietz, J. Vanhaecke, D. J. van Veldhuisen, J. Ostergren, C. B. Granger, S. Yusuf, M. A. Pfeffer, and K. Swedberg. Resource utilization and costs in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. European Heart Journal 27 (12):1447-1458, 2006.				
Study details	**Population & interventions**	**Health outcomes**	**Costs**	**Cost effectiveness**
Economic analysis: - Cost-consequence analysis for CHARM overall, alternative, added, and preserved; - Cost-effectiveness analysis for patients with LVEF < 0.40 (alternative, added, and the 2 pooled together); reporting cost per life-year gained.	**Population:** - Patients with NYHA class II-IV HF - CHARM-Added: patients with LVEF < 0.40 on ACEi - CHARM-Alternative: patients with LVEF < 0.40 intolerant of ACEi - CHARM-Preserved: patients with LVEF > 0.40 **Intervention 1:**	**Health outcomes:** - The primary outcome of the CHARM programme was a composite of cardiovascular death or hospital admission for worsening HF (hazard ratio): CHARM-Added: 0.85 (95% CI 0.75-0.96, P=0.011); CHARM-Alternative: 0.77 (0.67-0.89, P=0.0004; CHARM-	**Cost components incorporated:** - Drug treatment (for the candesartan arm, considering 4 GP visits and 4 biochemistry tests for drug initiation and up-titration) - Hospital admission – for cardiovascular reason and not (number of admission, length of stay, ward type) – Using 2 approaches: (1) DRG	**Cost-effectiveness and cost-consequence results:** See tables below **Sensitivity analysis:** - Increased the length of non-cardiovascular admissions of 30% - for the potential additional cost of certain adverse events (renal impairment) in the candesartan group - Adding cost of 1 GP visit for treatment related adverse events in the candesartan group (renal impairment and hypotension)

Study design: - Based on the CHARM programme - Within-trial cost-consequence and cost-effectiveness analyses of CHARM **Perspective:** UK NHS; France; Germany **Time horizon:** Within-trial analysis. Median follow-up of 41 months for CHARM-Added; 37 months for CHARM-preserved; 34 months for CHARM-Alternative; and 38 months for the overall CHARM programme. **Discounting:** Future costs and benefits were discounted at 3% per annum (3 perspectives) – 3.5% for the UK analysis in the sensitivity analysis.	Candesartan + optimal medical treatment (diuretic, digoxin, ACEi, ARB, BB spironolactone) **Intervention 2:** Placebo + optimal medical treatment Mean daily dose of candesartan was: CHARM-Added: 16.9mg; CHARM-Alternative: 16.8mg; CHARM-Preserved: 19mg.	Preserved: 0.89 (0.77-1.03, P=0.118); Overall CHARM programme: 0.84 (0.77-0.91), P<0.0001. - All-cause mortality (hazard ratio): Overall CHARM programme: 0.91 (0.83-1.00), P=0.055; Patients with LVEF < 0.40: 0.88 (0.79-0.98, P=0.018). - Clinical benefits considered for cost-consequence analyses were cardiovascular death and heart failure admissions - Clinical health outcome considered for cost-effectiveness analyses was all-cause mortality.	cost; (2) Per diem cost for hospital bed days. - Cardiovascular procedures **Currency & cost year:** - 2003-2004 local currency for UK, France, Germany.	not leading to admission - Length of hospital stay ± 20% - Use 3.5% as discount rate for the UK analysis
Data sources				
Health outcomes: CHARM programme **Cost sources:**				

- Government sources (UK, France, Germany) for all cost inputs (hospitalisation, drug treatment, cardiovascular procedures)
- In the UK: PSSRU; NHS reference cost database; and BNF.

Comments

Source of funding:
The CHARM programme was founded by AstraZeneca

Limitations:
- Within-trial time horizon
- No quality of life estimate incorporated to the analysis
- Use results from a multi-centre and multi-national study. Results applied to specific country contexts.

Overall quality*: *Potentially serious limitations* | **Overall applicability**: *Directly applicable***

Abbreviations: ICER = incremental cost-effectiveness ratio; NHS = National Health Service; BB = Beta-blockers; ACEi = Angiotensin-converting enzyme inhibitors; NYHA = New York Heart Association Classification; LVEF = Left Ventricular Ejection Fraction; CHARM = Assessment of Reduction in Mortality and morbidity; HF = Heart Failure.
*Very serious limitations/Potentially serious limitations/Minor limitations; **Directly applicable/Partially applicable/Not applicable

McMurray 2006 – Cost-consequence results

CHARM Trial	Clinical benefits vs placebo		UK		France		Germany	
	Cardiovascular death	Heart failure admission	DRG costs	Per diem costs	DRG costs	Per diem costs	DRG costs	Per diem costs
Alternative	-15%	-32%	Net increase €76±1150/year	Savings €391±2192/year	Savings €49±1475/year	Savings €428±2952/year	Net increase €117±1164/year	Savings €12±1529/year
Added	-16%	-17%	Savings €15±314/year	Savings €419±825/year	Savings €120±841/year	Savings €346±1397/year	Net increase €29±631/year	Savings €0.2±805/year
Preserved	-1% (ns)	-15%	Net increase €246±337/year	Net increase €276±787/year	Net increase €299±630/year	Net increase €321±1240/year	Net increase €327±460/year	Net increase €372±689/year
Overall	-12%	-21%	Net increase €116±352/year	Savings €122±749/year	Net increase €73±548/year	Savings €88±1045/year	Net increase €176±421/year	Net increase €153±563/year

McMurray 2006 – Cost-effectiveness results*

CHARM Trial	Life-year gained (LYG) (95%CI)	UK	France	Germany
Alternative	0.078 (0.003-0.15)	€2547 (-18171; 1059150)	Dominant**	€3881 (-17728; 1105920)
Added	0.061 (-0.002-0.12)	Dominant	Dominant	€1427 (-14479; -984755)

Reduced LVEF pooled	0.068 (0.02-0.12)	€1348 (-16225; 106600)	Dominant	€2997 (-19183; 121500)

* Unit cost in pound sterling were converted in Euro using 1 Euro = 0.67 GBP

** Dominant means that candesartan added to optimal medical management was more effective and less costly than adding placebo.

Rehabilitation

D. Georgiou, Y. Chen, S. Appadoo, R. Belardinelli, R. Greene, M. K. Parides, and S. Glied. Cost-effectiveness analysis of long-term moderate exercise training in chronic heart failure. American Journal of Cardiology 87 (8):984-988, 2001.				
Study details	**Population & interventions**	**Health outcomes**	**Costs**	**Cost effectiveness**
Economic analysis: - Cost-effectiveness analysis - Reporting cost per life-year gained **Study design:** - Decision analytic model - Based on a RCT (Belardinelli 1999) **Perspective**: - US societal perspective - Included direct medical costs (Medicare) and patient-level costs (wage lost). **Time horizon:** 10 years post RCT follow-up period (1,639 days)	**Population:** - Patients with stable chronic heart failure - NYHA class II-III HF patients between 55 and 64 years - Population of the Belardinelli 1999 trial **Intervention 1:** - Physical rehabilitation program - 14-month-long moderate exercise training (healthcare-based) - 3 sessions/week for 8 weeks, followed by 12-month maintenance program of 2 sessions/week - 1 hour session o 20 mins warm-up and	**Health outcomes:** <u>Survival</u> - Survival estimates from Belardinelli 1999 for the within-trial period (1,639 days) o Mortality rate of 18% for the treatment group (end of follow-up) o Mortality rate of 41% for the control group - 10-year post-trial period mortality rate o Same mortality rate applied for the treatment and control groups o From the *National Health and Nutrition Examination I* –	**Cost components incorporated:** <u>Cost of exercise training</u> - Equipment (bicycle); - Rented place (Hospital-based; New York City) - Trainer salary (1 trainer supervising 4 patients at a time) - Cardiopulmonary stress test cost including the physician component of interpretation and exercise prescription <u>Cost of wage lost</u> - 128 hours of wage lost per patient - Average wage of $19.60 per hour (US Census Bureau, 1998)	**Cost-effectiveness results:** $1,773 per life-year gained (Incremental cost=$3227 per patient; Incremental life-year gained in 15.5 years=1.82 per patient) **Sensitivity analysis:** The following factors were varied (95% CI): - Survival probabilities of the within-trial period: ICER from $8,274 to $1,012 per life-year gained - Survival probabilities post trial varying the ACEi survival rate adjustment: ICER from $1,698 to $1,855 per life-year gained - Within-trial rates of hospitalisation: ICER from $2,372 to 1,197 per life-year gained - Remove cost of wage lost: ICER=$395 per life-year gained

Discounting: Future costs and benefits were discounted at 3% per annum.	stretching o 40 mins on an electronically-braked cycle ergometer (bicycle) - Total of 128 sessions (128 hours) **Intervention 2:** - No physical rehabilitation program	*Epidemiologic follow-up Survey (1982 – 1986)* o Mortality rate adjusted with sex-specific rates using ratio from the Belardinelli 1999 trial o Survival rate adjusted upward by 23% considering patients taking ACEi (introduced after the national survey) (Pfeffer 1992; Garg 1995) <u>Hospitalisation rates</u> - Same rate of hospitalisation used post-trial for both cohorts (19%; assumption) - From difference of rates in Belardinelli 1999 o 10% and 29% (training and control groups)	<u>Hospitalisation cost</u> Cost of hospitalisation for patients with chronic heart failure estimated by Delea 1999. **Currency & cost year:** - 1999 US dollars	
Data sources				
Health outcomes: See above				

Cost sources: See above
Comments
Source of funding: The study was supported in part by a grant from Columbia University (New York), and by Merck & Co. Inc. **Limitations:** - The study only considered patient with NYHA class II-III HF, excluding class IV patients using the assumption that these patients are not appropriate candidates for exercise training (unable to carry out any physical activities without discomfort). - The trial was conducted predominantly on a male population; better health outcomes expected for women. - Trial conducted on a population of patients aged from 55 to 64 years. - Assumptions for post-trial hospitalisation rate (19%, same for both arms) and survival rate (same for both arms) - No quality of life measure was incorporated to the analysis: the *Minnesota Living with Heart Failure Questionnaire* estimates from Belardinelli 1999 cannot be translated in utility scores - Cost of exercise training calculated for a New York City Hospital; estimated roughly 20% more expensive than the national average - Inclusion of wage lost cost (societal perspective); using only direct medical cost is most relevant for decision-making from a public healthcare perspective.
Overall quality*: *Potentially serious limitations* **Overall applicability**: *Partially applicable***

Abbreviations: ICER = incremental cost-effectiveness ratio; ACEi = Angiotensin-converting enzyme inhibitors; NYHA = New York Heart Association Classification; RCT = Randomized controlled trial; HF = Heart Failure; CI = Coefficient Interval.

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

Serial measurement of natriuretic peptide concentration

T. Morimoto, Y. Hayashino, T. Shimbo, T. Izumi, and T. Fukui. Is B-type natriuretic peptide-guided heart failure management cost-effective? *International Journal of Cardiology* 96 (2):177-181, 2004.				
Study details	**Population & interventions**	**Health outcomes**	**Costs**	**Cost effectiveness**
Economic analysis: - Cost-effectiveness analysis	**Population:** Symptomatic CHF patients (NYHA class II-IV) aged 35-	**Health outcomes:** Utility values (symptomatic CHF patients with reduced	**Cost components incorporated:** - BNP measurement once per 3 months - Drugs for CHF (digoxin, diuretics, ACEi,	**Cost-effectiveness result (ICER):** - The base-case analysis shows that the BNP group dominates the clinical group (QALYs:

- Reporting cost per QALY gained **Study design:** - Decision analytic model based on a Markov framework (proposed by Paul 1994; for outpatient follow-up after hospitalisation for CHF) - Based on Troughton 2000 RCT and on Delea 1999 economic model (patients with heart failure) **Perspective:** US Medicare **Time horizon:** - 9 months (median of 9.5 months in Troughton 2000) - The time horizon was varied from 6 to 18 months in the sensitivity analysis **Discounting:** Future costs and	85, after hospital admission because of CHF with reduced LVEF. **Intervention 1:** Outpatient BNP-guided heart failure management once every 3 months (BNP group) (medication usage was increased to keep the BNP level below 200pmol/l) **Intervention 2:** No BNP measurement (clinical group)	LVEF) from data by Havranek 1999. **Probability estimates:** Variation between cohorts were calculated for: - Hospitalisation for CHF - Death for CHF - Frequency of ambulatory care - Dose of ACEi - Dose of diuretics - These probabilities were taken from Troughton 2000 and Delea 1999	and BB) - Dispensing fee - Ambulatory care for CHF - Inpatient care for CHF - Non-CHF related care - Cost data were all taken from Delea 1999 (converted in $2002), except the cost of BNP measurement which was derived from a price list of a University hospital in the US (University of Washington) – ref: News Flash (January 1, 2002). Department of Laboratory, University of Washington. (http://depts.washington.edu/labweb/test/nf/jan02.pdf). **Currency & cost year:** - 2002 US Dollars	0.57 vs 0.55; costs: $9577 vs $10,131) - See table below **Sensitivity analysis:** The sensitivity analysis varied all parameters: - 95% CI for utility scores - Ratios of increase in medication and ambulatory visits in BNP group were varied between 1 and 2 (base-case probabilities of 1.5 for ambulatory care and 1.4 for doses of ACEi and diuretics) - Other parameters were varied ±50% - The time horizon was varied from 6 to 18 months **Sensitivity analysis results:** - When varying the time horizon, the BNP group was dominant at 6, 9 and 12 months; ICER of $3491 per QALY gained at 15 months, and of $7787 per QALY gained at 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 cost of inpatient care for CHF. The ICER stayed cost-effective in the majority of simulations. - The BNP group ICER became not cost-effective (threshold of $50,000/QALY) when were decreased simultaneously the probability of first readmission for the clinical group and the cost of inpatient care

benefits were discounted at 3% per annum.				for CHF.

Data sources

Health outcomes:
See above

Cost sources:
See above

Comments

Source of funding:
Supported in part by a grant from the Ministry of Health, Labor and Welfare of Japan.

Limitations:
- The generalisation of these results in a UK context is questionable (this study was conducted from a US perspective, a healthcare system non-comparable to the UK NHS)
- Effectiveness data and probability estimates were taken from a clinical trial which might not illustrate properly the current clinical practice
- Cost data were taken from published studies and not from Government sources which can affect their relevance

Overall quality*: *Potentially serious limitations*	**Overall applicability**: *Partially applicable***	

Abbreviations: ICER = incremental cost-effectiveness ratio; NHS = National Health Service; BB = Beta-blockers; ACEi = Angiotensin-converting enzyme inhibitors; NYHA = New York Heart Association Classification; LVEF = Left Ventricular Ejection Fraction; CHF = Chronic Heart Failure; BNP = Brain Natriuretic Peptide.
*Very serious limitations/Potentially serious limitations/Minor limitations; **Directly applicable/Partially applicable/Not applicable

Results - Morimoto 2004					
	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	**$5577**	**$9577**	**$13,436**	**$17,155**	**$20,737**
Clinical Group					
QALY	**0.38**	**0.55**	**0.70**	**0.83**	**0.94**

Cost	**$6230**	**$10,131**	**$13,670**	**$16,861**	**$19,723**
Result					
ICER	**Dominant***	**Dominant***	**Dominant***	**$3491 per QALY**	**$7787 per QALY**

*Dominant means that the intervention was more effective and less costly

Tele-monitoring and self-monitoring

S. Scalvini, S. Capomolla, E. Zanelli, M. Benigno, D. Domenighini, L. Paletta, F. Glisenti, and A. Giordano. Effect of home-based telecardiology on chronic heart failure: costs and outcomes. *Journal of Telemedicine & Telecare* 11 Suppl 1:16-8, 2005.:16-18, 2005.				
Study details	**Population & interventions**	**Health outcomes**	**Costs**	**Cost effectiveness**
Economic analysis: Cost-consequence analysis **Study design:** Based on a prospective cohort study **Perspective**: Italian public healthcare system **Time horizon:** 1 year **Discounting:** Not applicable	**Population:** - Patients with stable chronic hearth failure (n=426) - Mean age of 59 years (SD9) **Intervention 1:** - Home-based telecardiology (n=230) - Trans-telephonic follow-up and ECG monitoring - ECG portable device given to patients, transferring data by mobile or fixed telephone line - ECG recording transmitted to a received station, where a nurse was available for reporting and interactive	**Health outcomes:** See table above 'Scalvini 2005 – Clinical outcomes'	**Cost components incorporated:** Home-based telecardiology cost: - Equipment (hardware and software, ECG recorders, dedicated telephone line) - Rental (dedicated lines, service centre) - Personnel (physicians, nurses) - Other (fax and photocopier, consumables, software maintenance, vocational training) Hospitalization cost **Currency & cost year:** - Euro (year not reported,	**Cost-effectiveness results:** Cost and clinical outcomes were presented separately in tables below. **Sensitivity analysis:** No sensitivity analysis was undertaken

	teleconsultations - Tele-assistance for patients when necessary - Home visit by paramedical and medical team if necessary **Intervention 2:** Usual care (n=196)		study published in 2005)	
Data sources				
Health outcomes: Prospective cohort study **Cost sources:** Not reported				
Comments				
Source of funding: Not reported **Limitations:** - No sensitivity analysis - Short time horizon - No quality of life estimates - Source of cost not reported - The analysis did not considered possible important cost components (drug, intervention, outpatient visit, emergency visit) - Usual care intervention not described				
Overall quality*: *Very serious limitations*	**Overall applicability**: *Partially applicable***			

Abbreviations: SD = Standard deviation; ECG = Electrocardiogram.

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

Scalvini 2005 – One-year clinical outcomes			
	Usual care (n=179)	**Home-based telecardiology (n=230)**	**Relative risk (95% CI)**
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)

Scalvini 2005 – One-year cost outcomes		
	Usual care (n=179)	**Home-based telecardiology (n=230)**
Hospitalisation cost	€140,874	€95,688
Telecare service cost	NA	€11,806
Total cost	**€140,874**	**€107,494**

Appendix H – Cost-effectiveness analysis

Cost-effectiveness analysis of serial measurement of circulating natriuretic peptide concentration in patients with heart failure

1. Background

Brain natriuretic peptide (BNP) and its aminoterminal portion (N-BNP) are secreted primarily from the left ventricle in response to changes in left ventricular wall stretch[1]. These agents are neurohormonal predictors of left-ventricular function and prognosis[2, 3, 4, 5]. The diagnostic and prognostic value of natriuretic peptide plasma level in heart failure was supported by many studies[6, 7, 8, 9, 10,11]. It was also proven that most drugs used to treat heart failure significantly reduce natriuretic peptide level[12,13,14,15,16,17].

Treatment optimization for patients with heart failure is based on physician assessment and patient tolerance. Circulating natriuretic peptide concentration can be reduced by intensification of drug therapy in heart failure, and monitoring plasma natriuretic peptide level has been proposed for optimizing medical treatment. Four randomised clinical trials were published comparing the management of patients' medical treatment according to natriuretic peptide concentration versus clinical assessment in secondary care and/or usual care in the community[18,19,20,21]. These clinical trials reported that serial measurement of natriuretic peptide concentration improved outcomes compared to clinical assessment or usual care.

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. One cost-effectiveness analysis was published assessing the management of medical treatment in chronic heart failure using BNP measurement compared to clinical assessment[22]. This analysis was based on one clinical trial[18] and it 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.

2. Objective

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

for patients in England and Wales with

1. chronic heart failure (CHF) , or
2. CHF and left ventricular systolic dysfunction (LVSD).

3. Model

In a systematic clinical review[see Section 7.1.2 of Full Guideline (2010)], four clinical trials were identified assessing serial measurement of natriuretic peptide concentration for optimizing the medical therapy in CHF (Troughton 2000[18], Jourdain 2007[20], Pfisterer 2009[19], Lainchbury 2010[21])[b]. Trougton 2000[18], Jourdain 2007[20], and Pfisterer 2009[19] compared serial measurement in secondary care of natriuretic peptide concentration and clinical assessment in secondary care. Lainchbury 2010[21] compared natriuretic peptide measurement in secondary care, clinical assessment in secondary care, and usual care in the community.

The Trougton 2000[18], Jourdain 2007[20], and Pfisterer 2009[19] clinical trials were conducted in patients with CHF and LVSD. Lainchbury 2010 clinical trial[21] was conducted on patients with CHF of any causes. Hence, outcomes of the three clinical trials on patients with LVSD [18], [20], [19] were meta-analysed for use in this economic analysis, and outcomes from the Lainchbury clinical trial[21] were utilized independently. Furthermore, age subgroups were assessed in Pfisterer[19] (<75 years / ≥75 years) and Lainchbury[21] (≤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 periods (Section 4.1.2 and 5.6). 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 patient was 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 patient 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) (Table 1) [21]. Therefore, cost-effectiveness assessments were conducted on these analyses on a three-year time horizon. In addition, for Lainchbury[21] 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 analyses were developed from an England and Wales NHS perspective; the health outcome considered was 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.

Table 1

Mortality (all-cause)* - Risk ratios (95% confidence intervals)				
Analysis	**Trial follow-up**	**Natriuretic peptide vs clinical assessment**	**Usual care vs clinical assessment**	**Natriuretic peptide vs usual care**
Jourdain	15 months	0.64 [0.26; 1.58]	N/A	N/A
Pfisterer all ages	18 months	0.72 [0.5; 1.04]	N/A	N/A
Pfisterer <75 years	18 months	0.47 [0.24; 0.92]	N/A	N/A
Pfisterer ≥75 years	18 months	0.91 [0.61; 1.37]	N/A	N/A
Lainchbury all ages	3 years	1.00 [0.7; 1.43]	0.99 [0.69, 1.42]	1.01 [0.70, 1.44]
Lainchbury ≤75 ages	3 years	0.50 [0.24; 1.03]	1.01 [0.59, 1.73]	0.50 [0.25, 1.00]
Lainchbury >75 ages	3 years	1.41 [0.93; 2.14]	0.99 [0.61, 1.61]	1.43 [0.92; 2.20]

* Troughton did not report all-cause mortality

[b] Beck-da-Silva published in 2005 results from a RCT[23] assessing serial measurement of natriuretic peptide concentration for beta-blocker up-titration as opposed to monitoring the entire drug usage in Troughton 2000[18], Jourdain 2007[20], Pfisterer 2009[19], and Lainchbury 2010[21]. For this reason, and considering that Beck-da-Silva trial[23] has a small cohort size (N=41) and did not reported sensible outcomes for economic modelling (all-cause mortality and heart failure-related hospitalizations), this study was not utilized for this economic analysis.

4. Quality-Adjusted Life 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).

4.1 Mortality

Within-trial mortality estimates were taken from the clinical trials themselves. Patients' mortality post-trial was assumed the same for each compared cohort in all the analyses. Post-trial mortality estimates were taken from the UK-based study conducted on patients with heart failure by Guili 2005[24].

4.1.1 Mortality within-trial

Two techniques were used to estimate life years for the within-trial periods. When survival curves were available, life years where calculated as the area under the survival curve. Alternatively, risk ratios at the end of trials were used assuming deaths occurred evenly over the trial follow-up period.

The area under the curve was calculated for assessments developed from Lainchbury[21] and Pfisterer[19]. Table 2 shows life years calculated from survival curves. As explained in Section 6, the Pfisterer trial[19] (all ages) was modelled independently as a sensitivity analysis.

Table 2

Within-trial life years* calculated as the area under the survival curve				
Analysis	**Trial follow-up**	**Natriuretic peptide**	**Clinical assessment**	**Usual care**
Lainchbury all ages	3 years	2.51 (2.44)	2.48 (2.41)	2.37 (2.30)
Lainchbury ≤75 years	3 years	2.75 (2.67)	2.46 (2.39)	2.31 (2.25)
Lainchbury >75 years	3 years	2.29 (2.23)	2.47 (2.40)	2.40 (2.33)
Pfisterer all ages	18 months	1.35 (1.34)	1.27 (1.26)	N/A
Pfisterer <75 years	18 months	1.41 (1.40)	1.31 (1.30)	N/A
Pfisterer ≥75 years	18 months	1.28 (1.26)	1.26 (1.24)	N/A

* Undiscounted (discounted); Discounting at 3.5% was applied after one year

Risk ratios were used to calculate life years in the cost-effectiveness assessment based on trials conducted on patients with CHF and LVSD (Troughton[18], Jourdain[20], and Pfisterer[19]). The meta-analysed risk ratio (Table 3) was applied at 18 months (Pfisterer trial[19] follow-up[c]). The baseline risk used was the death risk from Pfisterer[19], the largest trial, in the clinical assessment cohort at 18 months (Table 3). In addition, we modelled as part of the sensitivity analysis (Section 6) Jourdain[20] and Pfisterer[19] independently (Table 3).

Table 3

Mortality all-cause*					
	Risk ratio for natriuretic peptide vs clinical assessment at final follow-up (95% CI) { a }	**Probability of death**		**Mean life years Within trial follow-up period**	
Trial**		**Clinical assessment { b }**	**Natriuretic peptide { c = a x b }**	**Natriuretic peptide**	**Clinical assessment**

[c] The Pfisterer trial[19] follow-up (18 months) was the longest of the meta-analysed trials (15 months for Jourdain[20] and 9.5 months for Troughton[18]). Troughton[21] did not report all-cause mortality but only cardiovascular deaths.

Jourdain (15 months)	0.64 (0.26; 1.58)	0.100	0.064	1.21	1.19
Pfisterer (18 months)	0.72 (0.5; 1.04)	0.222	0.160	1.38	1.33
Meta-analysis	**0.70 (0.5; 0.99)**	**0.222[¥]**	**0.155**	**1.38**	**1.33**

* Discounting has not been applied

** Troughton 2000[18] did not report all-cause mortality

[¥] Assumed to be the same as Pfisterer[19], the largest trial.

4.1.2 Mortality post-trial

Giuli 2005[24] reported outcomes from an observational study using the *General Practice Research Database* in the UK. This study aimed to determine the incidence and prognosis of heart failure (HF) diagnosed by general practitioners. Incident cases of HF in 1991 were selected and followed for three-years. 686,884 patients 45 years and older were classified as definite HF, possible HF, or a prescription of diuretics without a diagnosis of HF. 6478 patients were classified as definite HF[d], and outcomes from this subgroup were considered relevant for this cost-effectiveness analysis.

The mean survival time for definite HF was 23.8 months (95% CI 23.4–24.1), 22.9 months in men and 24.5 months in women (p<0.001). The median survival was 30.8 and 36.5 months in men and women respectively. Sex- and age-group standardised mortality ratios (SMR) were reported. Each SMR was the ratio of the cumulative probability of dying in the study population to the cumulative probability of dying in an age and sex matched sample from the general population in England and Wales. We adjusted the SMRs to account for the effect on survival of ACEI and BB using data from meta-analyses by Flather 2000[25] for ACEI and Shibata 2001[26] for BB assuming no interaction between the two drugs[e]. Table 4 presents both the unadjusted SMR estimates from Guilli 2005[24] (untreated), and our adjusted estimates, which we used in our cost-effectiveness analysis.

Table 4

Standardised mortality ratios (definite HF vs general population)			
		SMR (untreated)	**SMR (treated)**
SMR male	65-74 years	5.73	2.80
	75-84 years*	4.07	2.00
	85+ years	2.41	1.18
SMR female	65-74 years	7.18	3.52
	75-84 years*	4.80	2.35
	85+ years	2.42	1.19

*SMR were presented by Guili 2005[24] for age subgroups 65-74 years and 85+ years at 3 years from diagnosis. Estimates for the age subgroup 75-84 years were assumed to be the unweighted average of the two other age subgroups.

We estimated life expectancy beyond the trial follow-up using the official life tables for England and Wales[27] but adjusting the mortality using the CHF-specific SMRs (Table 4). The life expectancies were based on the mean age at baseline from the trials and were at first calculated for men and women separately[18], [19], [20], [21]. Then, we calculated the average life expectancy for both sexes using the male/female ratio at baseline in clinical trials[18], [19], [20], [21]. Table 5 presents the life expectancies from trial baseline considered for our economic analysis.

Table 5

Life expectancy from baseline						
Analysis		**Mean age at**	**Males**		**Undiscounted**	**Discounted life**

[d] 45% men (n=2884), mean age 75 years (SD=9); 55% women (n=3594), mean age 79 years (SD=9).

[e] Effect of ACEI versus placebo: RR=0.86 (95% CI 0.81-0.91); Effect of BB versus placebo: RR=0.57 (95% CI 0.51-0.64); Combined effect of ACEI and BB = 0.4902.

	Trial follow-up	baseline** (years)	%**	Cohort	life expectancy (years)	expectancy* (years)
Lainchbury all ages	3 years	76	64%	NP	7.14	6.22
				Clinic	7.14	6.22
				UC	7.16	6.24
Lainchbury ≤75 years	3 years	69[¥]	64%[¥¥]	NP	10.34	8.44
				Clinic	9.00	7.45
				UC	8.97	7.43
Lainchbury >75 years	3 years	82[¥]	64%[¥¥]	NP	5.70	5.17
				Clinic	6.46	5.78
				UC	6.48	5.79
LVSD meta-analysis	18 months[Ω]	70	64%	NP	8.90	7.25
				Clinic	8.25	6.73
Jourdain	15 months	66	58%	NP	11.44	8.99
				Clinic	11.02	8.67
Pfisterer all ages	18 months	76	66%	NP	6.99	6.58
				Clinic	6.53	6.15
Pfisterer <75 years	18 months	69	75%	NP	9.64	7.81
				Clinic	8.51	6.91
Pfisterer ≥75 years	18 months	82	59%	NP	5.43	4.77
				Clinic	5.29	4.65

NP=Natriuretic Peptide; Clinic=Clinical assessment; UC=Usual Care
* Discounting at 3.5% applied after one year (except for year 2 in Pfisterer analyses, left undiscounted)
** Weighted average of trial arm estimates from clinical trials at baseline
[¥] Data from Pfisterer[19] age subgroups as not reported by subgroups in Lainchbury[21]
[¥¥] Ratio from Lainchbury main analysis[21] – all ages (not reported by subgroups)
[Ω] Pfisterer trial[19] follow-up which was the longest of meta-analysed trials

4.2 Utility scores

The four clinical trials[18], [19], [20], [21] did not report utility scores. There were some assessments of patients' health-related quality of life (HRQoL) and functional capacities[f], but these could not be used to estimate utility.

Gohler 2009[28] reported mean utility scores stratified by NYHA class for patients with CHF[g]. They used EuroQol 5D (EQ-5D) data collected from the EPHESUS trial[29] (multi-centre and multi-national trial), which assessed the addition of eplerenone to optimal medical treatment in patients with CHF and LVSD post myocardial infarction. During the EPHESUS trial[29], EQ-5D data were collected from a subsample of 1628 patients at baseline, three, six, 12, and 18 months. Gohler 2009[28] estimated utilities using all except the baseline data to mitigate the effect of acute myocardial infarction on the EQ-5D score (Table 6).

[f] Pfisterer assessed patients' quality of life using the Minnesota Living with Heart Failure questionnaire, the Duke Activity Status Index, and the Short Form 12, reporting no significant differences in the magnitude of improvements between strategies. Lainchbury administered the Minnesota Living with Heart Failure questionnaire and showed that Minnesota scores improved significantly and similarly in natriuretic peptide and clinical assessment cohorts. Troughton reported that quality of life scores remained stable for compared cohorts of patients.
[g] Study selected from a non-systematic search for utility scores in CHF. The Gohler paper was selected as being a recent assessment estimating utility scores in CHF using EQ-5D data collected from a well-recognized RCT on patients with CHF.

Table 6

Utility score – Patients with Chronic heart Failure[28]		
NYHA class	**Mean utility score**	**95% CI**
I	0.855	0.845-0.864
II	0.771	0.761-0.781
III	0.673	0.665-0.690
IV	0.532	0.480-0.584

We estimated average utility scores for each of our trials by weighting each of the utility scores in Table 6 with the proportion of patients in each NHYA class at trial baseline (Table 7) [18], [19], [20], [21]. In the absence of evidence to the contrary, we assumed that mean utility scores stayed constant over time and were the same for each intervention.

Table 7

Utility scores used in the economic analysis	
Analysis	**Utility score**
Lainchbury (all ages, ≤75 years, >75 years)*	0.753
Meta-analysis (LVSD)**	0.715
Jourdain[¥]	0.747
Pfisterer all ages[¥¥]	0.698
Pfisterer <75 years	0.707
Pfisterer ≥75 years	0.692

* NYHA classification at baseline was not reported for age subgroups in Lainchbury[21]. We used the main analysis' baseline classification (all ages) and applied it to age subgroups.
** Troughton[18] reported the percentage of patient in class II. We assumed others were in class III.
[¥] Jourdain[20] reported the mean NYHA class per cohort (natriuretic peptide=2.29; clinical assessment=2.21). We assumed that 80% of patients were in class II and others in class III for the clinical assessment cohort, and 70% in class II and others in class III for the natriuretic peptide cohort.
[¥¥] Pfisterer[19] reported the number of patients ≥ class III. We assumed that this proportion was in class III and others in class II.

5. Resource use and cost

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, a yearly cost per patient was applied.

5.1 Hospitalisation

To estimate hospitalisation costs, we used the risk ratio from the final trial follow-up and we assumed admissions occurred evenly over the follow-up period. The hospitalisation risk for the clinical assessment cohort was used as the baseline risk. For the analysis conducted on patients with CHF and LVSD (based on Troughton[18], Pfisterer[19], and Jourdain[20]), we applied the meta-analysed risk ratio to the baseline risk at 18 months in the Pfisterer[19] trial[h]. Table 8 details the trial hospitalisation data and the probabilities used in this cost-effectiveness analysis.

Table 8

[h] The Pfisterer trial[19] follow-up (18 months) was the longest of the meta-analysed trials (15 months for Jourdain[20] and 9.5 months for Troughton[18]).

Hospitalisation*					
			Probability of hospitalisation		
	RR (95% CI)	Trial follow-up	Natriuretic peptide	Clinical assessment	Usual care
Patients with CHF and LVSD**					
Jourdain	0.46 [0.3; 0.7]	15 months	0.20	0.44	N/A
Pfisterer all ages	0.74 [0.48; 1.15]	18 months	0.12	0.16	N/A
Troughton	0.42 [0.17; 1.05]	9.5 months	0.15	0.36	N/A
Meta-analysis	**0.57 [0.42; 0.76]**	**18 months¥**	**0.09**	**0.16¥¥**	**N/A**
Pfisterer subgroups					
Pfisterer <75	0.53 [0.25; 1.15]	18 months	0.08	0.16	N/A
Pfisterer ≥75	0.92 [0.57; 1.47]	18 months	0.18	0.20	N/A
Lainchbury (Natriuretic peptide versus clinical assessment)					
Lainchbury all	0.9 [0.65; 1.24]	3 years	0.36	0.40	N/A
Lainchbury ≤75	0.73 [0.44; 1.23]	3 years	0.29	0.40	N/A
Lainchbury >75	1.05 [0.7; 1.57]	3 years	0.43	0.41	N/A
Lainchbury (Usual care versus clinical assessment)					
Lainchbury all	0.83 [0.6; 1.15]	3 years	N/A	0.40	0.34
Lainchbury ≤75	0.9 [0.57; 1.42]	3 years	N/A	0.40	0.36
Lainchbury >75	0.76 [0.47; 1.23]	3 years	N/A	0.41	0.31

* No discounting applied

** Troughton 2000[18] was not modelled independently as Pfisterer[19] and Jourdain[20] (Section 6)

¥ Pfisterer trial[19] follow-up which was the longest of meta-analysed trials

¥¥ We used the Pfisterer[19] baseline risk (clinical assessment cohort risk) for the economic assessment on patients with CHF and LVSD based on the meta-analysis

The hospitalisation cost per hospital admission was calculated from reported figures of the NHS reference cost[30] database[i]. This cost was estimated to be £1,725 and was combined with the probabilities in Table 8 to give the hospitalisation cost.

5.2 Drug usage

The change in drug usage was calculated for all clinical trials (Lainchbury[21], Jourdain[20], Pfisterer[19], and Troughton[18]).In the cost-effectiveness assessment for patients with CHF and LVSD (based on Jourdain[20], Pfisterer[19], and Troughton[18]), the Pfisterer[19] drug usage was used for the base case. The drug usage from the other trials was used in sensitivity analyses, to see if the source of this component can affect the results of the analysis (Section 6).

The Lainchbury[21] drug usage was reported for the main analysis only (all ages). In the absence of better evidence, we assumed in our cost-effectiveness analysis that these data also applied to the age subgroups. The Pfisterer[21] drug usage was calculated separately for the main analysis (all ages) and for the age subgroups.

5.2.1 Lainchbury

For the Lainchbury main analysis, mean daily drug doses per patient were reported at every follow-up assessment for furosemide (loop diuretic), enalapril (ACEI), metoprolol[j] (BB), and spironolactone (Table 9).

[i] A weighted average cost was calculated considering elective and non-elective inpatient admissions for heart failure. Excess bed days were added to this calculation[30].

[j] The drug usage was reported for BB in metoprolol equivalent. Metoprolol is an available treatment in the UK, but not licensed for use in heart failure[31]. We costed metoprolol to be consistent with clinical trial outcomes. We consider this is not likely to affect the applicability of our results in a UK context.

Table 9

Lainchbury drug usage (mg/day)[21]											
		Time (months)									
		0		3		6		12		24	
Medications	Treatment Group*	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Furosemide	Natriuretic peptide	128	23	138	20	140	22	182	22	200	27
	Clinical assessment	149	23	144	21	134	21	166	23	197	28
	Usual care	124	22	121	21	119	21	123	22	140	25
Enalapril	Natriuretic peptide	12.7	6	13	6	13.3	6	13.1	6	12.4	7
	Clinical assessment	13.3	6	14.7	6	14.6	6	14.2	6	14	7
	Usual care	10.3	6	11.3	6	11	6	11	6	10.8	6
Metoprolol	Natriuretic peptide	76	11	83	9	95	9	95	10	94	11
	Clinical assessment	80	11	91	9	95	9	99	10	99	12
	Usual care	73	10	74	9	75	9	73	10	72	10
Spironolactone	Natriuretic peptide	20	6	22	4	22	4	20	5	16	7
	Clinical assessment	21	6	22	5	24	5	23	5	20	6
	Usual care	20	2	20	2	21	2	21	2	21	3

* Natriuretic peptide n=121; Clinical assessment n=121; Usual care n=122

We assumed that drug dosages changed at the mid-point between follow-ups. The usage at 24 months was assumed to stay constant up to 36 months (end of trial[21]). We combined these trial data with drug unit costs[31]; Table 10 presents costs of drug treatment for compared cohorts.

Table 10

Lainchbury drug treatment cost per patient*			
	Total 24-month cost per patient	Cost from 24 to 36 months	Total cost per patient
Natriuretic peptide	£289	£126	**£415**
Clinical assessment	£299	£134	**£433**
Usual care	£246	£104	**£350**

* Discounting at 3.5% applied after one year

5.2.2 Pfisterer

Pfisterer[19] presented at baseline the mean percentage of target dose per patient for ACEI/ARB, BB, and loop diuretic. In the absence of better data, these figures at baseline were assumed the same for the main analysis (all ages) and for age subgroups (<75 years, ≥75 years). Changes in drug usage were reported by age subgroups only, in percentage of target doses, for ACEI/ARB and BB. For the cost-effectiveness assessment based on the main analysis (all ages), changes in ACEI/ARB and BB usage were assumed to be the unweighted average of the reported changes for age subgroups. For jointly reported figures for ACEI and ARB, we costed the use of enalapril (ACEI), considering a target dose of 10mg b.i.d.[k] Carvedilol was costed as BB, considering a target dose of 25mg b.i.d.[k] No change in usage was reported for loop diuretic and this treatment was excluded from cost-effectiveness assessments[l]. Table 11 presents data for ACEI and BB used for cost-effectiveness assessments.

Table 11

Pfisterer* drug usage[19]						
	Clinical assessment			Natriuretic peptide		
	Baseline**	Changes	6 months	Baseline**	Changes	6 months

[k] Target doses as recommended by the *European Society of Cardiology*[32], [33], referred to in the RCTs[19], [20].

[l] The baseline usage was the same for compared cohorts

	Mean % target dose	SD / IQR	Mean % target	SE	Mean % target dose	Mean % target dose	SD / IQR	Mean % target	SE	Mean % target dose
All ages										
ACEI	0.5	0.36	0.153	0.063	0.653	0.53	0.41	0.2715	0.067	0.8015
BB	0.25	0.125-0.5	0.1415	0.06	0.3915	0.25	0.05-0.5	0.241	0.054	0.491
< 75 years										
ACEI	0.5	0.36	0.155	0.054	0.655	0.53	0.41	0.292	0.067	0.822
BB	0.25	0.125-0.5	0.162	0.06	0.412	0.25	0.05-0.5	0.281	0.054	0.531
≥ 75 years										
ACEI	0.5	0.36	0.151	0.063	0.651	0.53	0.41	0.251	0.051	0.781
BB	0.25	0.125-0.5	0.121	0.041	0.371	0.25	0.05-0.5	0.201	0.052	0.451

* Clinical assessment: n=248 (all ages); n=102 (<75 years); n=146 (≥75 years). Natriuretic peptide: n=251 (all ages); n=108 (<75 years); n=143 (≥75 years).
** Age subgroups are assumed to be the same as complete cohort.

The number of patients taking spironolactone or eplerenone at baseline and at the end of interventions (6 months) was presented for the Pfisterer main analysis (all ages). In the absence of better data, these figures were also applied to the age-subgroup analyses. We assumed patients were taking spironolactone or eplerenone at a dose of 25mg/day. Table 12 presents drug usage data for spironolactone and eplerenone.

Table 12

Pfisterer drug usage[19]		
	Clinical assessment (no. of patients)	**Natriuretic peptide (no. of patients)**
Spironolactone	56	76
Eplerenone	100	103

* Clinical assessment: n=248; Natriuretic peptide: n=251.

We assumed that drug treatments changed at three months (mid-point between the baseline and the end of interventions), and we assumed that the drug usage at six months stayed constant up to the end of follow-up (18 months)[19]. Table 13 presents costs of drug treatment for the compared cohorts.

Table 13

Pfisterer drug treatment cost per patient*		
	Clinical assessment	**Natriuretic peptide**
All ages		
6-month cost per patient	£86	£92
6 months to 18 months	£291	£313
Total cost per patient	£377	£404
< 75 years		
6-month cost per patient	£86	£93
6 months to 18 months	£293	£317
Total cost per patient	£379	£410
≥75 years		
6-month cost per patient	£85	£91
6 months to 18 months	£290	£308
Total cost per patient	£375	£399

* Discounting at 3.5% applied after one year

5.2.3 Jourdain

Jourdain[20] reported changes in drug usage for ACEI/ARB, BB, and furosemide (loop diuretic). The mean percentage of daily target dose per patient was reported at baseline and 3 months (end of the trial intervention) for ACEI/ARB and BB. The mean daily dose per patient at baseline and 3 months was reported for furosemide. For jointly reported figures for ACEI and ARB, we costed the use of enalapril (ACEI), assuming a target dose of 10mg b.i.d.[k] Carvedilol was costed as the BB, assuming a target dose of 25mg b.i.d.[k] Table 14 presents the drug usage data from Jourdain[20].

Table 14

Jourdain* drug usage[20]					
	Baseline		Changes		3 months
	Mean daily dose (mg)	SD	Increase (mg)	SD	mg
Loop diuretic					
Clinical assessment					
Furosemide	52	60	9	20	61
Natriuretic peptide					
Furosemide	50	48	9	20	59
ACEI and BB					
Clinical assessment	**Baseline (% of recommended daily dose)**				**3 months (% of recommended daily dose)**
Enalapril (ACEI)	94				98
Carvedilol (BB)	57				67
Natriuretic peptide					
Enalapril (ACEI)	94				106**
Carvedilol (BB)	58				77

* Clinical assessment n=110; Natriuretic peptide n=110.

** This means that the mean daily dose was above the recommended dose.

The change in drug usage was assumed at 1.5 months (mid-point between the baseline and the end of interventions). In the absence of better data, we kept constant the drug usage at three months up to the end of Jourdain follow-up (15 months)[20] for the analysis based on this trial alone (sensitivity analysis – Section 6), or up to 18 months, the Pfisterer[19] follow-up period[m], when applying the Jourdain drug usage to the analysis developed on patients with CHF and LVSD (sensitivity analysis – Section 6). Table 15 presents costs of drug treatment for compared cohorts.

Table 15

Jourdain drug treatment cost per patient*		
	Clinical assessment	Natriuretic peptide
3-month cost per patient	£29	£31
3 months to 15 months	£122	£134
15-months cost per patient	**£152**	**£165**
15 months to 18 months	£29	£32
18-months cost per patient	**£181**	**£197**

* Discounting at 3.5% applied after one year

5.2.4 Troughton

Troughton[18] reported the mean dose per patient at baseline and the mean dose increase per patient during the intervention period (6 months) for enalapril (ACEI) and furosemide (loop diuretic). The

[m] In sensitivity analyses, Troughton[18] and Jourdain[20] drug usages were applied to the cost-effectiveness assessment developed on patients with CHF and LVSD based on Pfisterer[19], Jourdain[20], and Troughton[18]. For this assessment, outcomes from trials were assumed at 18 months, the Pfisterer follow-up[19] being the longest one (15 months for Jourdain[20] and 9.5 months for Troughton[18]).

number of patients taking spironolactone and a BB at baseline and six months was also reported. We assumed that spironolactone was taken at a dose of 25mg/day, and that the BB carvedilol was taken at a dose of 25mg bd. Table 16 details the drug usage from Troughton[18].

Table 16

Troughton* drug usage[18]						
	Baseline		Increase		6 months	
	Mean dose (mg)	SD	Mean dose (mg)	SD	Mean dose (mg)	SD
ACEI and loop diuretic						
Clinical assessment						
Enalapril (ACEI)	13.1	6.7	1.2	6.9	14.3	
Furosemide (loop diuretic)	87	119	54		141	263
Natriuretic peptide						
Enalapril (ACEI)	15.3	7.9	4.8	5.9	20.1	
Furosemide (loop diuretic)	123	145	74		197	237
BB and spironolactone						
Clinical assessment	**Baseline (no. of patients)**				**6 months (no. of patients)**	
Spironolactone	0				1	
Carvedilol (BB)	1				2	
Natriuretic peptide						
Spironolactone	0				6	
Carvedilol (BB)	4				4	

* Clinical assessment n=36; Natriuretic peptide n=33.

The change in drug usage was assumed at three months (mid-point between baseline and the end of trial intervention)[18]. We kept constant the drug usage at six months up to 18 months, which was the follow-up time of Pfisterer[19] trial[m]. Table 17 presents costs of drug treatment for the compared cohorts.

Table 17

Troughton drug treatment cost per patient*		
	Clinical assessment	Natriuretic peptide
0 to 6-months	£35	£49
6 months to 9.5 months	£23	£34
0 to 9.5-months**	**£58**	**£83**
9.5 months to 18 months	£55	£80
Total cost (18 months)	**£113**	**£163**

* Discounting at 3.5% applied after one year

** 9.5 months was the follow-up time for Troughton 2000[18]

Drug usages were costed using drug unit costs proposed by the *British National Formulary*[31] (Table 18).

Table 18

Drug prices*			
Drug	**Dose (mg)**	**No. per pack**	**Price per pack**
Furosemide	40	28	£0.85
Enalapril	5	28	£1.03
Carvedilol**	12.5	28	£1.54
Carvedilol**	25	28	£2.17
Metoprolol	50	28	£1.28
Spironolactone	25	28	£1.79

Eplerenone	25	28	£42.72

* BNF No. 58[31]

** When carvedilol was costed per 25mg dose, we used the 25mg tablet cost. Otherwise, we used the 12.5mg cost (when carvedilol usage was reported in percentage of target dose)[31].

5.3 Outpatient visits

Table 19 presents numbers of outpatient visits attended from each of the four clinical trials. Troughton[18] was the only clinical trial reporting additional (unplanned) outpatient visits. In the absence of better data, we assumed the Troughton figures for additional visits in our analyses of the Jourdain and Pfisterer trials. For Lainchbury, we assumed Troughton figures of additional visits for natriuretic peptide and clinical assessment cohorts, and no additional visit was assumed for the usual care cohort.

Table 19

Outpatient visits				
	Troughton[18]	**Jourdain[20]**	**Pfisterer[19]**	**Lainchbury[21]**
Therapy frequency	Every 3 months; Every 2 weeks when target not met; Intervention at every visit	Every month for 3 months (intervention); Then every 3 months as follow-up	Visits at 1, 3, 6 months (intervention); Visits at 12 and 18 months as follow-up	Every 3 months for 2 years (intervention); Additional visit for NP and Clinic cohorts triggered by symptoms / measurement (not usual care)
Trial follow-up	Median 9.5 months	Median 15 months	18 months	3 years
Planned outpatient visits (for intervention)	4	4	4	9
Additional outpatient visit (for intervention)	NP = 0.9 per patient; Clinic = 0.3 per patient*	NR	NR	NP = Clinic NP & Clinic > Usual care **
Total	NP = 4.9 Clinic = 4.3	NR	NR	NR
Number of visit assumed in the model	**NP = 4.9** **Clinic = 4.3**	**NP = 4.9** **Clinic = 4.3**	**NP = 4.9** **Clinic = 4.3**	**NP = 9.9[¥]** **Clinic = 9.3** **Usual care = 9**

NP = Natriuretic peptide cohort; Clinic = Clinical assessment cohort

* Additional visits to intensify drug therapy were needed in 18/33 patients in the natriuretic peptide cohort and 14/36 patients in the clinical assessment cohort (p=0.34). The average number of extra visits per patient was 1.7 in the natriuretic peptide cohort and 0.8 in the clinical assessment cohort (p=0.19)[18].

** Data not presented

[¥] For all Lainchbury cohorts, four outpatient visits were assumed during the second year and were discounted.

Natriuretic peptide and clinical assessment interventions were offered in secondary care at a specialist level in every clinical trial. The outpatient visit cost for these cohorts was calculated using figures reported by the National reference cost[30] database[n], and was estimated to be £98 per visit. In the Lainchbury usual care cohort, it was conservatively assumed that all attendances were with the general practitioner. The mean cost per GP visit in the community was estimated nationally to be £52[34].

[n] A weighted average cost was calculated considering cardiology follow-up visits (not leading to admission), by consultant and non-consultant, with or without a multiprofessional approach.

5.4 Natriuretic peptide assessment

Natriuretic peptide assessments were undertaken at every outpatient visit in the natriuretic peptide cohort. There is no national price for this test in England and Wales. The tariff price at St George's Healthcare Trust (London) is £27.71 for NT-proBNP testing[o]. This cost was used for base-case cost-effectiveness assessments and added to the cost of an outpatient visit (Section 5.3)[p]. To allow for a potentially lower cost for natriuretic peptide testing, for example if this test is made available to a large number of patients, we used in the sensitivity analysis a cost of £20 (Section 6).

5.5 Biochemistry testing

When initiating or modifying dosages of ACEI, diuretic, and spironolactone/eplerenone, biochemistry testing for renal function is current practice. Numbers of treatment modifications per cohort were reported by Jourdain[20] for these drugs (Table 20). Pfisterer[19] reported the number of patients per cohort adding spironolactone/eplerenone to their drug therapy during interventions (none were taking spironolactone/eplerenone at baseline) (Table 20). We calculated probabilities of treatment modifications for natriuretic peptide and clinical assessment cohorts using data from Jourdain[20] for ACEI, and diuretic, and pooled data from Jourdain[20] and Pfisterer[19] for spironolacone/eplerenone (Table 20). In the absence of data for Lainchbury usual care cohort, we assumed no biochemistry testing for this group of patients.

The probability of treatment modification was multiplied by the average cost of a biochemistry test: £1.34 from the NHS Reference costs[30]. The cost of biochemistry testing may have been overestimated for natriuretic peptide and clinical assessment cohorts, as multiple treatment modifications may occur during a single physician visit. However, since the cost of biochemistry testing is so small, the impact on the results of our cost-effectiveness analysis is minimal.

Table 20

Treatment modifications			
	Natriuretic peptide	**Clinical assessment**	
Jourdain[20] - Number of treatment modifications			
	Treatment modification		
Drug	**Natriuretic peptide (n=110)**	**Clinical assessment (n=110)**	**p-value**
Diuretic	55	26	<0.05
ACEI	21	9	<0.05
Spironolactone	17	7	<0.05
Pfisterer[19] - Addition of spironolactone/eplerenone			
	Number of patient		
Drug	**Natriuretic peptide (n=251)**	**Clinical assessment (n=248)**	
Spironolactone or eplerenone	179	156	
Probabilities of treatment modification* - Jourdain and Pfisterer**			
Drug	**Natriuretic peptide**	**Clinical assessment**	
Diuretic	50.0%	23.6%	
ACEI	19.1%	8.2%	
Spironolactone/eplerenone**	54.3%	45.5%	

* We assumed all treatment modifications during year one and therefore no discounting was applied
** Data from Jourdain[20] and Pfisterer[19] were combined for spironolactone/eplerenone only.

[o] Test costs are equivalent for BNP and NT-proBNP
[p] For cost-effectiveness assessments based on Lainchbury[21], four natriuretic peptide tests were assumed during year two and were discounted (as for outpatient visits – Section 5.3)

5.6 Post-trial cost

Stewart 2002[35] published a cost-of-illness analysis of heart failure developed from a UK NHS perspective. Cost components incorporated in the analysis were hospitalisation, hospital-based outpatient consultations, GP consultations, drug treatment, and nursing-home care. The yearly cost per patient was estimated in 2000 to be £896[q]. Using the prices index for hospital and community health services[34], we estimated this cost in 2008 GBP to be £1,171 per patient per year. This yearly cost per patient was used in the post-trial period of the model was assumed the same for the different cohorts.

6. Sensitivity analysis

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[19] drug usage was used for the base case, and drug usages from Jourdain[20] and Troughton[18] (Section 5.2) were applied to sensitivity analyses.

Secondly, Jourdain[20] and Pfisterer[19] clinical trials were modelled independently in addition to the assessment combining outcomes from Pfisterer[19], Jourdain[20], and Troughton[18], because of some inconsistencies in outcomes[r]. Troughton[18] was not modelled independently since it was small and did not report all-cause mortality[s].

Furthermore, as discussed in Section 3, the same number of patients was 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) (Table 1)[21]. Thereby, the cost-effectiveness assessment from Lainchbury[21] main analysis was conducted on a three-year time horizon, and cost-effectiveness assessments from Lainchbury[21] age-subgroup analyses were conducted on both a three-year and a lifetime horizons. Moreover, cost-effectiveness assessments conducted on patients with CHF and LVSD were developed on a lifetime horizon in the base-case analysis. These cost-effectiveness assessments were based on trial follow-ups shorter than three years (18 months[19] and 15 months[20]). 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[21] main analysis, we conducted additional analyses on patients with CHF and LVSD on a three-year time horizon[t].

Finally, as discussed in Section 5.4, we used in the sensitivity analysis a cost of £20 for natriuretic peptide testing in all cost-effectiveness analyses in addition to the £27.71 used in the base case.

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[q] £905 million (1.91% of total NHS expenditure); 1.01 million cases[35].

[r] (1) Hospitalisation data: (a) Pfisterer[19] (all ages) baseline risk (clinical assessment cohort) = 0.16; RR (natriuretic peptide vs clinical assessment) = 0.74 [0.48; 1.15]. (b) Jourdain[20] baseline risk = 0.44; RR = 0.46 [0.3; 0.7]. (2) Mortality: (a) Pfisterer[19] baseline risk = 0.22; RR = 0.72 [0.5; 1.04]. (b) Jourdain[20] baseline risk = 0.10; RR = 0.64 [0.26; 1.58]. (c) We used area under curves for Pfisterer[19] main analysis (all ages) to estimate life years instead of end-of-trial RR as in the combined analysis (CHF and LVSD – Section 4.1.1).

[s] Troughton[18] did not report all-cause mortality; has a small cohort size (N=69); and this trial was conducted before BB were commonly used in CHF. We considered that modelling Troughton[18] independently would not add value to this economic analysis.

[t] We assumed the same mortality rate and yearly cost per patient up to three years after trial periods.

7. Probabilistic analysis

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. A gamma distribution (bounded at 0) was applied to cost estimates and to standardized mortality ratios. A beta distribution (bounded between 0 and 1) was applied to utility scores and probabilities. Finally, a lognormal distribution (bounded at 0) was applied to risk ratios, mean drug dosage[u] and mean number of outpatient visits (refer to Table 25 on Section 11). The results of each analysis (base-case analyses and sensitivity analyses) were re-calculated 5000 times, with all the model parameters set simultaneously, selected at random from the respective parameter distribution. We present the results in terms of the mean of the 5000 computed simulations.

8. Results

This economic analysis assessed two populations of patients: patients with CHF and LVSD; and patients with heart failure of any cause. For these two populations, age subgroups were also assessed (Pfisterer <75 years, ≥75 years; Lainchbury ≤75 years, >75 years).

8.1 Patients with CHF and LVSD

Table 21 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[19], Jourdain[20], and Troughton[18] trials. Table 22 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[20] with a three-year time horizon, the natriuretic peptide option was actually cost-saving compared to clinical assessment.

Table 21

Cost and QALY results*: Patients with CHF and LVSD (lifetime horizon)			
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

[u] Due to a 'bug', excel cannot calculate the gamma distribution when the standard error is very small compared with the mean. This was the case with some mean drug dosage and therefore we used the lognormal distribution instead.

Table 22

Cost-effectiveness results: Patients with CHF and LVSD (natriuretic peptide vs clinical assessment)							
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 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

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8.2 Patients with CHF due to any cause

The population assessed in Lainchbury[21] was patients with CHF due to any cause. Based on Lainchbury[21], we assessed the cost-effectiveness of serial measurement in secondary care of natriuretic peptide concentration compared to a) clinical assessment in secondary care and to b) usual care in the community. In addition to the base-case cost-effectiveness assessment developed from the main Lainchbury results, age subgroups analyses were also conducted (<75 years, ≥75 years)[21].

Table 23 presents a breakdown of cost components, life years, and QALYs for the base-case cost-effectiveness analysis developed from Lainchbury[21]. Table 24 shows results of this cost-effectiveness analysis modelled on a three-year time horizon (Section 3). Comparing an intervention with the next

best alternative (Figure 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 (Section 3), the diagram of the cost-effectiveness plane (Figure 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 24).

For the age-subgroup cost-effectiveness assessment conducted on patients *older than 75 years* and developed on three-year and lifetime horizons (Section 3), the natriuretic peptide option is dominated by usual care (usual care is more effective and less costly – Figure 2). However, clinical assessment is cost-effective compared to usual care (Table 24). 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 – Section 5.4).

Table 23

Cost and QALY results*: Patients with CHF of any cause - Lainchbury (3 years time horizon)					
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 1: Cost-effectiveness results (CHF any cause; base case)

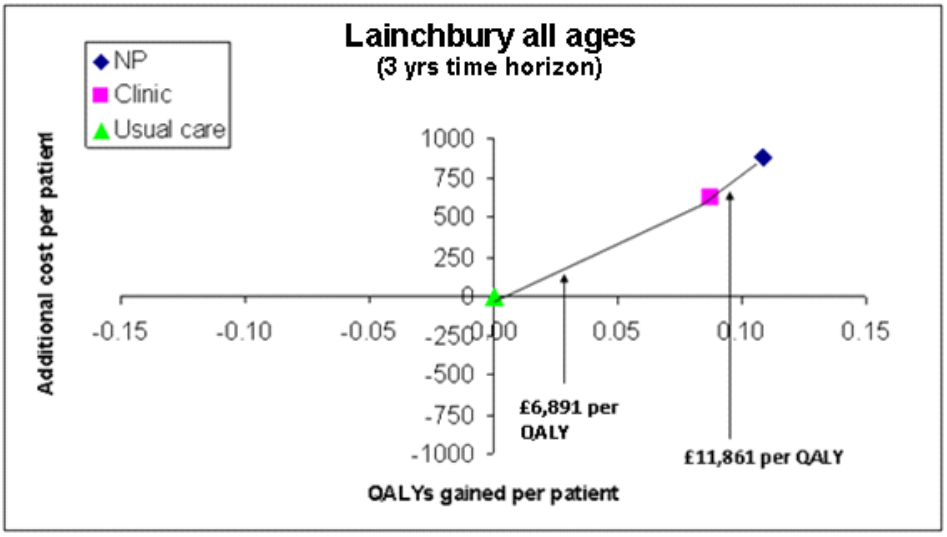


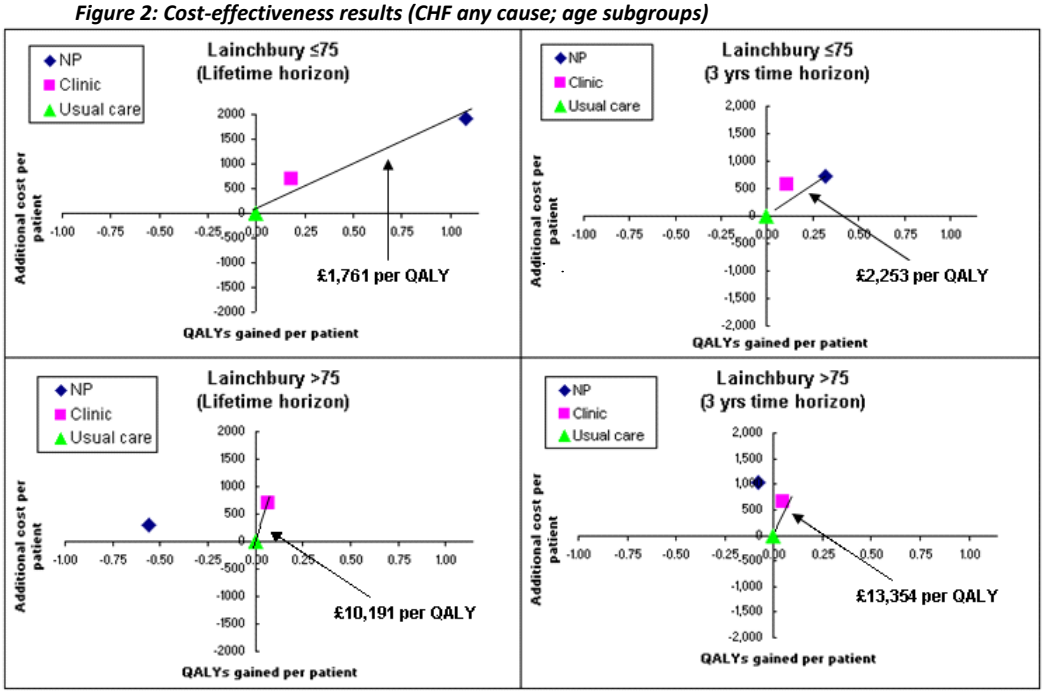
Table 24

Cost-effectiveness: CHF of any cause - Lainchbury							
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 2: Cost-effectiveness results (CHF any cause; age subgroups)



9. Discussion

We assessed the use of serial measurement in secondary care of natriuretic peptide for optimizing medical therapy in patients admitted to hospital because of chronic heart failure, compared to both clinical assessment in secondary care and to 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 exception of the analysis based on Jourdain[20] and the one based on Lainchbury[21] >75)
- Natriuretic peptide monitoring was more effective and cost-effective compared to clinical assessment (with exception of the analysis based on Lainchbury[21] >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[21], the same number of patients was alive in the three compared cohorts. In the base-case cost-effectiveness analysis based on Lainchbury[21] (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[18] only and were applied to all cost-effectiveness analyses for natriuretic peptide and clinical assessment cohorts. Troughton[18] 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[21] (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[21] (>75) or from Pfisterer[19] (≥75). The natriuretic peptide intervention improved survival in Pfisterer[19] and decreased it in Lainchbury[21] (compared to clinical assessment). It might be because patients with heart failure and preserved ejection fraction (HFPEF) were included in Lainchbury[21] and excluded in Pfisterer[19], and drug treatments 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 can also 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 guided intervention in general practices was not assessed in clinical trials and no conclusion can 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 practices. Additional research is needed.

10. Conclusion

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. However, the use of natriuretic peptide measurement in patients older than 75 years may be harmful and not cost-effective, which suggests that careful patient selection is important. However, for patients older than 75 years, the optimization of drug therapy in chronic heart failure by clinical assessment in secondary care without natriuretic peptide monitoring was still cost-effective compared to usual care in the community.

11. Parameters used in probabilistic analyses

Table 25

Parameters used in probabilistic analyses				
Description of variable	**Mean value**	**Probability distribution**	**Parameters**	**Source**
Lainchbury				
Mortality risk ratio				
Lainchbury (all ages) NP vs Clinic	1.00	lognormal	95% CI = 0.7; 1.43	Lainchbury[21]
Lainchbury (all ages) UC	0.99	lognormal	95% CI = 0.69; 1.42	Lainchbury[21]

vs Clinic				
Lainchbury (≤75 yrs) NP vs Clinic	0.50	lognormal	95% CI = 0.24; 1.03	Lainchbury[21]
Lainchbury (≤75 yrs) UC vs Clinic	1.01	lognormal	95% CI = 0.59; 1.73	Lainchbury[21]
Lainchbury (>75 yrs) NP vs Clinic	1.41	lognormal	95% CI = 0.93; 2.14	Lainchbury[21]
Lainchbury (>75 yrs) UC vs Clinic	0.99	lognormal	95% CI = 0.61; 1.61	Lainchbury[21]
Mortality baseline risk				
Lainchbury (all ages)	0.33	Beta	α = 40; β = 81	Lainchbury[21]; clinic cohort
Lainchbury (≤75 years)	0.31	Beta	α = 17; β = 38	Lainchbury[21]; clinic cohort
Lainchbury (>75 years)	0.35	Beta	α = 23; β = 43	Lainchbury[21]; clinic cohort
Hospitalisation for heart failure risk ratio				
Lainchbury all ages - NP vs Clinic	0.90	lognormal	95% CI = 0.65; 1.24	Lainchbury[21]
Lainchbury ≤75 - NP vs Clinic	0.73	lognormal	95% CI = 0.44; 1.23	Lainchbury[21]
Lainchbury >75 - NP vs Clinic	1.05	lognormal	95% CI = 0.7; 1.57	Lainchbury[21]
Lainchbury all ages - UC vs Clinic	0.83	lognormal	95% CI = 0.6; 1.15	Lainchbury[21]
Lainchbury ≤75 - UC vs Clinic	0.90	lognormal	95% CI = 0.57; 1.42	Lainchbury[21]
Lainchbury >75 - UC vs Clinic	0.76	lognormal	95% CI = 0.47; 1.23	Lainchbury[21]
Hospitalisation for heart failure; Baseline risk				
Lainchbury all ages	0.40	beta	α = 49; β = 72	Lainchbury[21]; clinic cohort
Lainchbury ≤75 yrs	0.40	beta	α = 22; β = 33	Lainchbury[21]; clinic cohort
Lainchbury >75 yrs	0.41	beta	α = 27; β = 39	Lainchbury[21]; clinic cohort
Drug usage (mg)				
Furosemide				
NP baseline	128	lognormal	SE = 2.09	Lainchbury[21]
Clinic baseline	149	lognormal	SE = 2.09	Lainchbury[21]
UC baseline	124	lognormal	SE = 1.99	Lainchbury[21]
NP 3 months	138	lognormal	SE = 1.82	Lainchbury[21]
Clinic 3 months	144	lognormal	SE = 1.91	Lainchbury[21]
UC 3 months	121	lognormal	SE = 1.9	Lainchbury[21]
NP 6 months	140	lognormal	SE = 2	Lainchbury[21]
Clinic 6 months	134	lognormal	SE = 1.91	Lainchbury[21]
UC 6 months	119	lognormal	SE = 1.9	Lainchbury[21]
NP 12 months	182	lognormal	SE = 2	Lainchbury[21]
Clinic 12 months	166	lognormal	SE = 2.09	Lainchbury[21]
UC 12 months	123	lognormal	SE = 1.99	Lainchbury[21]
NP 24 months	200	lognormal	SE = 2.45	Lainchbury[21]
Clinic 24 months	197	lognormal	SE = 2.55	Lainchbury[21]

UC 24 months	140	lognormal	SE = 2.26	Lainchbury[21]
Enalapril				
NP baseline	12.7	lognormal	SE = 0.55	Lainchbury[21]
Clinic baseline	13.3	lognormal	SE = 0.55	Lainchbury[21]
UC baseline	10.3	lognormal	SE = 0.54	Lainchbury[21]
NP 3 months	13.0	lognormal	SE = 0.55	Lainchbury[21]
Clinic 3 months	14.7	lognormal	SE = 0.55	Lainchbury[21]
UC 3 months	11.3	lognormal	SE = 0.54	Lainchbury[21]
NP 6 months	13.3	lognormal	SE = 0.55	Lainchbury[21]
Clinic 6 months	14.6	lognormal	SE = 0.55	Lainchbury[21]
UC 6 months	11.0	lognormal	SE = 0.54	Lainchbury[21]
NP 12 months	13.1	lognormal	SE = 0.55	Lainchbury[21]
Clinic 12 months	14.2	lognormal	SE = 0.55	Lainchbury[21]
UC 12 months	11.0	lognormal	SE = 0.54	Lainchbury[21]
NP 24 months	12.4	lognormal	SE = 0.64	Lainchbury[21]
Clinic 24 months	14.0	lognormal	SE = 0.64	Lainchbury[21]
UC 24 months	10.8	lognormal	SE = 0.54	Lainchbury[21]
Sprionolactone				
NP baseline	20	lognormal	SE = 0.55	Lainchbury[21]
Clinic baseline	21	lognormal	SE = 0.55	Lainchbury[21]
UC baseline	20	lognormal	SE = 0.18	Lainchbury[21]
NP 3 months	22	lognormal	SE = 0.36	Lainchbury[21]
Clinic 3 months	22	lognormal	SE = 0.45	Lainchbury[21]
UC 3 months	20	lognormal	SE = 0.18	Lainchbury[21]
NP 6 months	22	lognormal	SE = 0.36	Lainchbury[21]
Clinic 6 months	24	lognormal	SE = 0.45	Lainchbury[21]
UC 6 months	21	lognormal	SE = 0.18	Lainchbury[21]
NP 12 months	20	lognormal	SE = 0.45	Lainchbury[21]
Clinic 12 months	23	lognormal	SE = 0.45	Lainchbury[21]
UC 12 months	21	lognormal	SE = 0.18	Lainchbury[21]
NP 24 months	16	lognormal	SE = 0.64	Lainchbury[21]
Clinic 24 months	20	lognormal	SE = 0.55	Lainchbury[21]
UC 24 months	21	lognormal	SE = 0.27	Lainchbury[21]
Sprionolactone				
NP baseline	76	lognormal	SE = 11	Lainchbury[21]
Clinic baseline	80	lognormal	SE = 11	Lainchbury[21]
UC baseline	73	lognormal	SE = 10	Lainchbury[21]
NP 3 months	83	lognormal	SE = 9	Lainchbury[21]
Clinic 3 months	91	lognormal	SE = 9	Lainchbury[21]
UC 3 months	74	lognormal	SE = 9	Lainchbury[21]
NP 6 months	95	lognormal	SE = 9	Lainchbury[21]
Clinic 6 months	95	lognormal	SE = 9	Lainchbury[21]
UC 6 months	75	lognormal	SE = 9	Lainchbury[21]
NP 12 months	95	lognormal	SE = 10	Lainchbury[21]
Clinic 12 months	99	lognormal	SE = 10	Lainchbury[21]
UC 12 months	73	lognormal	SE = 10	Lainchbury[21]
NP 24 months	94	lognormal	SE = 11	Lainchbury[21]
Clinic 24 months	99	lognormal	SE = 12	Lainchbury[21]
UC 24 months	72	lognormal	SE = 10	Lainchbury[21]
Pfisterer				
Mortality risk ratio				
Pfisterer (all ages)	0.72	lognormal	95% CI = 0.5; 1.04	Pfisterer[19]
Pfisterer (<75 yrs)	0.47	lognormal	95% CI = 0.24; 0.92	Pfisterer[19]

Pfisterer (≥75 yrs)	0.91	lognormal	95% CI = 0.61; 1.37	Pfisterer[19]
Mortality baseline risk				
Pfisterer (all ages)	0.22	Beta	α = 55; β = 193	Pfisterer[19]; clinic cohort
Pfisterer (<75 years)	0.22	Beta	α = 22; β = 80	Pfisterer[19]; clinic cohort
Pfisterer (≥75 years)	0.25	Beta	α = 37; β = 109	Pfisterer[19]; clinic cohort
Hospitalisation for heart failure risk ratio				
Pfisterer (all ages)	0.74	lognormal	95% CI = 0.48; 1.15	Pfisterer[19]
Pfisterer <75 yrs	0.53	lognormal	95% CI = 0.25; 1.15	Pfisterer[19]
Pfisterer ≥75 yrs	0.92	lognormal	95% CI = 0.57; 1.47	Pfisterer[19]
Hospitalisation for heart failure; Baseline risk				
Pfisterer all ages	0.16	beta	α = 40; β = 208	Pfisterer[19]; clinic cohort
Pfisterer <75 yrs	0.16	beta	α = 16; β = 86	Pfisterer[19]; clinic cohort
Pristerer ≥75 yrs	0.20	beta	α = 29; β = 117	Pfisterer[19]; clinic cohort
Drug usage				
All ages				
ACEI\ARB, baseline dose, Clinic	0.50	lognormal	SE = 0.023	Pfisterer[19]
ACEI\ARB, dose change, Clinic	0.15	lognormal	SE = 0.063	Pfisterer[19]
BB, dose change, Clinic	0.14	lognormal	SE = 0.06	Pfisterer[19]
ACEI\ARB, baseline dose, NP	0.53	lognormal	SE = 0.026	Pfisterer[19]
ACEI\ARB, dose change, NP	0.27	lognormal	SE = 0.067	Pfisterer[19]
BB, dose change, NP	0.24	lognormal	SE = 0.054	Pfisterer[19]
BB, baseline dose, Clinic	0.25	beta	α = 62; β = 186	Pfisterer[19]
BB, baseline dose, NP	0.25	beta	α = 62.75; β = 188.25	Pfisterer[19]
< 75 years				
ACEI\ARB, dose change, Clinic	0.16	lognormal	SE = 0.054	Pfisterer[19]
BB, dose change, Clinic	0.16	lognormal	SE = 0.06	Pfisterer[19]
ACEI\ARB, dose change, NP	0.29	lognormal	SE = 0.067	Pfisterer[19]
BB, dose change, NP	0.28	lognormal	SE = 0.054	Pfisterer[19]
≥ 75 years				
ACEI\ARB, dose change, Clinic	0.15	lognormal	SE = 0.063	Pfisterer[19]
BB, dose change, Clinic	0.12	lognormal	SE = 0.041	Pfisterer[19]
ACEI\ARB, dose change, NP	0.25	lognormal	SE = 0.051	Pfisterer[19]
BB, dose change, NP	0.20	lognormal	SE = 0.052	Pfisterer[19]
All patients / <75 years / ≥75 years				
Spironolactone, probability of use, Clinic	0.23	beta	α = 56; β = 192	Pfisterer[19]
Eplerenone, probability of use, Clinic	0.40	beta	α = 100; β = 148	Pfisterer[19]

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Spironolactone, probability of use, NP	0.30	beta	α = 76; β = 175	Pfisterer[19]
Eplerenone, probability of use, NP	0.41	beta	α = 103; β = 148	Pfisterer[19]
Jourdain				
Mortality risk ratio	0.64	lognormal	95% CI = 0.26; 1.58	Jourdain[20]
Mortality baseline risk	0.10	Beta	α = 11; β = 99	Jourdain[20]; clinic cohort
Hospitalisation for heart failure risk ratio	0.46	lognormal	95% CI = 0.3; 0.7	Jourdain[20]
Hospitalisation for heart failure; Baseline risk	0.44	beta	α = 48; β = 62	Jourdain[20]; clinic cohort
Treatement modification (biochemistry testing)				
Diuretic, NP group	0.5	beta	α = 55; β = 55	Jourdain[20]
ACEI, NP group	0.19	beta	α = 21; β = 89	Jourdain[20]
Spironolactone\eplereno ne, NP group	0.54	beta	α = 196; β = 165	Combined data from Jourdain[20] and Pfisterer[19]
Diuretic, Clinic group	0.24	beta	α = 26; β = 84	Pfisterer[19]
ACEI ,Clinic group	0.08	beta	α = 9; β = 101	Pfisterer[19]
Spironolactone\eplereno ne, Clinic group	0.46	beta	α = 163; β = 195	Combined data from Jourdain[20] and Pfisterer[19]
Drug usage				
ACEI\ARB, baseline dose, Clinic	18.8	lognormal	SE = 10 (assumed 50% of target dose as SE)	Jourdain[20]
BB, baseline dose, Clinic	28.5	lognormal	SE = 25 (assumed 50% of target dose as SE)	Jourdain[20]
ACEI\ARB, 3 months dose, Clinic	19.6	lognormal	SE = 10 (assumed 50% of target dose as SE)	Jourdain[20]
BB, 3 months dose, Clinic	33.5	lognormal	SE = 25 (assumed 50% of target dose as SE)	Jourdain[20]
ACEI\ARB, baseline dose, NP	18.8	lognormal	SE = 10 (assumed 50% of target dose as SE)	Jourdain[20]
BB, baseline dose, NP	29.0	lognormal	SE = 25 (assumed 50% of target dose as SE)	Jourdain[20]
ACEI\ARB, 3 months dose, NP	21.2	lognormal	SE = 10 (assumed 50% of target dose as SE)	Jourdain[20]
BB, 3 months dose, NP	38.5	lognormal	SE = 25 (assumed 50% of target dose as SE)	Jourdain[20]
Furosemide, baseline dose, Clinic	52.0	lognormal	SE = 5.72	Jourdain[20]
Furosemide, dose change, Clinic	9.0	lognormal	SE = 1.91	Jourdain[20]
Furosemide, baseline dose, NP	50.0	lognormal	SE = 4.58	Jourdain[20]
Furosemide, dose change, NP	9.0	lognormal	SE = 1.91	Jourdain[20]
Troughton				
Hospitalisation for heart failure (Risk ratio)	0.42	lognormal	95% CI = 0.17; 1.05	Troughton[18]
Outpatient visits				
Additional outpatient visit per patient; Clinic	0.30	lognormal	SE = 0.15	Troughton[18]

group				
Additional outpatient visit per patient; NP group	0.90	lognormal	SE = 0.45	Troughton[18]
Drug usage				
ACEI\ARB, baseline dose, Clinic	13.1	lognormal	SE = 1.12	Troughton[18]
Furosemide, baseline dose, Clinic	87.0	lognormal	SE = 19.83	Troughton[18]
ACEI\ARB, dose change, Clinic	1.2	lognormal	SE = 1.15	Troughton[18]
Furosemide, 6 months, Clinic	141.0	lognormal	SE = 43.83	Troughton[18]
ACEI\ARB, baseline dose, NP	15.3	lognormal	SE = 1.38	Troughton[18]
Furosemide, baseline dose, NP	123.0	lognormal	SE = 25.24	Troughton[18]
ACEI\ARB, dose change, NP	4.8	lognormal	SE = 1.03	Troughton[18]
Furosemide, 6 months, NP	197.0	lognormal	SE = 41.26	Troughton[18]
Spironolactone, probability of use, 6 months, Clinic	0.028	beta	α = 1; β = 35	Troughton[18]
BB, probability of use, baseline, Clinic	0.028	beta	α = 1; β = 35	Troughton[18]
BB, probability of use, 6 months, Clinic	0.056	beta	α = 2; β = 34	Troughton[18]
Spironolactone, probability of use, 6 months, NP	0.18	beta	α = 6; β = 27	Troughton[18]
BB, probability of use, baseline, NP	0.12	beta	α = 4; β = 29	Troughton[18]
BB, probability of use, 6 months, NP	0.12	beta	α = 4; β = 29	Troughton[18]
Patient with CHF and LVSD (meta-analysis of Pfisterer, Jourdain, and Troughton)				
Mortality risk ratio				
Meta-analysis of Pfisterer (all ages) and Jourdain	0.70	lognormal	95% CI = 0.5; 0.99	Pfisterer and Jourdain
Hospitalisation for heart failure risk ratio				
Meta-analysis (Jourdain, Pfisterer, and Troughton)	0.57	lognormal	95% CI = 0.42; 0.76	Jourdain[20], Pfisterer[19], and Troughton[18]
Mean cost (£)				
Hospitalisation cost				
Elective Inpatient				
Heart Failure or Shock with CC	3954	gamma	SE = 2114 / α = 3.50; β = 1130.34 / Using interquartile range (20001; 4703)	NHS reference cost[30]
Heart Failure or Shock without CC	2756	gamma	SE = 1862 / α = 2.19; β = 1258.09 / Using interquartile range (1262; 3562)	NHS reference cost[30]
Elective Inpatient Excess Bed Day				
Heart Failure or Shock	186	gamma	SE = 56.5 / α = 10.79; β = 17.20 /	NHS reference cost[30]

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with CC			Using interquartile range (113; 187)	
Heart Failure or Shock without CC	238	gamma	SE = 95.5 / α = 6.22; β = 38.29 / Using interquartile range (177; 302)	NHS reference cost[30]
Non-Elective Inpatient (Long Stay) HRG Data				
Heart Failure or Shock with CC	2608	gamma	SE = 774 / α = 11.35; β = 229.73 / Using interquartile range (1949; 2976)	NHS reference cost[30]
Heart Failure or Shock without CC	1692	gamma	SE = 508 / α = 11.10; β = 152.50 / Using interquartile range (1268; 1942)	NHS reference cost[30]
Non-Elective Inpatient (Long Stay) Excess Bed Days HRG Data				
Heart Failure or Shock with CC	193	gamma	SE = 59 / α = 10.67; β = 18.06 / Using interquartile range (152; 230)	NHS reference cost[30]
Heart Failure or Shock without CC	189	gamma	SE = 57 / α = 11.01; β = 17.18 / Using interquartile range (151; 228)	NHS reference cost[30]
Non-Elective Inpatient (Short Stay) HRG Data				
Heart Failure or Shock with CC	356	gamma	SE = 120 / α = 8.81; β = 40.44 / Using interquartile range (248; 406)	NHS reference cost[30]
Heart Failure or Shock without CC	340	gamma	SE = 106 / α = 10.29; β = 33.04 / Using interquartile range (248; 388)	NHS reference cost[30]
Cardiologist outpatient visit cost				
Consultant Led: Follow up Attendance Non-Admitted Face to Face	105	gamma	SE = 35.5 / α = 8.80; β = 11.97 / Using interquartile range (75; 122)	NHS reference cost[30]
Consultant Led: Follow up Attendance Multiprofessional Non-Admitted Face to Face	125	gamma	SE = 11 / α = 129.01; β = 0.97 / Using interquartile range (123; 138)	NHS reference cost[30]
Non-Consultant Led: Follow up Attendance Non-Admitted Face to Face	71	gamma	SE = 44 / α = 2.62; β = 27.19 / Using interquartile range (38; 93)	NHS reference cost[30]
Non-Consultant Led: Follow up Attendance Multiprofessional Non-Admitted Face to Face	117	gamma	SE = 27 / α = 18.85; β = 6.22 / Using interquartile range (85; 121)	NHS reference cost[30]
Mean utility scores				
NYHA class I	0.855	Beta	95% CI = 0.845; 0.864 / α = 1391.94; β = 236.06	Gohler 2009[28]
NYHA class II	0.771	Beta	95% CI = 0.761; 0.781 / α = 1255.19; β = 372.81	Gohler 2009[28]
NYHA class III	0.673	Beta	95% CI = 0.665; 0.690 / α = 1095.64; β = 532.36	Gohler 2009[28]
NYHA class IV	0.532	Beta	95% CI = 0.480; 0.584 / α = 866.1; β = 761.9	Gohler 2009[28]
Other				
Standard Mortality ratios (Mean %)				
Male, 65-74 years	573	Gamma	95% CI = 521; 631 / SE = 30 / α = 364.81; β = 1.57	Guili 2005[24]
Male, 85+ years	241	Gamma	213; 272 / SE = 15 / α = 258.14; β =	Guili 2005[24]

			0.93	
Female, 65-74 years	718	Gamma	641; 804 / SE = 42 / α = 292.25; β = 2.46	Guili 2005[24]
Female, 85+ years	242	Gamma	223; 262 / SE = 14 / α = 298.80; β = 0.81	Guili 2005[24]
Effect of ACEI on survival (Risk ratio)	0.86	lognormal	95% CI = 0.81; 0.91	Flather 2000[25]
Effect of BB on survival (Risk ratio)	0.57	lognormal	95% CI = 0.51; 0.64	Shibata 2001[26]
Biochemistry test cost (£)	1.34	gamma	SE = 0.59 / α = 5.16; β = 0.26 / Using interquartile range (0.79; 1.56)	NHS reference cost[30]

NP = Natriuretic Peptide; Clinic = Clinical assessment; UC = Usual Care

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Appendix J – Practical notes

Background:

The course of heart failure patients is characterised by periods of clinical deterioration and potential need for changes to pharmacological therapy to be made. It is essential to maintain patients on therapy proven to reduce the risks of hospitalisation and improve the chances of survival. The adherence to this general advice is made difficult by practitioners' concerns about side effects of therapy. In particular, many clinicians are concerned about renal impairment and reduced blood pressure in patients with heart failure.

The 2003 guideline included tables of practical recommendations that were based on the publication by McMurray {McMurray, 2001 1466 /id}). These covered aspects of clinical management that were not included in the evidence reviewed but which the GDG considered important.

In updating the guideline the GDG reviewed these recommendations and agreed that they were helpful to all practitioners caring for patients with heart failure, and would enable patients and practitioners avoid the frequent scenario where essential medications for heart failure are inappropriately discontinued. Where appropriate, the GDG adopted the advice from Chronic Kidney Disease: Early identification and management of chronic kidney disease in adults in primary and secondary care. NICE clinical guideline 73 (2008).

These practical notes were written by the Guideline Development Group for publication in August 2010. They will not be revised before the guideline is considered for review in 2013. For all current NICE guidance, see www.nice.org.uk

General Advice:

For optimal prognostic and symptomatic benefit doses of ACEI and β blocker should be up-titrated to the maximum tolerated. This may require repeated or prolonged supervision in some patients.

The dose of diuretic should be the minimum necessary to control oedema.

Communication with Patients:

Identify a clinician from whom patients may seek advice regarding heart failure.

Explain the purpose of the medication prescribed and the importance of up-titration to optimal dose.

Explain the need for regular monitoring and at times alteration of medication.

Explain that improvement with ACEI or β blockers may take time to accrue.

Explain that minor worsening of symptoms may occur when β blockers are being initiated.

Encourage individuals to monitor their weight and to report any change

Renal function:

Monitor in all patients routinely. Check the renal function before the initiation of ACEI/ARB, and monitor the urea, creatinine, eGFR and electrolytes following each dose increment, and then at regular intervals every three months.

Measure serum urea, creatinine and electrolytes at initiation of an ACE inhibitor/ARB and after each dose increment.

Monitor more frequently patients taking combined loop and thiazide diuretic therapy, and in those taking aldosterone antagonists.

In people with CKD, measure serum potassium concentrations and estimate the GFR before starting ACEI/ARB therapy. Repeat these measurements between 1 and 2 weeks after starting ACEI/ARB therapy and after each dose increase. (Chronic Kidney Disease: Early identification and management of chronic kidney disease in adults in primary and secondary care. NICE clinical guideline 73 (2008). R48

ACEI/ARB therapy should not normally be started if the pre-treatment serum potassium concentration is significantly above the normal reference range (typically >5.0 mmol/l). (Chronic Kidney Disease: Early identification and management of chronic kidney diseae in adults in primary and secondary care. NICE clinical guideline 73 (2008). R49.

Stop ACEI/ARB therapy if the serum potassium concentration rises to above 6.0 mmol/l and other drugs known to promote hyperkalaemia have been discontinued. (Chronic Kidney Disease: Early identification and management of chronic kidney diseae in adults in primary and secondary care. NICE clinical guideline 73 (2008). R52

Following the introduction or dose increase of ACEI/ARB, do not modify the dose if either the GFR decrease from pre-treatment baseline is <25% or the plasma creatinine increase from baseline is <30%. (Chronic Kidney Disease: Early identification and management of chronic kidney disease in adults in primary and secondary care. NICE clinical guideline 73 (2008). R53

If there is a fall in eGFR or rise in plasma creatinine after starting or increasing the dose of ACEI/ARB, but it is less than 25% (eGFR) or 30% (serum creatinine) of baseline, the test should be repeated in a further 1–2 weeks. Do not modify the ACE/ARB dose if the change in eGFR <25% or change in plasma creatinine is <30%. (Chronic Kidney Disease: Early identification and management of chronic kidney diseae in adults in primary and secondary care. NICE clinical guideline 73 (2008). R54.

If the eGFR change is ≥25% or change in plasma creatinine is ≥30%:

1. investigate other causes of a deterioration in renal function such as volume depletion or concurrent medication (e.g. non-steroidal anti-inflammatory drugs (NSAIDS)
2. if no other cause for the deterioration in renal function is found, stop the ACEI/ARB therapy or reduce the dose to a previously tolerated lower dose. (Chronic Kidney Disease: Early identification and management of chronic kidney disease in adults in primary and secondary care. NICE clinical guideline 73 (2008). R55.

Before starting aldosterone antagonists, measure urea, creatinine, eGFR and electrolytes.

Comment [AA1]:

Comment [AA2]: Nan, there is no need to remove this. I am re-instating it:

In patients taking aldosterone antagonists, measure urea, creatinine, eGFR and electrolytes at 1 week, and at 1, 2, 3, and 6 months and 6 monthly thereafter.

Halve the aldosterone antagonist dose if the potassium rose to 5-5-5.9 mmol/l.

Stop the aldosterone antagonist if the potassium rises above 6 mmol/l or the creatinine above 220 µmol/l.

Blood pressure:

Monitor in all patients routinely.

If blood pressure is low, first consider discontinuing nitrates, calcium channel blockers and other vasodilators.

If blood pressure is low, reduce diuretics in patients who do not have signs of congestion.

In asymptomatic hypotension do not alter dose of ACEI or β blockers.

Where at all possible maintain treatment with both ACEI and BB, at reduced dose if necessary.

Increasing congestion/fatigue:

If Temporary deterioration occurs during the initiation or up-titration of β blockers

diuretic dose may need to be briefly increased.

If congestion occurs increase diuretics and consider reducing dose of β blocker (but not discontinuing).

Where there is extreme fatigue (or bradycardia < 50bpm) consider reducing the dose of β blocker.

Seek specialist advice if serious deterioration (fatigue, oedema, weight gain and dyspnoea) does not improve

Consider Specialist review (see above):

Where fluid retention is resistant.

When commencing ACEI in patients taking large doses of diuretics.

Where renal function continues to deteriorate or deteriorated rapidly.

Where there are concerns about low blood pressure.

Where fatigue, oedema, weight gain and dyspnoea do not rapidly improve**.**

Appendix K - Criteria for selecting high priority research recommendations

Criterion	RP1 Beta Blocker or ACEI in Heart Failure with Preserved Left Ventricular Ejection Fraction	RP2 Telemonitoring, Natriuretic Peptide Monitoring or Clinical Monitoring in HF with LVSD	RP3 The use of natriuretic peptides in determining prognosis and resource allocation in the heart failure team	RP4 SPIRONOLACTONE OR Angiotensin receptor blocker in HF patients intolerant of ACEI	RP5 Hydralazine and or Nitrates in HFPEF
Importance to patients or the population	This is of major importance to a large population of patients with heart failure.	Efficient affordable strategies for optimal management of heart failure afford the best opportunity to maintain or improve patient quality of life and independence.	A population with heart failure is best served by alignment of resource with need. The ability to stratify need (and prognosis) would allow targeting of limited resource where patient need is greatest	We do not currently know which regimen would optimise RAAS inhibition in those intolerant of ACE inhibitors. It is important that this is clarified.	Therapeutic intervention has been found to significantly improve the prognosis of heart failure and LVSD. It would be of great advantage to see if either agent or the combination would be effective in HF with preserved LV ejection fraction.
Relevance to NICE guidance	High. Current NICE guidance highlights lack of evidence of benefit.	High The research is essential to inform future updates of key recommendations in the guidelines.	High: Facilitate implementation of existing guidance.	High: Research would inform future recommendations.	High. Would inform future guidance.
Relevance to the NHS	Heart failure with preserved ejection fraction is responsible for repeated hospital admissions and significant	Financial strategy and management of heart failure in the community	Financial advantage by alignment of resource allocation with clinical need and therefore reducing redundancy in care input.	Would streamline care for the patients intolerant of one of the cornerstones of therapy for HF with LVSD	Unmet treatment need.

Criterion	RP1 Beta Blocker or ACEI in Heart Failure with Preserved Left Ventricular Ejection Fraction	RP2 Telemonitoring, Natriuretic Peptide Monitoring or Clinical Monitoring in HF with LVSD	RP3 The use of natriuretic peptides in determining prognosis and resource allocation in the heart failure team	RP4 SPIRONOLACTONE OR Angiotensin receptor blocker in HF patients intolerant of ACEI	RP5 Hydralazine and or Nitrates in HFPEF
	impairment of quality of life. Improvement in both would be beneficial to healthcare planning and to patient quality of life.				
National priorities	National priorities and national strategy emphasise on reduction of hospitalisation use.	National priorities and national strategy emphasise on reduction of hospitalisation use	National priorities and national strategy emphasise on reduction of hospitalisation use		National priorities and national strategy emphasise on reduction of hospitalisation use
Current evidence base	Current evidence is limited but shows potential benefit of beta-blocker and ACE inhibitors in preserved ejection fraction population A large study with clearly defined population is required. (See Section 2.2.1)	Interpretation of current studies available is difficult because of differing research methodologies used and differences in what constitutes 'usual care'. (See Chapter 7 - Monitoring)	Studies show potential reduction in mortality in some groups when natriuretic peptides are used to guide titration. The overall utility of BNP in the broader HF population is unclear. (See Section 6.1 and Section 4.2)	It is currently unclear whether angiotensin receptor blocker or spironolcatone are the most effective treatments in those intolerant to ACEI. (See Sections 2.2.1)	There is evidence of benefit of nitrate and hydralazine in combination compared to placebo in caucasian LVSD population and of hydralazine and nitrates in black LVSD population on therapy with ACEI and beta blockers. (See Section 5.2.4)
Equality	There is a lack of effective treatments for			It is not known in this population how to replace an essential agent in treating HF	There is a lack of effective treatments for

Criterion	RP1 Beta Blocker or ACEI in Heart Failure with Preserved Left Ventricular Ejection Fraction	RP2 Telemonitoring, Natriuretic Peptide Monitoring or Clinical Monitoring in HF with LVSD	RP3 The use of natriuretic peptides in determining prognosis and resource allocation in the heart failure team	RP4 SPIRONOLACTONE OR Angiotensin receptor blocker in HF patients intolerant of ACEI	RP5 Hydralazine and or Nitrates in HFPEF
	this population			with LVSD	this population
Feasibility	Highly feasible	Highly feasible	Highly feasible	Feasible, but there is the difficulty of overcoming the current practice of automatically commence ARB whenever there is intolerance of ACEI	Highly feasible
Other comments					

Appendix L - Declarations of Interest

Introduction

All members of the GDG and all members of the NCGC staff were required to make formal declarations of interest at the outset, and these were updated at every subsequent meeting throughout the development process. The chair reviewed the declarations of interest at the start of each meeting and, with one exception, none were deemed in conflict with the agenda topics and clinical questions under discussion at the meetings. Dr Fuat (deputy for Dr Davis) did not take part in the discussions on Angiotensin Receptor Blockers as he has been a member of an Advisory Board on the use of Candesartan for heart failure for Takeda Pharmaceuticals since February 2009.

Declarations of interests of the GDG members

Dr Abdallah Al-Mohammad

GDG meeting	Declaration of Interests
GDG Application (14th November 2008)	AAM declared the following items of **personal pecuniary interest**: • Hospitality from Novartis in March 2008 to attend the American College of Cardiology meeting in Chicago (Conference registration fee, flights and hotel). • Honoraria for delivering educational lectures to general practitioners, heart failure nurses and Matrons on three occasions in the 12 months to the 14th of November 2008: AAM declared the following items of **personal non-pecuniary interest**: • Authored and co-authored papers on issues related to heart failure and imaging. • Investigator in several projects (funded by the industry and by scientific grants) on heart failure that are ongoing. • Honorary senior clinical lecturer in the University of Sheffield • Fellow of the Royal Colleges of Physicians of Edinburgh and London. • Member of the British Cardiovascular Society, the British Society of Heart Failure, the British Nuclear Cardiology Society, the European Association of Echocardiography, the European Society of Cardiology and the British Medical Association. AAM did not declare any items of **personal family interest or personal non-pecuniary interest**
GDG Induction meeting **(30th January 2009)**	No change in declaration
First GDG meeting (27th February 2009)	No change in declaration
Second GDG Meeting **(27th March 2009)**	No change in declaration
Third GDG Meeting **(1st May 2009)**	No change in declaration
Fourth GDG Meeting **(5th June 2009)**	No change in declaration
Fifth GDG Meeting	No change in declaration

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(3rd July 2009)	
Sixth GDG Meeting **(31st July 2009)**	No change in declaration.
Seventh GDG Meeting **(18th September 2009)**	No change in declaration
Eighth GDG Meeting **(16th October 2009)**	No change in declaration
Ninth GDG Meeting **(13th November 2009)**	No change in declaration
Tenth GDG Meeting (9th April 2010)	No change in declaration
Eleventh GDG meeting (June 2010)	No change in declaration

Dr Mark Davis

GDG meeting	Declaration of Interests
GDG Application 23/10/08	MD declared the following item of **personal pecuniary interest** • (Honorarium from Menarini for taking part in an Advisory Board (Feb 2008) MD did not declare any items of **personal pecuniary interest, personal family interest, non-personal pecuniary interest** or **personal non-pecuniary interest**
GDG Induction meeting **(30th January 2009)**	No change in declaration
First GDG meeting (27th February 2009)	DNA Potential conflict of interest from attending Advisory Board for Menarini expires.
Second GDG Meeting **(27th March 2009)**	As above plus: MD declared the following item of **personal pecuniary interest:** • Received a fee to attend a Takeda meeting on Practice Based Commissioning at which the role of ARBs in heart failure was discussed (6/3/09)
Third GDG Meeting **(1st May 2009)**	No change in declaration
Fourth GDG Meeting **(5th June 2009)**	No change in declaration
Fifth GDG Meeting **(3rd July 2009)**	DNA
Sixth GDG Meeting **(31st July 2009)**	DNA
Seventh GDG Meeting **(18th September 2009)**	No change in declaration
Eighth GDG Meeting **(16th October 2009)**	No change in declaration
Ninth GDG Meeting **(13th November 2009)**	No change in declaration
Tenth GDG Meeting (9th April 2010)	As above, plus: MD declared the following item of **personal pecuniary interest:** • Attended Takeda advisory board to discuss substitutions within ARB class
Eleventh GDG meeting (June 2010)	No change in declaration

Dr Paresh Dawda

GDG meeting	Declaration of Interests
GDG Application	PD did not declare any items of personal pecuniary interest, **personal family interest, non-personal pecuniary interest** or **personal non-pecuniary interest**
GDG Induction meeting **(30th January 2009)**	No change to declaration
First GDG meeting (27th February 2009)	PD declared the following item of **personal family interest:** • Sister is employed by Takeda Pharmaceuticals
Second GDG Meeting **(27th March 2009)**	No change to declaration
Third GDG Meeting **(1st May 2009)**	No change to declaration
Fourth GDG Meeting **(5th June 2009)**	No change to declaration
Fifth GDG Meeting **(3rd July 2009)**	As above plus: PD declared the following item of **non-personal pecuniary interest:** • His organisation was paid backfill by the NHS National Institute for Innovation and Improvement to cover his attendance at a Leadership in Patient Safety Course for 1 week (22/6/09-26/6/09).
Sixth GDG Meeting **(31st July 2009)**	No change to declaration
Seventh GDG Meeting **(18th September 2009)**	As above plus: PD declared the following item of **personal pecuniary interest:** • Supported by NHS Institute for Innovation and Improvement to attend a patient safety course at Institute for Healthcare Improvement in Boston USA (10-16 Sept 09)
Eighth GDG Meeting **(16th October 2009)**	As above plus: PD declared the following item of **personal pecuniary interest:** • Consultancy work for NHS Institute for Innovation and Improvement (from 7/10/09)
Ninth GDG Meeting **(13th November 2009)**	No change to declaration
Tenth GDG Meeting (9th April 2010)	No change to declaration
Eleventh GDG meeting (June 2010)	No change in declaration

Dr Paul Foley (Deputy for Dr Leyva)

GDG meeting	Declaration of Interests
GDG Application	Not applicable
GDG Induction meeting **(30th January 2009)**	DNA
First GDG meeting (27th February 2009)	DNA
Second GDG Meeting **(27th March 2009)**	DNA
Third GDG Meeting **(1st May 2009)**	DNA
Fourth GDG Meeting **(5th June 2009)**	DNA
Fifth GDG Meeting **(3rd July 2009)**	DNA
Sixth GDG Meeting **(31st July 2009)**	FL declared the following item of **personal pecuniary interest:** • The Heart of England NHS Foundation Trust receives payment from Medtronic Inc which goes towards his Research Fellow's salary PF declared no items of **personal family interest, non-personal pecuniary interest** or **personal non-pecuniary interest**
Seventh GDG Meeting **(18th September 2009)**	DNA
Eighth GDG Meeting **(16th October 2009)**	DNA
Ninth GDG Meeting **(13th November 2009)**	DNA
Tenth GDG Meeting (9th April 2010)	As above plus; PF declared the following item of **personal pecuniary interest:** • Chaired research meeting for Medtronic at which clinical research fellow presented data And the following item of personal non-pecuniary interest: • ongoing research into CRT
Eleventh GDG meeting (June 2010)	DNA

Dr Ahmet Fuat – Deputy for Dr Davis

GDG meeting	Declaration of Interests
GDG Application	Not applicable
GDG Induction meeting **(30th January 2009)**	DNA
First GDG meeting (27th February 2009)	AF declared the following items of **personal non-pecuniary interest:** • Chair of National GPs with specialist interest in Cardiology National Forum • Hon Sec of Primary care Cardiovascular Society AF did not declare any items of **personal pecuniary interest, personal family interest,** or **non-personal pecuniary interest**
Second GDG Meeting **(27th March 2009)**	DNA
Third GDG Meeting **(1st May 2009)**	DNA
Fourth GDG Meeting **(5th June 2009)**	DNA
Fifth GDG Meeting **(3rd July 2009)**	AF declared the following item of **personal pecuniary interest:** • Member of an Advisory Board on use of Candesartan for heart failure for Takeda Pharmaceuticals since February 2009. The chair reviewed the declarations of interest and noted the declarations of interest.
Sixth GDG Meeting **(31st July 2009)**	DNA
Seventh GDG Meeting **(18th September 2009)**	DNA
Eighth GDG Meeting **(16th October 2009)**	DNA
Ninth GDG Meeting **(13th November 2009)**	DNA AF declared the following item of **personal pecuniary interest:** • Honoraria from Pfizer for lecturing (Nov 2010).
Future commitments	AF declared the following item of **personal pecuniary interest:** • Honoraria from Pfizer for lecturing (Feb 2010).
Tenth GDG Meeting (9th April 2010)	DNA
Eleventh GDG meeting (June 2010)	DNA

Ms Jane Gilmour

GDG meeting	Declaration of Interests
GDG Application **(5th Nov 2008)**	JG did not declare any items of **personal pecuniary interest, personal family interest, non-personal pecuniary interest, personal non-pecuniary interest**
GDG Induction meeting **(30th January 2009)**	No change to declaration
First GDG meeting (27th February 2009)	No change to declaration
Second GDG Meeting **(27th March 2009)**	No change to declaration
Third GDG Meeting **(1st May 2009)**	No change to declaration
Fourth GDG Meeting **(5th June 2009)**	No change to declaration
Fifth GDG Meeting **(3rd July 2009)**	No change to declaration
Sixth GDG Meeting **(31st July 2009)**	No change to declaration
Seventh GDG Meeting **(18th September 2009)**	No change to declaration
Eighth GDG Meeting **(16th October 2009)**	No change to declaration
Ninth GDG Meeting **(13th November 2009)**	No change to declaration
Tenth GDG Meeting (9th April 2010)	JG declared an item of **non-personal non-pecuniary interest:** • Panel member at heart failure education event sponsored by Takeda (22/4/10)
Eleventh GDG meeting (June 2010)	No change in declaration

Dr Suzanna Hardman

GDG meeting	Declaration of Interests
GDG Application 19/11/08	SH declared the following items of **personal pecuniary interest:** • Share holdings in Glaxo and Astra Zeneca • Honorarium from Otsuku for taking part in an Advisory Board.(June 2008) • Travel expenses/accommodation from Takeda to attend ESC meeting (June 2008) • Honorarium from Menarini for taking part in an Advisory Board (Feb 2008) SH also declared the following item of **personal family interest:** • Husband has an investment with Glaxo Welcome SH declared the following item of **personal non-pecuniary interest** • Chair–elect of the British Society for Heart Failure SH did not declare any item of **non-personal pecuniary interest**
GDG Induction meeting **(30th January 2009)**	No change to declaration
First GDG meeting **(27th February 2009)**	Potential conflict of interest from attending Advisory Board for Menarini expires.
Second GDG Meeting **(27th March 2009)**	DNA
Third GDG Meeting **(1st May 2009)**	No change to declaration
Fourth GDG Meeting **(5th June 2009)**	No change to declaration
Fifth GDG Meeting **(3rd July 2009)**	No change to declaration
Sixth GDG Meeting **(31st July 2009)**	No change to declaration
Seventh GDG Meeting **(18th September 2009)**	No change to declaration
Eighth GDG Meeting **(16th October 2009)**	No change to declaration
Ninth GDG Meeting **(13th November 2009)**	No change to declaration
Tenth GDG Meeting (9th April 2010)	As above plus: SH declared the following item of **personal non-pecuniary interest:** • Speaker at Acute to Chronic Cardiovascular disease meeting on 25th March 2010 (Supported by Pfizer).
Eleventh GDG meeting (June 2010)	SH declared an item of **personal non-pecuniary interest:**

	• Discussions with Milliman re development of an ICP for heart failure

Dr Francisco Leyva

GDG meeting	Declaration of Interests
GDG Application 12/11/08	FL declared the following item of **non-personal pecuniary interest:** • The pacemaker industry (Medtronic Inc and St Jude Medical) provide funding for the salary of two of his research fellows who are involved in pacemaker and imaging research. Medtronic Inc has also funded a pacemaker research trial under his direction FL did not declare any items of **personal pecuniary interest, personal family interest or personal non-pecuniary interest**.
GDG Induction meeting **(30th January 2009)**	No change in declaration
First GDG meeting (27th February 2009)	No change in declaration
Second GDG Meeting **(27th March 2009)**	No change in declaration
Third GDG Meeting **(1st May 2009)**	No change in declaration
Fourth GDG Meeting **(5th June 2009)**	As above plus: FL declared an item of **personal pecuniary interest:** • Menarini provided funding for travel and accommodation for a conference in Barcelona
Fifth GDG Meeting **(3rd July 2009)**	No change in declaration
Sixth GDG Meeting **(31st July 2009)**	DNA
Seventh GDG Meeting **(18th September 2009)**	No change in declaration
Eighth GDG Meeting **(16th October 2009)**	No change in declaration
Ninth GDG Meeting **(13th November 2009)**	No change to declaration
Tenth GDG Meeting (9th April 2010)	No change to declaration
Eleventh GDG meeting (June 2010)	No change in declaration

Dr Hugh McIntyre

GDG meeting	Declaration of Interests
GDG Application 14/11/08	HM declared the following items of **personal pecuniary interest:** • Member of Advisory Board for Otsuku (Tolvaptan- prelicence product – possibly of heart failure) (June 2008) • Member of Advisory Board for Servier (Ivabradine – Angina) Oct 2009 • Reimbursement from Novartis, MSD, Pfizer for lecturing, in the 12montsh prior to Nov 2008 • Reimbursement from Servier (July 2008) and MSD (Jan 2008) for programme development and event chairing. • Expenses and hospitality to attend meetings and conferences 12 months before the GDG started HM declared the following item of **personal non-pecuniary interest:** • Consultancy (unpaid) to Extralife (independent provider of left ventricular assist devices) • Member of the Editorial board of the European Journal of Heart Failure (2008 onwards) HM declared the following item of **non-personal pecuniary interest:** • Educational grant from Takeda to support two year doctorate Research Fellow investigating socioeconomic gradient in heart failure (From Jan 2009). This does not involve any medical or product application or research • Member of ESC heart failure association committee on heart failure with preserved ejection fraction (From 2008) • Member of ESC heart failure association committee on education (From 2008) HM did not declare any items of **personal family interest**
GDG Induction meeting **(30th January 2009)**	No change to declaration
First GDG meeting (27th February 2009)	No change to declaration
Second GDG Meeting **(27th March 2009)**	No change to declaration
Third GDG Meeting **(1st May 2009)**	No change to declaration
Fourth GDG Meeting **(5th June 2009)**	As above plus: HM declared the following item of **personal pecuniary interest:** • Meeting fees, travel and accommodation for the Heart Failure Update meeting of the European Society of cardiology (NICE, May 30 – June 2nd) provided by Takeda pharmaceuticals • Meeting fees, travel and accommodation for the annual meeting of the European Society of Cardiology (Aug 30th – Sept 2nd) – provided by Servier pharmaceuticals
Fifth GDG Meeting **(3rd July 2009)**	No change to declaration
Sixth GDG Meeting **(31st July 2009)**	No change to declaration

Seventh GDG Meeting **(18th September 2009)**	No change to declaration
Eighth GDG Meeting **(16th October 2009)**	HM declared the following item of personal pecuniary interest: • Involved in a mathematical economic modelling project, funded by Novartis, on costing pathways. (From June 2009)
Ninth GDG Meeting **(13th November 2009)**	HM declared the following item of **personal pecuniary interest:** Received expenses from the Heart Failure Association of the European Society of Cardiology to attend and contribute to a meeting on heart failure with preserved ejection fraction (August 2009)
Future commitments	HM declared the following future commitments with **personal pecuniary interest:** • Member of Advisory Board for Takeda (Hypertension: Ivabradine – angina) (Nov 2009) • Member of Advisory Board for Sanofi (Dabigatron – prelicence anticoagulant (Dec 09) • Member of Advisory Board for MSD (Atrial fibrillation) (Dec09) • Member of Advisory Board for MSD (Sitagliptin – Diabetes) (Jan 2010)
Tenth GDG Meeting (9th April 2010)	No change to declaration
Eleventh GDG meeting (June 2010)	No change in declaration

Professor Jonathan Mant

GDG meeting	Declaration of Interests
GDG Application	JM declared the following items of **personal pecuniary interest:** • Consultancy for Expert-24, which advises on the Norwich Union HealthCare Site • Consultancy for PharmaSwiss, a drug company that markets drugs to parts of Southern and Eastern Europe. • Member of Regional Advisory Board for Boehringer Ingelheim (one meeting 10/11/2009). JM declared the following item of **personal family interest:** • Brother, Professor Tim Mant, is employed by Quintiles, which is a bioctech company involved in drug development. JM declared the following item of **personal non-pecuniary interest:** • Associate Director, Stroke Research Network JM did not declare any items of **non-personal pecuniary interest**
GDG Induction meeting **(30th January 2009)**	No change in declaration
First GDG meeting (27th February 2009)	No change in declaration
Second GDG Meeting **(27th March 2009)**	No change in declaration
Third GDG Meeting **(1st May 2009)**	No change in declaration
Fourth GDG Meeting **(5th June 2009)**	No change in declaration
Fifth GDG Meeting **(3rd July 2009)**	No change in declaration
Sixth GDG Meeting **(31st July 2009)**	No change in declaration
Seventh GDG Meeting **(18th September 2009)**	As above plus JM declared the following item of **personal pecuniary interest:** • Travel grant from Boehringer Ingelheim to attend European Society of Cardiology meeting at end of August 2009.
Eighth GDG Meeting **(16th October 2009)**	No change to declaration
Ninth GDG Meeting **(13th November 2009)**	No change to declaration
Tenth GDG Meeting (9th April 2010)	No change in declaration
Eleventh GDG meeting (June 2010)	No change in declaration

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Mr Richard Mindham

GDG meeting	Declaration of Interests
GDG Application 11/11/08	RM did not declare any items of **personal pecuniary interest, personal family interest, non-personal pecuniary interest, personal non-pecuniary interest**
GDG Induction meeting **(30th January 2009)**	No change in declaration
First GDG meeting (27th February 2009)	No change in declaration
Second GDG Meeting **(27th March 2009)**	No change in declaration
Third GDG Meeting **(1st May 2009)**	No change in declaration
Fourth GDG Meeting **(5th June 2009)**	No change in declaration
Fifth GDG Meeting **(3rd July 2009)**	No change in declaration
Sixth GDG Meeting **(31st July 2009)**	No change in declaration
Seventh GDG Meeting **(18th September 2009)**	No change in declaration
Eighth GDG Meeting **(16th October 2009)**	No change in declaration
Ninth GDG Meeting **(13th November 2009)**	No change to declaration
Tenth GDG Meeting (9th April 2010)	No change to declaration
Eleventh GDG meeting (June 2010)	No change in declaration

Mr Adrian Price

GDG meeting	Declaration of Interests
GDG Application 30/1/09	AP did not declare any items of **personal pecuniary interest, personal family interest, non-personal pecuniary interest, personal non-pecuniary interest**
GDG Induction meeting **(30th January 2009)**	No change to declaration
First GDG meeting (27th February 2009)	No change to declaration
Second GDG Meeting **(27th March 2009)**	No change to declaration
Third GDG Meeting **(1st May 2009)**	No change to declaration
Fourth GDG Meeting **(5th June 2009)**	No change to declaration
Fifth GDG Meeting **(3rd July 2009)**	No change to declaration
Sixth GDG Meeting **(31st July 2009)**	No change to declaration
Seventh GDG Meeting **(18th September 2009)**	No change to declaration
Eighth GDG Meeting **(16th October 2009)**	No change to declaration
Ninth GDG Meeting **(13th November 2009)**	No change to declaration
Tenth GDG Meeting (9th April 2010)	No change to declaration
Eleventh GDG meeting (June 2010)	No change in declaration

Dr Paul Collinson (Expert Advisor)

GDG meeting	Declaration of Interests
GDG Application	Not applicable
GDG Induction meeting **(30th January 2009)**	DNA
First GDG meeting (27th February 2009)	PC declared no items of **personal pecuniary interest, personal family interest, non-personal pecuniary interest or personal non-pecuniary interest**
Second GDG Meeting **(27th March 2009)**	No changes to declaration
Third GDG Meeting **(1st May 2009)**	DNA
Fourth GDG Meeting **(5th June 2009)**	DNA
Fifth GDG Meeting **(3rd July 2009)**	DNA
Sixth GDG Meeting **(31st July 2009)**	No changes to declaration
Seventh GDG Meeting **(18th September 2009)**	DNA
Eighth GDG Meeting **(16th October 2009)**	DNA
Ninth GDG Meeting **(13th November 2009)**	DNA
Tenth GDG Meeting (9th April 2010)	DNA
Eleventh GDG meeting (June 2010)	DNA

Ms Aynsley Cowie (Expert Advisor)

GDG meeting	Declaration of Interests
GDG Application	Not applicable
GDG Induction meeting **(30th January 2009)**	DNA
First GDG meeting (27th February 2009)	DNA
Second GDG Meeting **(27th March 2009)**	DNA
Third GDG Meeting **(1st May 2009)**	DNA
Fourth GDG Meeting **(5th June 2009)**	DNA
Fifth GDG Meeting **(3rd July 2009)**	AC declared no items of **personal pecuniary interest, personal family interest, non-personal pecuniary interest or personal non-pecuniary interest**
Sixth GDG Meeting **(31st July 2009)**	DNA
Seventh GDG Meeting **(18th September 2009)**	DNA
Eighth GDG Meeting **(16th October 2009)**	DNA
Ninth GDG Meeting **(13th November 2009)**	DNA
Tenth GDG Meeting (9th April 2010)	DNA
Eleventh GDG meeting (June 2010)	DNA

Appendix M – 2003 Guideline

See separate file

Appendix N – 2003 deleted recommendations

Diagnosis

R2 Healthcare professionals should seek to exclude a diagnosis of heart failure through the following investigations:

- 12lead ECG
- And or natriuretic peptides (BNP or NT-proBNP) – where available

If one or both are abnormal a diagnosis of heart failure cannot be excluded and transthoracic Doppler 2D echocardiography should be performed because it consolidates the diagnosis and provides information on the underlying functional abnormality of the heart

R9 If the diagnosis is unclear or if a diagnosis of diastolic heart failure is being considered refer the patient for more specialist assessment

Treatment - Lifestyle

R12 Patients with heart failure should be encouraged to adopt regular aerobic and/or resistive exercise. This may be more effective when part of an exercise programme or a programme of rehabilitation.

Treatment – Pharmacological treatment

R22 All patients with heart failure due to left ventricular systolic dysfunction should be considered for treatment with an ACE inhibitor.

R23 ACE inhibitor therapy should be instituted in patients with heart failure due to left ventricular systolic dysfunction before beta-blockade is introduced.

R26 Beta-blockers licensed for use in heart failure should be initiated in patients with heart failure due to LV systolic dysfunction after diuretic and ACE inhibitor therapy (regardless of whether or not symptoms persist).

R32 At the time of issue of this guideline, angiotensin-II receptor antagonists (see Table 8) are not licensed in the UK for heart failure and studies are ongoing. However, angiotensin-II receptor antagonists may provide an alternative to ACE inhibitors for patients intolerant of ACE inhibitors (for example, because of cough

R33 The triple combination of ACE inhibitor, beta-blocker and angiotensin-II receptor antagonist should be avoided, pending the results of further trials.

R 37 Anticoagulation is indicated for patients with the combination of heart failure and atrial fibrillation.

R40 Patients with the combination of heart failure and known atherosclerotic vascular disease should receive statins only in accordance with the current indications. Specific trials in this area are ongoing.

R41 An isosorbide/hydralazine combination may be used in patients with heart failure who are intolerant of ACE inhibitors or angiotensin-II receptor antagonists.

R52 For patients with heart failure and atrial fibrillation, specialist advice should be sought as to whether the aim is improvement of heart rate control or cardioversion (return to sinus rhythm).

R59 The principles of pharmacological management should be the same for all patients with heart

failure, regardless of ethnicity.

Treatment - Cardiac resynchronisation therapy

R47 Resynchronisation therapy should be considered in selected patients with left ventricular systolic dysfunction (LVEF <= 35%), drug refractory symptoms, and a QRS duration > 120 ms. The result of ongoing trials will help guide appropriate patient selection. [2003, R47]

Treatment - Implantable cardioverter-defibrillators (ICDs)

R48 Recommendation from NICE Technology Appraisal Guidance No. 11 Guidance on the use of implantable cardioverter defibrillators for arrhythmias (www.nice.org.uk/Docref.asp?d=10239):

The use of implantable cardioverter defibrillators (ICDs) should be routinely considered for patients in the following categories:

"Secondary prevention" ie for patients who present, in the absence of a treatable cause, with:

- Cardiac arrest due to either ventricular tachycardia (VT) or ventricular fibrillation (VF).
- Spontaneous sustained VT causing syncope or significant haemodynamic compromise.
- Sustained VT without syncope/cardiac arrest, and who have an associated reduction in ejection fraction (less than 35%) but are no worse than class 3 of the New York Heart Association functional classification of heart failure.

"Primary prevention" for patients (see paragraph 2.5 for definition) with:

- a history of previous myocardial infarction (MI) and all of the following:
- i) non sustained VT on Holter (24 hour ECG) monitoring;
- ii) inducible VT on electrophysiological testing;
- iii) left ventricular dysfunction with an ejection fraction (EF) less than 35% and no worse than class III of the New York Heart Association functional classification of heart failure.
- A familial cardiac condition with a high risk of sudden death, including long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome, arrhythmogenic right ventricular dysplasia (ARVD) and following repair of Tetralogy of Fallot.[2003, R48]