CHRONIC HEART FAILURE: THE MANAGEMENT OF ADULTS WITH CHRONIC HEART FAILURE IN PRIMARY AND SECONDARY CARE (PARTIAL UPDATE)

National clinical guideline for CHF (partial update)

DRAFT FOR CONSULTATION
January 2010

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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.

Invited Experts

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

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) and Susan Latchem (Guideline Commissioning Manager, NICE) for their support and help.
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Preface

<<To be added after consultation – to written by Bernard Higgins (tbc)>>
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# Chronic heart failure

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   - Measurement of circulating natriuretic peptide concentration
   - Recommendations for diagnosing heart failure
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2. **Lifestyle**
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6. **Treatment algorithm**

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2. **Clinical Methodological introduction**
3. **Clinical evidence statements**
4. **Health Economic Methodological introduction**
5. **Health economic evidence statements**
6. **Summary of evidence statements**
7. **From evidence to recommendations**
8. **Recommendations for rehabilitation**
9. **Recommendations to be deleted**

## MONITORING
### Glossary

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACEI</td>
<td>Angiotensin-converting enzyme inhibitors.</td>
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<tr>
<td>AF</td>
<td>Atrial fibrillation.</td>
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<tr>
<td>AMI</td>
<td>Acute myocardial infarction</td>
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<tr>
<td>ARB</td>
<td>Angiotensin receptor blocker</td>
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<tr>
<td>BB</td>
<td>Beta blocker</td>
</tr>
<tr>
<td>BNF</td>
<td>British national formulary</td>
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<tr>
<td>BNP</td>
<td>B-type natriuretic peptide.</td>
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<tr>
<td>BP</td>
<td>Blood pressure</td>
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<tr>
<td>CABG</td>
<td>Coronary artery bypass grafting.</td>
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<tr>
<td>CHD</td>
<td>Coronary heart disease.</td>
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<tr>
<td>CHF</td>
<td>Chronic heart failure.</td>
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<tr>
<td>CI</td>
<td>Confidence interval.</td>
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<tr>
<td>CM</td>
<td>Cardiomyopathy</td>
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<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
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<tr>
<td>CRT</td>
<td>Cardiac resynchronisation therapy</td>
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<tr>
<td>CV mortality</td>
<td>Cardiovascular mortality</td>
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<tr>
<td>DM</td>
<td>Diabetes mellitus</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram.</td>
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<tr>
<td>ER</td>
<td>Emergency room</td>
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<tr>
<td>ESC</td>
<td>European society of cardiology</td>
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<tr>
<td>GDG</td>
<td>Guideline development group.</td>
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<tr>
<td>GP</td>
<td>General practitioner.</td>
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<tr>
<td>GPP</td>
<td>Good practice point.</td>
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<tr>
<td>GRADE</td>
<td>Grading of Recommendations assessment, development and evaluation</td>
</tr>
<tr>
<td>Haemodynamic</td>
<td>Relating to the circulation of the blood.</td>
</tr>
<tr>
<td>HF</td>
<td>Heart failure.</td>
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<tr>
<td>HFPEF</td>
<td>Heart failure with preserved ejection fraction</td>
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<tr>
<td>HTA</td>
<td>Health Technology Assessment</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>Heart abnormality characterised by thickening of the heart muscle due to a genetic cause.</td>
</tr>
<tr>
<td>ICD</td>
<td>Implantable cardioverter defibrillator.</td>
</tr>
<tr>
<td>ICER</td>
<td>Incremental cost-effectiveness</td>
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<tr>
<td>IHD</td>
<td>Ischaemic heart disease</td>
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<tr>
<td>INR</td>
<td>International normalised ratio.</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>--------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Ischaemia</td>
<td>Insufficient blood supply to an organ or tissue.</td>
</tr>
<tr>
<td>ISDN+Hyd</td>
<td>Isosorbide dinitrate and hydralazine.</td>
</tr>
<tr>
<td>ISWT</td>
<td>Incremental Shuffle Walk Test</td>
</tr>
<tr>
<td>IVRT</td>
<td>Isovolumic relaxation time</td>
</tr>
<tr>
<td>JVP</td>
<td>Jugular venous pressure</td>
</tr>
<tr>
<td>K+</td>
<td>Potassium.</td>
</tr>
<tr>
<td>LV</td>
<td>Left ventricular.</td>
</tr>
<tr>
<td>LVADs</td>
<td>Left ventricular assist devices.</td>
</tr>
<tr>
<td>LVEF</td>
<td>Left ventricular ejection fraction.</td>
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<tr>
<td>LVSD</td>
<td>Left ventricular systolic dysfunction.</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction.</td>
</tr>
<tr>
<td>MICE</td>
<td>Male, history of myocardial infarction, crepitations, ankle oedema</td>
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<tr>
<td>MID</td>
<td>Minimal important difference</td>
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<tr>
<td>MLHF</td>
<td>MLHF.</td>
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<tr>
<td>MLWHFQ</td>
<td>Minnesota living with heart failure questionnaire</td>
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<tr>
<td>6MWT</td>
<td>6 minute walk test</td>
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<tr>
<td>NCC-CC</td>
<td>National Collaborating Centre – Chronic Conditions</td>
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<tr>
<td>NCGC or NCGC-ACC</td>
<td>National Clinical Guideline Centre for Acute and Chronic Conditions</td>
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<tr>
<td>NHS</td>
<td>National health service</td>
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<tr>
<td>NICE</td>
<td>National Institute for Clinical Excellence.</td>
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<tr>
<td>NP</td>
<td>Natriuretic peptide</td>
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<tr>
<td>NSF</td>
<td>National Service Framework.</td>
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<tr>
<td>NTproBNP</td>
<td>N-terminal pro-B-type natriuretic peptide.</td>
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<tr>
<td>NYHA</td>
<td>New York Heart Association (functional classification).</td>
</tr>
<tr>
<td>PICO</td>
<td>Population, Intervention, Comparison and Outcome</td>
</tr>
<tr>
<td>PCT</td>
<td>Primary care trust.</td>
</tr>
<tr>
<td>PND</td>
<td>Paroxysmal nocturnal dyspnoea</td>
</tr>
<tr>
<td>PPIP</td>
<td>Patient and Public Involvement Programme</td>
</tr>
<tr>
<td>PWD</td>
<td>Pulsed wave doppler</td>
</tr>
<tr>
<td>QALY</td>
<td>Quality adjusted life year</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>QUADAS</td>
<td>Quality Assessment of Diagnostic Studies</td>
</tr>
<tr>
<td>Rehabilitation</td>
<td>Process to assist patients to achieve optimal function. May include a period of exercise training.</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>SR</td>
<td>Systematic review</td>
</tr>
<tr>
<td>TDI</td>
<td>Tissue Doppler imaging</td>
</tr>
<tr>
<td>Titration</td>
<td>The administration of small incremental doses of a drug until a either the target dose or the maximum tolerated dose had been reached</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom.</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>A type of serious heart rhythm problem characterized by very rapid, irregular, uncoordinated electrical activity of the ventricles with no pumping effect, it is fatal if not corrected immediately</td>
</tr>
<tr>
<td>(VT) Ventricular tachycardia</td>
<td>A type of serious heart rhythm problem arising in the ventricles resulting in (usually) very rapid contraction of the ventricles.</td>
</tr>
<tr>
<td>WTP</td>
<td>Willingness to pay</td>
</tr>
</tbody>
</table>
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, and those signs caused by complications of both heart failure and its therapy.

Initially, research into heart failure concentrated on the 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. However, 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.

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 5 – 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.

In the context of this guideline a specialist is defined as a secondary care Consultant with sub speciality interest in HF, who will usually be a Cardiologist, and who will work with a multi-disciplinary HF team.

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. Both the incidence and
prevalence of heart failure increase steeply with age, with the average age at first diagnosis being 76 years. 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. 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. 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.

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. A history of hypertension is also common, 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. 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, 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: just under 40% of patients diagnosed with heart failure die within a year – but thereafter the mortality is less than 10% per year. Survival rates are similar to those from cancer of the colon, and worse than those from cancer of the breast or prostate. Younger patients do better, as do patients with no other medical problems. Heart failure has a major impact on quality of life, and is associated with mood disorders.

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. 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.

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. 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. Admissions tend to be protracted: averaging 11 days in Europe, and readmissions are common (about 1 in 4 patients are readmitted in three months).

Associated co-morbidity accounts for a substantial proportion of admissions of people with a diagnosis of heart failure. 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.

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 may not be as great as for other chronic conditions).
1 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. \(^{17}\)

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.\(^{18}\)

### 1.4 Rationale for the partial 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).\(^{19}\)

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](http://www.nice.org.uk)) or, within the UK, from the NHS Response Line (0870 1555 455).

### 1.6 Principles for guideline development

The main principles behind the development of this partial 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
1. Indicate areas of uncertainty or controversy needing further research.
2. Provide a choice of guideline versions for different audiences.

1.7 Scope of partial 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. The scope for the partial 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.


1.9 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 review 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[21].

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. The rest of the guideline development followed the methods of the NICE Guideline manual 2009.

2.2 The Developers

2.2.1 The National Clinical Guideline Centre for Acute and Chronic Conditions

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 for Acute and Chronic Conditions (NCGC-ACC) 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. 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 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-ACC 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
2.3.1 Identifying areas of existing guidance that need updating

The NCGC-ACC 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

<table>
<thead>
<tr>
<th>Component</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review question</td>
<td>The review question as agreed by the GDG.</td>
</tr>
<tr>
<td>Objectives</td>
<td>Short description; for example ‘To estimate the effects and cost effectiveness of…’ or ‘To estimate the diagnostic accuracy of…’.</td>
</tr>
<tr>
<td>Criteria for considering studies for the review</td>
<td>Using the PICO (population, intervention, comparison and outcome) framework. Including the study designs selected.</td>
</tr>
<tr>
<td>How the information will be searched</td>
<td>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.)</td>
</tr>
<tr>
<td>The review strategy</td>
<td>The methods that will be used to review the evidence, outlining exceptions and subgroups. Indicate if meta-analysis will be used.</td>
</tr>
</tbody>
</table>

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 print 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 but 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’.

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.
1 **Quality of evidence**

2 The quality of clinical evidence is graded as follows:

3 **Table 2.2: Quality of evidence**

<table>
<thead>
<tr>
<th>Quality</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Further research is very unlikely to change our confidence in the estimate of effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</td>
</tr>
<tr>
<td>Low</td>
<td>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</td>
</tr>
<tr>
<td>Very low</td>
<td>Any estimate of effect is very uncertain.</td>
</tr>
</tbody>
</table>

4 The quality of the evidence is dependent on the following factors:

5 - study design
6 - limitations
7 - inconsistency
8 - indirectness
9 - imprecision

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

**Study design**

13 The quality of evidence for RCT studies is reduced according to the factors specified above.

14 The quality of observational evidence or any other evidence can be increased if

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

**Limitations in the design**

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

21 - unclear allocation concealment
22 - lack of blinding
23 - 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%
24 - 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**

31 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 ReviewManager 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 of 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. Data was pooled using a fixed effects model. 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. 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 optimizing 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 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.

Evidence tables are available on-line at (to be completed upon publication)

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**

<table>
<thead>
<tr>
<th>Version</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full version:</td>
<td>Details the recommendations, the supporting evidence base and the expert considerations of the GDG. Published by the NCGC-ACC. Available at (to be completed upon publication)</td>
</tr>
<tr>
<td>NICE version:</td>
<td>Documents the recommendations without any supporting evidence. Available at (to be completed upon publication)</td>
</tr>
<tr>
<td>&quot;Quick reference guide&quot;:</td>
<td>An abridged version. Available at (to be completed upon publication)</td>
</tr>
<tr>
<td>&quot;Understanding NICE guidance&quot;:</td>
<td>A lay version of the guideline recommendations Available at (to be completed upon publication)</td>
</tr>
</tbody>
</table>

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 or www.rcplondon.ac.uk/pubs/books/chf/].

For diagnostic reviews, the clinical and health economic evidence from each full paper was distilled into an evidence table [Appendix E or www.rcplondon.ac.uk/pubs/books/chf/] 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, Rx]**
  - Recommendation (number Rx) from the 2003 guideline where the **evidence has not been formally reviewed** for the 2010 update. The recommendation is shaded in grey. Grey text in these recommendations is not open for stakeholder comment. Yellow highlight in these recommendations indicates where wording has been changed for purposes of clarification only.

- **[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. These changes are not highlighted)

- **[new 2010]**
  - Recommendation from 2003 guideline which has been **changed following review of evidence**
  - New recommendation **following review of evidence**

Recommendations from the 2003 guideline that are to be deleted are marked in strikethrough font and are listed at the end of each section. These are included for the consultation only.
3 Key recommendations and algorithms

3.1 Key recommendations

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 echocardiography and specialist assessment within 2 weeks. [new 2010] [R4]

2. Measure serum natriuretic peptides in patients with suspected heart failure without previousMI. [new 2010] [R5]

3. Refer patients with suspected heart failure and very high levels of serum natriuretic peptides urgently, to have echocardiography and specialist assessment within 2 weeks. [new 2010] [R6]

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] [R29]

5. Offer beta-blockers licensed for heart failure to all patients with heart failure due to left ventricular systolic dysfunction, including those with:
   - peripheral vascular disease
   - erectile dysfunction
   - diabetes mellitus
   - interstitial pulmonary disease and
   - chronic obstructive pulmonary disease (COPD) without reversibility.

   There is no upper age limit. [new 2010] [R32]

6. Offer an aldosterone antagonist to patients with heart failure due to left ventricular systolic dysfunction if moderate to severe symptoms persist despite optimal therapy with an ACE inhibitor and beta-blocker. [new 2010] [R35]

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.

   - Include a psychological and educational component in the programme.

---

1 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.
• The programme may be incorporated within an existing cardiac rehabilitation programme [new 2010] [R66]

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 and creatinine² [2003] [R67]

9. Ongoing management of patients admitted to hospital with heart failure should be guided by the opinion of a specialist in heart failure. [new 2010] [R71]

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] [R77]

---

² 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

*Other recommended tests:
- ECG
- chest X-ray
- blood tests: U&Es, creatinine, FBC, TFTs, glucose, and lipids
- urinalysis,
- peak flow or spirometry

**Non-HF causes of rises of NP:**
LVH, ischaemia, tachycardia, RV overload, hypoxaemia, renal dysfunction, infection, sepsis, advanced age, cirrhosis of the liver.

***Factors lowering NP:**
Obesity and diuretics

α: assess HF severity, aetiology, precipitating and exacerbating factors and type of cardiac dysfunction. Correctable causes must be identified.

δ: Heart failure specialist: The secondary care consultant with a subspeciality interest in heart failure, who is usually a cardiologist, and who will work in a multi-disciplinary team
3.3 Algorithm for the pharmacological treatment of symptomatic heart failure

HF Diagnosed by specialist

HF-PEF
Symptomatic Treatment (diuretics) + Manage co-morbidities (e.g. BP, DM, HF, inherited CM)

Specialist opinion

HF-LVSD
ACEI* + β Blockers

Specialist opinion

Still Symptomatic

ACEI* + β Blockers

Specialist opinion

Still Symptomatic

• Consider CRT-P/D (where appropriate)
• Consider digoxin (all)
• Consider Hydralazine + Nitrates (Black patient)

*For practical recommendations on the use of ACEI, beta blockers and aldosterone antagonists refer to Appendix J.

For practical recommendations on the use of ACEI, beta blockers and aldosterone antagonists refer to Appendix J.
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 echocardiography unless otherwise specified.

4.1 Symptoms, signs and investigation

DIAG: 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. Authors 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.

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). 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. 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.

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

<table>
<thead>
<tr>
<th>Class</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No limitations. Ordinary physical activity does not cause fatigue breathlessness or palpitation. (Asymptomatic left ventricular dysfunction is included in this category)</td>
</tr>
<tr>
<td>II</td>
<td>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)</td>
</tr>
</tbody>
</table>
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. None of these symptoms are specific for heart failure, and therefore cannot be relied upon alone to make the diagnosis of heart failure. 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 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. 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. Only systematic reviews were included.

Three systematic reviews (SR) were included. 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. One of the SRs 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.
- All the SRs looked at the diagnostic accuracy of each symptom and sign alone which may not be useful in practice when a combination would be used to make a diagnosis of chronic heart failure.
- 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.
- 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

<table>
<thead>
<tr>
<th>Overlap of included studies</th>
<th>Population/Setting</th>
<th>Symptoms/signs</th>
<th>Reference standard</th>
</tr>
</thead>
</table>
| MANT 2009 N=15 studies      | 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 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
<table>
<thead>
<tr>
<th>Study</th>
<th>N of studies</th>
<th>Description</th>
<th>N of patients</th>
<th>Diagnostic Tests</th>
<th>Echocardiogram</th>
</tr>
</thead>
<tbody>
<tr>
<td>WANG 2005</td>
<td>22</td>
<td>4 of the same 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.</td>
<td>N= 10,710 patients</td>
<td>Symptoms, signs (history of MI, diabetes, hypertension; 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)</td>
<td>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.</td>
</tr>
</tbody>
</table>
### 4.1.3 Clinical evidence statements

#### a) Dyspnoea

Two of the SRs reported on the diagnostic accuracy of dyspnoea \(^{34,35}\).

**Table 4.4: Diagnostic accuracy of dyspnoea**

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive likelihood ratio (95% CI)</th>
<th>Negative likelihood ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All settings + patients (MANT 2009)</td>
<td>83</td>
<td>54</td>
<td>1.79 (1.30-2.47)</td>
<td>0.31 (0.12-0.79)</td>
</tr>
<tr>
<td>LVSD in primary care (MADHOK 2008)</td>
<td>-</td>
<td>-</td>
<td>1.15 (1.09 - 1.21)</td>
<td>0.50 (0.20 - 1.26)</td>
</tr>
</tbody>
</table>

#### b) Dyspnoea on exertion

One SR reported on the diagnostic accuracy of dyspnoea on exertion \(^{33}\).

**Table 4.5: Diagnostic accuracy of dyspnoea on exertion**

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive likelihood ratio (95% CI)</th>
<th>Negative likelihood ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency department (WANG 2005)</td>
<td>84</td>
<td>34</td>
<td>1.3 (1.2-1.4)</td>
<td>0.48 (0.35-0.67)</td>
</tr>
</tbody>
</table>

#### c) Orthopnoea

All three SRs reported on the diagnostic accuracy of orthopnoea \(^{33-35}\).

**Table 4.6: Diagnostic accuracy of orthopnoea**

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

One study reported on the diagnostic accuracy of orthopnoea in a subgroup of patients with a history of asthma or COPD \(^{33}\).
Table 4.7: Diagnostic accuracy of orthopnea in patients with history of asthma or COPD

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive likelihood ratio (95% CI)</th>
<th>Negative likelihood ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency department</td>
<td>70</td>
<td>44</td>
<td>1.3 (1.1-1.5)</td>
<td>0.68 (0.48-0.95)</td>
</tr>
<tr>
<td>(WANG 2005)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

d) Paroxysmal nocturnal dyspnoea (PND)
Two of the SRs reported individual results on the diagnostic accuracy of PND\textsuperscript{33,35}

Table 4.8: Diagnostic accuracy of PND

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive likelihood ratio (95% CI)</th>
<th>Negative likelihood ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVSD in primary care</td>
<td>-</td>
<td>-</td>
<td>1.71 (range 1.12 - 2.23)</td>
<td>0.87 (range 0.75 - 0.99)</td>
</tr>
<tr>
<td>(MADHOK 2008)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency department</td>
<td>41</td>
<td>84</td>
<td>2.6 (1.5-4.5)</td>
<td>0.70 (0.54-0.91)</td>
</tr>
<tr>
<td>(WANG 2005)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

e) Oedema
Two of the SRs reported on the diagnostic accuracy of oedema\textsuperscript{33,34}

Table 4.9: Diagnostic accuracy of oedema

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive likelihood ratio (95% CI)</th>
<th>Negative likelihood ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All settings + patients</td>
<td>53</td>
<td>72</td>
<td>3.91 (1.51-10.11)</td>
<td>0.63 (0.53-0.74)</td>
</tr>
<tr>
<td>(MANT 2009)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency department</td>
<td>51</td>
<td>76</td>
<td>2.1 (0.92-5.0)</td>
<td>0.64 (0.39-0.91)</td>
</tr>
<tr>
<td>(WANG 2005)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

One SR reported on the diagnostic accuracy of lower extremity oedema\textsuperscript{33} in all patients and a subgroup of patients with a history of asthma or COPD.

Table 4.10: Diagnostic accuracy of lower extremity oedema

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive likelihood ratio (95% CI)</th>
<th>Negative likelihood ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency department</td>
<td>50</td>
<td>78</td>
<td>2.3 (1.5-3.7)</td>
<td>0.64 (0.47-0.87)</td>
</tr>
<tr>
<td>(WANG 2005)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-all patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subgroup</td>
<td>69</td>
<td>75</td>
<td>2.7 (2.2-3.5)</td>
<td>0.41 (0.30-0.57)</td>
</tr>
</tbody>
</table>
f) Elevated JVP

All three SRs reported on the diagnostic accuracy of elevated JVP.  

Table 4.11: Diagnostic accuracy of elevated JVP

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive likelihood ratio (95% CI)</th>
<th>Negative likelihood ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All settings + patients</td>
<td>52</td>
<td>70</td>
<td>1.73 (1.23-2.43)</td>
<td>0.68 (95% CI 0.56-0.84)</td>
</tr>
<tr>
<td>LVSD in primary care</td>
<td>-</td>
<td>-</td>
<td>4.36 (range 2.66 - 7.44)</td>
<td>0.88 (0.83 - 0.91)</td>
</tr>
<tr>
<td>Emergency department</td>
<td>39</td>
<td>92</td>
<td>5.1 (3.2-7.9)</td>
<td>0.66 (0.57-0.77)</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive likelihood ratio (95% CI)</th>
<th>Negative likelihood ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency department</td>
<td>41</td>
<td>90</td>
<td>4.3 (2.8-6.5)</td>
<td>0.65 (0.54-0.78)</td>
</tr>
</tbody>
</table>

g) Displaced apex beat

One SR reported on the diagnostic accuracy of a displaced apex beat.

Table 4.13: Diagnostic accuracy of displaced apex beat

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive likelihood ratio (95% CI)</th>
<th>Negative likelihood ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVSD in primary care</td>
<td>-</td>
<td>-</td>
<td>15.96 (8.24 - 30.93)</td>
<td>0.58 (range 0.35 - 0.93)</td>
</tr>
</tbody>
</table>

h) Added heart sounds

All three SRs reported on the diagnostic accuracy of added heart sounds.

Table 4.14: Diagnostic accuracy of added heart sounds

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive likelihood ratio (95% CI)</th>
<th>Negative likelihood ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All settings + patients</td>
<td>11</td>
<td>99</td>
<td>12.1 (95% CI 5.74-25.4)</td>
<td>0.90 (95% CI 0.82-0.99)</td>
</tr>
</tbody>
</table>
One study reported on the diagnostic accuracy of a third heart sound in a subgroup of patients with a history of asthma or COPD. 

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

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive likelihood ratio (95% CI)</th>
<th>Negative likelihood ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LVSD in primary care (MADHOK 2008)</strong> (added 3rd heart sound)</td>
<td>-</td>
<td>-</td>
<td>7.34 (range 1.56 - 32.37)</td>
<td>0.92 (range 0.77 - 0.96)</td>
</tr>
<tr>
<td><strong>Emergency department (WANG 2005)</strong> (added third heart sound)</td>
<td>13</td>
<td>99</td>
<td>11 (4.9-25.0)</td>
<td>0.88 (0.83-0.94)</td>
</tr>
<tr>
<td><strong>Emergency department (WANG 2005)</strong> (added fourth heart sound)</td>
<td>5</td>
<td>97</td>
<td>1.6 (0.47-5.5)</td>
<td>0.98 (0.93-1.0)</td>
</tr>
</tbody>
</table>

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

i) Lung crepitations/ rales/ abnormal breath sounds

All three SRs reported on the diagnostic accuracy of lung crepitation/ rales/ abnormal breath sounds. 

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

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive likelihood ratio (95% CI)</th>
<th>Negative likelihood ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Emergency department (WANG 2005)</strong></td>
<td>17</td>
<td>100</td>
<td>57.0 (7.6-425)</td>
<td>0.83 (0.75-0.91)</td>
</tr>
</tbody>
</table>

All settings + patients (MANT 2009)

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive likelihood ratio (95% CI)</th>
<th>Negative likelihood ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LVSD in primary care (MADHOK 2008)</strong></td>
<td>-</td>
<td>-</td>
<td>1.53 (1.17 - 1.19)</td>
<td>0.85 (range 0.64 - 0.94)</td>
</tr>
<tr>
<td><strong>Emergency department (WANG 2005)</strong></td>
<td>60</td>
<td>78</td>
<td>2.8 (1.9-4.1)</td>
<td>0.51 (0.37-0.70)</td>
</tr>
</tbody>
</table>

One study reported on the diagnostic accuracy of abnormal breath sounds in a subgroup of patients with a history of asthma or COPD.
Table 4.17: Diagnostic accuracy of abnormal breath sounds in patients with history of asthma or COPD

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive likelihood ratio (95% CI)</th>
<th>Negative likelihood ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency department</td>
<td>71</td>
<td>73</td>
<td>2.6 (2.1-3.3)</td>
<td>0.39 (0.28-0.55)</td>
</tr>
<tr>
<td>(WANG 2005)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

j). Fatigue

Two of the SRs reported on the diagnostic accuracy of fatigue

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive likelihood ratio (95% CI)</th>
<th>Negative likelihood ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVSD in primary care</td>
<td>-</td>
<td>-</td>
<td>1.03 (0.84 - 1.25)</td>
<td>0.98 (range 0.88 - 1.17)</td>
</tr>
<tr>
<td>(MADHOK 2008)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency department</td>
<td>31</td>
<td>70</td>
<td>1.0 (0.74-1.4)</td>
<td>0.99 (0.85-1.1)</td>
</tr>
<tr>
<td>(WANG 2005) (+ weight gain)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive likelihood ratio (95% CI)</th>
<th>Negative likelihood ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency department</td>
<td>74</td>
<td>34</td>
<td>1.1 (0.96-1.3)</td>
<td>0.79 (0.54-1.2)</td>
</tr>
<tr>
<td>(WANG 2005)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

k). Hepatomegaly/ hepatic congestion

One SR reported on the diagnostic accuracy of hepatomegaly

Table 4.20: Diagnostic accuracy of hepatomegaly

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive likelihood ratio (95% CI)</th>
<th>Negative likelihood ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All settings + patients</td>
<td>17</td>
<td>97</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(MANT 2009)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

One SR reported on the diagnostic accuracy of hepatic congestion in a subgroup of patients with a history of asthma or COPD
Table 4.21: Diagnostic accuracy of heaptic congestion in patients with history of asthma or COPD

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive likelihood ratio (95% CI)</th>
<th>Negative likelihood ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency department</td>
<td>14</td>
<td>94</td>
<td>2.4 (1.2-4.7)</td>
<td>0.91 (0.84-1.0)</td>
</tr>
<tr>
<td>(WANG 2005)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4.1.4 Health Economic Methodological Introduction

The 2003 Guideline 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) presented an 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 MICE scoring system); (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 6-month delay 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 QALYs gained from early diagnosis (impact of early diagnosis on survival and quality of life) estimated for a 3-year time horizon. The threshold was estimated as QALYs gained from an early diagnosis x £20,000 (the NICE threshold per QALY gained) + the 6-month cost incurred by the delay in diagnosis. WTP thresholds using QALYs gained were also calculated for a 5- and a 10-year time horizons for use in the sensitivity analysis.

---

3 Clinical Scoring System to determine risk of heart failure (Male; Infarction; Crepitations; Edema)
The sensitivity and specificity of natriuretic peptide measurement at different cut off points were taken from the meta-analysis presented in the HTA. A sensitivity of 100% for echocardiography (including specialist assessment) was assumed. 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Study quality*</th>
<th>Study applicability**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mant 2009</td>
<td>Minor limitations (a)</td>
<td>Directly applicable</td>
</tr>
</tbody>
</table>

*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. These results suggested that, if a 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. When the analysis did not consider life expectancy and quality of life (QALYs), conclusions varied depending on the original MICE score: do not refer for further investigations; refer patients to natriuretic peptide measurement prior to echo; or refer patients directly to echo. The QALY analysis is more in agreement with the NICE reference case and are of more interest for the decision-making.

The main limitation of this analysis is that if there is a limited access to echo then there could be a delay in investigation and it may affect the results by limiting the direct access to echo (through increasing hospitalisation costs and WTP thresholds). This was not assessed in the sensitivity. In addition, it was assumed 100% sensitivity and specificity for echo + clinical assessment. This assumption was judged to be reasonable. However, most would believe the sensitivity and specificity of the combined clinical assessment and echocardiography are high; it is unlikely for them to be as high as 100%.
### 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              | 12              | 13              | 14              | 15              |
| **NP cut off point** | 38              | 23              | 18              | 11              | 8               |                |                |                |                |                |                |                |                |                |                |

#### Incremental Cost Effectiveness analysis

- **ICER (echo v NP)**: £3,227 / £810
- **ICER (echo v nothing)**: £1,111 / £667 / £500 / £323 / £270
- **ICER (NP v nothing)**: £981 / £661 / £520 / £355 / £302

**Decision**: NP

#### Sensitivity analysis – WTP £2,370 – Considering QALY gain at 3 years – Echo £150; NP £10 (least favourable to echo)

<table>
<thead>
<tr>
<th><strong>MICE score</strong></th>
<th>0</th>
<th>2</th>
<th>3</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NP cut off point</strong></td>
<td>58</td>
<td>36</td>
<td>28</td>
<td>17</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### 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 / £559 / £472 / £408

**Decision**: NP

#### Sensitivity analysis – WTP £2,370 – Considering QALY gain at 5 years – Echo £150; NP £10 (least favourable to echo)

<table>
<thead>
<tr>
<th><strong>MICE score</strong></th>
<th>0</th>
<th>2</th>
<th>3</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NP cut off point</strong></td>
<td>39</td>
<td>24</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Incremental Cost Effectiveness analysis

- **ICER (echo v NP)**: £6,934 / £3,470 / £2,017
- **ICER (echo v nothing)**: £1,667 / £1,000
- **ICER (NP v nothing)**: £1,281 / £900 / £712

**Decision**: NP

#### Sensitivity analysis – WTP £2,370 – Considering QALY gain at 10 years – Echo £150; NP £10 (least favourable to echo)

<table>
<thead>
<tr>
<th><strong>MICE score</strong></th>
<th>0</th>
<th>2</th>
<th>3</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NP cut off point</strong></td>
<td>24</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Incremental Cost Effectiveness analysis
<table>
<thead>
<tr>
<th>Decision</th>
<th>NP</th>
<th>Echo</th>
<th>Echo</th>
<th>Echo</th>
<th>Echo</th>
<th>Echo</th>
<th>Echo</th>
<th>Echo</th>
<th>Echo</th>
<th>Echo</th>
</tr>
</thead>
<tbody>
<tr>
<td>WTP £270 – Not considering QALYs – Echo £100; NP £15</td>
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</tr>
<tr>
<td>MICE score</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>NP cut off point</td>
<td>490</td>
<td>305</td>
<td>240</td>
<td>149</td>
<td>117</td>
<td>92</td>
<td>72</td>
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<td></td>
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<tr>
<td>ICER (echo v NP)</td>
<td>£1,356</td>
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<td>£200</td>
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<td>£669</td>
</tr>
<tr>
<td>ICER (echo v nothing)</td>
<td>£1,111</td>
<td>£667</td>
<td>£500</td>
<td>£332</td>
<td>£270</td>
<td>£222</td>
<td>£192</td>
<td>£169</td>
<td>£152</td>
<td>£139</td>
</tr>
<tr>
<td>ICER (NP v nothing)</td>
<td>£669</td>
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<td>£300</td>
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<td>£187</td>
<td>£166</td>
<td>£157</td>
<td>£149</td>
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<td>No test</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>Echo</td>
<td>Echo</td>
<td>Echo</td>
<td>Echo</td>
</tr>
<tr>
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</tr>
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<td>8</td>
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<tr>
<td>NP cut off point</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ICER (echo v NP)</td>
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<td>£410</td>
<td>£263</td>
<td>Echo*</td>
<td>Echo*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICER (echo v nothing)</td>
<td>£556</td>
<td>£333</td>
<td>£250</td>
<td>£161</td>
<td>£135</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>ICER (NP v nothing)</td>
<td>£498</td>
<td>£310</td>
<td>£247</td>
<td>£182</td>
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<td></td>
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</tr>
<tr>
<td>Decision</td>
<td>No test</td>
<td>No test</td>
<td>Echo</td>
<td>Echo</td>
<td>Echo</td>
<td>Echo</td>
<td>Echo</td>
<td>Echo</td>
<td>Echo</td>
<td>Echo</td>
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<tr>
<td>Sensitivity analysis – WTP £270 – Not considering QALYs – Echo £100; NP £10 (least favourable to echo)</td>
<td></td>
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</tr>
<tr>
<td>MICE score</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
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</tr>
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<td>NP cut off point</td>
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<td>194</td>
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<td>120</td>
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<td>75</td>
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<tr>
<td>ICER (echo v NP)</td>
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<td>£627</td>
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<td>------</td>
</tr>
<tr>
<td>ICER (echo v nothing)</td>
<td>£1,667</td>
<td>£1,000</td>
<td>£750</td>
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<td>£405</td>
<td>£333</td>
<td>£288</td>
<td>£254</td>
<td>£208</td>
<td>£181</td>
</tr>
<tr>
<td>ICER (NP v nothing)</td>
<td>£878</td>
<td>£458</td>
<td>£353</td>
<td>£261</td>
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<td>£222</td>
<td>£211</td>
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</table>

<table>
<thead>
<tr>
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<th>No test</th>
<th>No test</th>
<th>NP</th>
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<th>NP</th>
<th>NP</th>
<th>NP</th>
<th>NP</th>
<th>NP</th>
<th>Echo</th>
<th>Echo</th>
</tr>
</thead>
</table>

* Echo dominates NP
4.1.6 Summary of evidence statements

Three reviews were considered from different healthcare settings. The clinical evidence review demonstrated that several symptoms and signs were sensitive, but with low specificity for the diagnosis of heart failure. These include: dyspnoea, dyspnoea on exertion, orthopnoea in patients with asthma/COPD and fatigue in patients with asthma/COPD. The sensitivity of the symptoms decreased from 83% for dyspnoea to 70% for fatigue in patients with asthma/COPD.

Specific symptoms and signs were insensitive. These include: orthopnoea, paroxysmal nocturnal dyspnoea, oedema, elevated jugular venous pressure, added heart sounds, lung crepitations, fatigue and hepatomegaly. The specificity of these symptoms and signs ranged from 70% to 100%. Nonetheless, none of these symptoms and signs could be relied upon singularly to establish the diagnosis.

A collection of symptoms, signs and risk factors with different weights make up the MICE score (Male X 2, history of myocardial infarction X 6, crepitations X 5, and ankle oedema X 3). When the score is 11 or greater, the positive likelihood ratio of a heart failure diagnosis is >12, and the specificity is >98%.

The health economic assessment presented was based on the systematic review by Mant et al. It integrated the MICE scoring system to different diagnostic pathways. It was clear that with an original high MICE score, the most cost-effective diagnostic pathway should be to an echocardiogram. With an original lower MICE score, the patient should have the natriuretic peptide measured and then be referred for echocardiography.

4.1.7 From evidence to recommendations

The GDG recognised that definition of heart failure was crucial to interpretation of results of diagnostic studies, and that studies focussing on LVSD alone would have different results from those that used a more inclusive definition of heart failure that included 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 use of a constellation of symptoms and signs in a scoring system. Taking the clinical and health economic evidence on the MICE score at face value, this 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, and had reservations over the value of ankle oedema and lung crepitations as signs because of doubts as to their reliability. The GDG agreed with the concept that patients who had 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 therefore the GDG felt it was appropriate that it should be recommended that it was carried out within two weeks. The GDG noted that diagnosis did not revolve purely around the results of the 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 that they should be reviewed by a specialist.
The GDG discussed what factors might initiate an urgent referral straight for echocardiography without any ‘rule out’ tests. The GDG agreed that history of myocardial infarction was important, as per the MICE score. 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, however 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). Presence of these risk factors would not significantly alter the probability of heart failure in the context of presenting symptoms, and so felt that 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.

**4.1.8 Recommendations**

The recommendations were drafted after all the evidence for circulating natriuretic peptides had also 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, renal dysfunction, infection, 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 in two diagnostic settings:

1. The diagnosis of heart failure, as a screening test for patients suspected of having heart failure (similar to NICE guidance),
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 systolic function is preserved.

The GDG agreed to look at the issue of natriuretic peptides as a diagnostic tool for heart failure with preserved left ventricular systolic function and in serial monitoring through three separate questions.

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).

‘Gold standard’ was defined as a prospective planned evaluation of: a clinical diagnosis including all information, for example using European Society of Cardiology criteria (ECS).

The HTA excluded studies with an inappropriate reference standard, e.g., 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.

The meta-analysis pooled the sensitivities, specificities and likelihood ratio’s 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.

<table>
<thead>
<tr>
<th>Setting</th>
<th>Prevalence (true positives/population) (%)</th>
<th>Prevalence range minimum – maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population N=5030 (N=20)</td>
<td>2056/5030 (40.87%)</td>
<td>5.49 to 91.67%</td>
</tr>
<tr>
<td>General practice setting N=678 (N=2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Reference standard

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

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 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.

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

Prevalence

See table below for a breakdown of the prevalence of clinically diagnosed heart failure reported according to referral setting.

Table 4.25: Prevalence of heart failure according to referral setting

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

The reference tests included ECS criteria 2 or more cardiologists (N=4 studies) and clinical consensus typically two cardiologists (N=8 studies).

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 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.

4.2.2.2 Clinical evidence statements

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.

Table 4.26: Diagnostic accuracy of BNP compared to clinical diagnosis

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

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

<table>
<thead>
<tr>
<th>Setting (no. of studies)</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>Positive likelihood ratio (95%CI)</th>
<th>Negative likelihood (95%CI)</th>
<th>Diagnostic Odd Ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (N=16)</td>
<td>0.93 (0.88 to 0.96)</td>
<td>0.65 (0.56 to 0.74)</td>
<td>2.70 (2.12 to 3.43)</td>
<td>0.11 (0.07 to 0.18)</td>
<td>24.6 (14.4 to 42.2)</td>
</tr>
<tr>
<td>General Practice (N=8)</td>
<td>0.90 (0.81 to 0.96)</td>
<td>0.60 (0.50 to 0.70)</td>
<td>2.28 (1.82 to 2.86)</td>
<td>0.16 (0.09 to 0.30)</td>
<td>14.3 (7.73 to 26.5)</td>
</tr>
</tbody>
</table>
4.2.2.3 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) 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.

4.2.2.4 Health economic evidence statements

As detailed in Section 4.1.5, the Mant et al. (2009) cost-effectiveness analysis 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.

4.2.2.5 Summary of evidence statements

In the health technology assessment of the use of natriuretic peptides in the diagnosis of heart failure there were 20 studies comparing B-type natriuretic peptide to the standard diagnosis of heart failure. These studies suggested the prevalence of heart failure is between 44-52% of the hospital patients suspected of heart failure. In general practice the prevalence varies between 10% and 30%.

There were 16 studies comparing N-terminal-pro-BNP to the standard diagnosis of heart failure. These studies suggested the prevalence of heart failure is between 38-60% of the hospital patients suspected of heart failure. In general practice the corresponding prevalence is 4-15%.

The combined studies suggested sensitivities and specificities for BNP and NT-pro-BNP also varied between the general population of patients with heart failure, and those studied in general practice. Thus in general practice the sensitivity and specificity of BNP in the diagnosis of heart failure are 84% and 73%, respectively. In the general population, the sensitivity and specificity of BNP in the diagnosis of heart failure are 93% and 74%, respectively. N-terminal-pro-BNP in the diagnosis of heart failure in general practice has sensitivity of 90% and a specificity of 60%. In the general population the sensitivity and specificity of N-terminal-pro-BNP in the diagnosis of heart failure are 93% and 65%, respectively.

The health economic evidence was derived from a UK healthcare system perspective using the systematic review developed by Mant et al. It looked at different strategies including symptoms and signs assessment, natriuretic peptide measurement, and echocardiography. Several combinations were compared.

The findings considered the cost incurred by a delayed diagnosis and the cost of the tests, the level of natriuretic peptide concentration, and the risk of having heart failure as determined by the MICE score. The authors suggest that if there is a high risk of heart failure (particularly in the presence of previous myocardial infarction), then the patient should proceed directly to echocardiography, with a formal specialist opinion. However, if the risk is not high, natriuretic peptide concentration should be measured before echocardiography is undertaken.

4.2.2.6 From evidence to recommendations

The GDG noted that the systematic review was confined to studies that investigated the value of natriuretic peptides in diagnosing heart failure, thus the review excluded studies of diagnosis of left ventricular systolic dysfunction (LVSD). The GDG discussed the advantages and disadvantages of not considering studies that looked
at the natriuretic peptides’ contribution to the diagnosis of left ventricular systolic
dysfunction. It was felt that including studies that look 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, the GDG were of
the opinion that 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 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.

The GDG discussed whether specific cut off points should be recommended for what
level of BNP should initiate a referral for echocardiography and specialist opinion. It
was recognised that the appropriate cut off point would depend upon the clinical
features (as per Mant et al analysis), and the assay used. Therefore, the GDG felt
that this should be a decision to be made locally, informed by advice from local
cardiac networks.

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 also felt that the higher the level of natriuretic peptide is, the worse is the
prognosis, (and the more likely that the diagnosis is heart failure) and thus the more
urgent the diagnosis and management have to be. Therefore, it was agreed that
people with a high natriuretic peptide level should receive urgent echocardiography
and specialist review. The GDG considered whether a specific cut-point should be
recommended as constituting a ‘high’ natriuretic peptide level, but again felt that this
should be a decision made locally, informed by the local cardiac networks, since the
optimum level would depend upon the assay used.

For other cases (i.e no history of myocardial infarction and moderately raised
natriuretic peptide without rapid deterioration of symptoms), that non-urgent referral
for echocardiography and specialist review was reasonable. However, in this
circumstance, the GDG believes that the waiting time should not exceed 6 weeks.

The reasoning for this was based on the health economic evidence (that assumed
immediate assessment), and comparison with current best practice in cancer
management, given that heart failure prognosis is worse than most cancers.

The GDG discussed limitations of the cost-effectiveness analysis presented. Several
assumptions had been made. First, the analysis considered that natriuretic peptide
measurement and echocardiography can be done immediately. In the current
practice, access to echocardiography is constrained by waiting time. Secondly, the
analysis assumed that cardiologist opinion in the light of the echocardiography was
100% accurate. Thirdly, the GDG noted that no utility in the health economic analysis
was attached to the value of natriuretic peptide measurement except as a gateway to
echocardiography.

Despite these limitations, the GDG were of the opinion that a natriuretic peptide test
was useful to determine if echocardiography was warranted in patients who had not
had a previous myocardial infarction (who would be referred straight for
echocardiography – as outlined above).

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 Mant
et al had found ECG to be inferior to natriuretic peptide testing as a diagnostic test in
heart failure. However, 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. Therefore, while it was no longer recommended as part of the diagnostic
pathway for heart failure (being replaced by natriuretic peptide), it was still an
appropriate investigation to perform.

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 value) 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 \(^{37-44}\). The table below
summarises the populations covered by the studies, these varied from a population
sample of adults 60 to 86 yrs \(^{39}\) to patients with preserved LV function and normal LV
dimensions as determined by echocardiography and ventriculography \(^{41}\).

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 \(^{37,38,41}\). One
study compared results with healthy controls \(^{37}\).

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 \(^{39,40,42-44}\). Two studies compared results with a group of healthy controls
\(^{40,43}\).
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. 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.

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>
<thead>
<tr>
<th>Study</th>
<th>Aim of trial</th>
<th>Population</th>
<th>Type of test</th>
<th>Comparison</th>
<th>Diagnosis of diastolic dysfunction</th>
</tr>
</thead>
</table>
| Islamoglu 2008 | 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)           | NT-proBNP         | Echocardiogram (E/Ea ratio ≤15)                  | When the echo measures:  
- Ea < 8 cm/s  
- E/Ea > 15 the diastolic functional stage was defined as abnormal. |
| Hettwer 2007   | 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 dysfunction  
3) longstanding arterial hypertension | NT-proBNP         | Echocardiogram (Myocardial relaxation velocity, Flow propagation velocity of transmital 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. pseudonormal pattern  
3. restrictive pattern (- figures provided) |
| Tschope        | To look at                                                                    | Patients with NT-                                                       | Echocardiography  | In agreement with the                           |                                                                                                  |

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

<table>
<thead>
<tr>
<th>Year</th>
<th>Aim of trial</th>
<th>Population</th>
<th>Type of test</th>
<th>Comparison</th>
<th>Diagnosis of diastolic dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>the accuracy of NT-proBNP at detecting isolated diastolic dysfunction in comparison to left and right heart catheterization, transmitral Doppler echo, pulmonary venous Doppler and tissue Doppler imaging in patients with suspected chronic heart failure despite preserved LV systolic function.</td>
<td>preserved LV function and normal LV dimensions as determined by echocardiography and ventriculography.</td>
<td>proBNP</td>
<td>Diastolic dysfunction diagnosed by abnormal values Tau, IVRT, DT, and/or by the E/A ratio</td>
<td>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&gt;50%). (- figures provided)</td>
</tr>
</tbody>
</table>

**Key Terms:**

- **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, usually 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Aim of trial</th>
<th>Population</th>
<th>Type of test</th>
<th>Comparison</th>
<th>Diagnosis of diastolic dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knebel 2008 N=137</td>
<td>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.</td>
<td>Patients with a clinical indication for echo from medical and surgical departments who were clinically stable (inpatients and outpatients)</td>
<td>Echocardiogram</td>
<td>NT-proBNP</td>
<td>Normal LVEF (≥55%), E/E&gt;10, E/A &lt;1. The transmitral flow and TDI measures were adjusted to age-related cut off points.</td>
</tr>
<tr>
<td>Dong 2006 N=191</td>
<td>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 &lt;55% Compared with healthy controls</td>
<td>Patients with a 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 &lt;55%</td>
<td>Echocardiogram</td>
<td>E/Em = mitral early filling wave to Doppler tissue early diastolic mitral annulus velocity ratio</td>
<td>Assessed by pulsed wave Doppler (PWD) transmitral inflow (LVEF, Em, E/Em ratio, DT, IVRT, A wave and E wave). (no figures provided)</td>
</tr>
<tr>
<td>Study</td>
<td>Aim of trial</td>
<td>Population</td>
<td>Type of test</td>
<td>Comparison</td>
<td>Diagnosis of diastolic dysfunction</td>
</tr>
<tr>
<td>-------</td>
<td>------------------------------------------------------------------------------</td>
<td>----------------------------------------------------</td>
<td>------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Abhayaratna 2006</td>
<td>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).</td>
<td>Population sample of adults 60 to 86 yrs (n=43)</td>
<td>NT-proBNP</td>
<td>Echocardiography: Tissue Doppler measures used to determine diastolic dysfunction.</td>
<td>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)</td>
</tr>
<tr>
<td>Lubien 2002</td>
<td>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.</td>
<td>Patients referred for echo to evaluate LV dysfunction (n=294)</td>
<td>Triage BNP assay</td>
<td>Echocardiography: Echo Doppler velocity (E, A velocities, IVRT, DT)</td>
<td>Classified in 3 categories: 1. impaired relaxation 2. pseudonormal 3. restrictive like According to echo measures (E/A, IVRT, DT, PVd/PVs) (- figures provided)</td>
</tr>
<tr>
<td>Wei 2005</td>
<td>To assess the value of bedside testing of BNP in the diagnosis of diastolic dysfunction in hypertensive patients. (no data for echo)</td>
<td>Consecutive Chinese patients with a history of hypertension for an average of 9.3 ± 7.8 (1-30 yrs) (n=135)</td>
<td>BNP</td>
<td>Echocardiogram Measures: Doppler echo of transmitral flow, E and A peaks, diastolic time and the isovolumic relaxation time.</td>
<td>Based on 3 criteria: 1.) the presence of signs or symptoms of congestive heart failure, 2.) the echo measured LVEF &gt;50% 3.) Echo evidence of abnormalities of left</td>
</tr>
</tbody>
</table>

Chronic heart failure_Full_Guideline_for consultationDRAFT (January 2010) 55
<table>
<thead>
<tr>
<th>Aim of trial</th>
<th>Population</th>
<th>Type of test</th>
<th>Comparison</th>
<th>Diagnosis of diastolic dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ventricular relaxation: E/A ratio &lt;1.0 (&lt;55 yrs old) or &gt;0.8 (&gt;55 yrs old); E peak deceleration time of more than 240 ms or isovolumic relaxation time &lt;90ms.</td>
</tr>
</tbody>
</table>

1. **Echo measures:**

2. **Diastolic transmitral Doppler parameters:**
3. - IVRT = Isovolumic relaxation time
4. - DT = early diastolic deceleration time
5. - E/A ratio = peak of early E and late A diastolic mitral flow velocities (early filling/atrial filling peak velocities)
6. - FPV = LV flow propagation velocity
7. - E/Em ratio: mitral E wave to Doppler tissue early diastolic lateral annulus velocity ratio
8. PVs and PVd = Pulmonary vein velocities during systole and diastole
9. 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
10. LVESD and LVEDD = LV end-systolic and end-diastolic diameters
11. LVMI = Left ventricular mass index (evaluates hypertrophy)
12. PWI = end-diastolic LV posterior wall thickness
13. IVST = end-diastolic intraventricular septal thickness
14. LVEF = LV ejection fraction (systolic dysfunction = <55% EF)
15. TDI= tissue Doppler imaging
4.2.3.2 Clinical evidence statements

1. Sensitivity

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

Three studies reported on the sensitivity of NT-proBNP in comparison to different echo measures $^{37,38,41}$.

One study $^{36}$ reported:

- NT-proBNP >854 pg/ml: Sensitivity 87.5%
- E/Ea ratio >13.5: Sensitivity 87.5%

One study $^{37}$ reported:

- NT-proBNP >11.1 pmol/l: Sensitivity 65.6%
- Myocardial relaxation velocity <6.31 cm/s: Sensitivity 82.8%
- Flow propagation velocity of transmittal inflow: below 55.9 cm/s: Sensitivity 74.2%

One study $^{41}$ reported:

- NT-proBNP (at a cut off point of 120 pg/ml): Sensitivity 69%
- E/A ratio: Sensitivity 71%
- E/A: Sensitivity 53%
- IVRT: Sensitivity 69%
- DT: Sensitivity 33%

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

One study $^{43}$ reported the sensitivity of NT-proBNP to discriminate between normal LVEF (n=88) and reduced LVEF (n=49):

- The best cut off point NT-proBNP was 489 pg/ml: Sensitivity 81.6%

One study $^{40}$ reported on the sensitivity of different NT-proBNP levels to predict raised E/Em (an echo measure used to measure LV filling):

- E/Em ≥ 8: best cut off value NT-proBNP 150 pg/ml: sensitivity: 0.74
- E/Em >15: best cut off value NT-proBNP 550 pg/ml: sensitivity: 1.0

One study $^{39}$ reported on the sensitivity of NT-proBNP in diagnosing diastolic dysfunction (as determined by echo and tissue Doppler) and the differences between men and women:

- Men 60 to 86 yr moderate DD (N=46, 7.7%): NT-pro BNP cut off point 30 pmol/L 240 pg/mL: Sensitivity 83%
- Women 60 to 86 yr moderate DD (N=45, 7.3%): NT-pro BNP cut off point 32 pmol/L 270 pg/mL: Sensitivity 89%

One study $^{44}$ reported on the sensitivity of different BNP levels in diagnosing diastolic dysfunction (as determined by echo and tissue Doppler):
Cut point off BNP 17.5 pg/mL: Sensitivity 97% (92 to 99%)
Cut off point BNP 62 pg/mL: Sensitivity 85% (77 to 90%)
Cut off point BNP 92 pg/mL: Sensitivity 74% (65 to 81%)
Cut off point BNP 130 pg/mL: Sensitivity 62% (53 to 71%)

One study \(^4\) reported on the sensitivity of BNP in diagnosing diastolic dysfunction (as determined by echo and signs and symptoms of heart failure) in patients with a history of hypertension:

- BNP cut off point of 40 pg/ml: Sensitivity: 79%

2. Specificity

Natriuretic peptides vs. Echo measures (N=3):
Three studies reported on the specificity of NT-proBNP in comparison to different echo measures \(^3^7,3^8,4^1\).
One study \(^3^8\) reported:
- NT-proBNP >854pg/ml: Specificity 55%
- E/Ea ratio >13.5: Specificity 86.4%

One study \(^3^7\) reported:
- NT-pro BNP >11.1 pmol/l: Specificity 77.8%
- Myocardial relaxation velocity <6.31 cm/s: Specificity 77.8%
- Flow propagation velocity of transmittal inflow: below 55.9 cm/s: Specificity 77.8%

One study \(^4^1\) reported:
- NT-pro BNP (at a cut off point of 120pg/ml): Specificity 91%
- E/A ratio: Specificity 87%
- E/A: Specificity 79%
- IVRT: Specificity 60%
- DT: Specificity 79%

Different natriuretic peptide levels and their concordance with echo (N=5):
One study \(^4^3\) reported the specificity of NT-proBNP to discriminate between normal LVEF (n=88) and reduced LVEF (n=49):
- The best cut off point NT-proBNP was 489 pg/ml: Specificity 85.2%

One study \(^4^0\) reported on the specificity of different NT-proBNP levels to predict raised E/Em (an echo measure used to measure LV filling):
- E/Em ≥ 8: best cut off point NT-proBNP 150pg/ml: specificity: 0.71
- E/Em >15: best cut off point NT-proBNP 550pg/ml: specificity: 1.0
One study \( ^{39} \) reported on the specificity of NT-proBNP in diagnosing diastolic dysfunction (as determined by echo and tissue Doppler) and the differences between men and women:

- Men 60 to 86 yr moderate DD (N=46, 7.7%): NT-pro BNP cut off point 30 pmol/L 240 pg/mL: specificity 85%
- Women 60 to 86 yr moderate DD (N=45, 7.3%): NT-pro BNP cut off point 32 pmol/L 270 pg/mL: specificity 86%

One study \( ^{44} \) reported on the specificity of different BNP levels in diagnosing diastolic dysfunction (as determined by echo and tissue Doppler):

- Cut off point BNP 17.5 pg/mL: Specificity 45% (37 to 52%)
- Cut off point BNP 62 pg/mL: Specificity 83% (77 to 88%)
- Cut off point BNP 92 pg/mL: Specificity 98% (94 to 99%)
- Cut off point BNP 130 pg/mL: Specificity 98% (94 to 99%)

One study \( ^{42} \) reported on the specificity of BNP in diagnosing diastolic dysfunction (as determined by echo and signs and symptoms of heart failure) in patients with a history of hypertension:

- BNP cut off point of 40 pg/ml: Specificity: 92%

3. Positive and negative predictive value

Natriuretic peptides vs. Echo measures (N=1):

One study reported on the positive and negative predictive values of NT-proBNP compared to different echo measures \( ^{41} \).

Table 4.30: Positive and negative predictive values compared to echo measures

<table>
<thead>
<tr>
<th>NT-pro BNP</th>
<th>E/A ratio</th>
<th>E/A</th>
<th>IVRT</th>
<th>DT</th>
</tr>
</thead>
<tbody>
<tr>
<td>(at a cut off point of 120pg/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive predictive value (%)</td>
<td>63</td>
<td>55</td>
<td>36</td>
<td>27</td>
</tr>
<tr>
<td>Negative predictive value (%)</td>
<td>93</td>
<td>93</td>
<td>88</td>
<td>90</td>
</tr>
</tbody>
</table>

Different natriuretic peptide levels and their concordance with echo (N=2):

One study \( ^{43} \) reported the positive and negative predictive values of NT-proBNP to discriminate between normal LVEF (n=88) and reduced LVEF (n=49):

- Positive predictive value (%): 75.5%
- Negative predictive value (%): 89.3%
One study \(^4\) reported on the positive and negative predictive values of different BNP levels in diagnosing diastolic dysfunction (as determined by echo and tissue Doppler):

<table>
<thead>
<tr>
<th>BNP (pg/ml)</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.5</td>
<td>54 (47 to 81)</td>
<td>95 (88 to 98)</td>
<td>66%</td>
</tr>
<tr>
<td>62</td>
<td>78 (70 to 84)</td>
<td>89 (83 to 93)</td>
<td>84%</td>
</tr>
<tr>
<td>92</td>
<td>96 (89 to 98)</td>
<td>85 (79 to 89)</td>
<td>88%</td>
</tr>
<tr>
<td>130</td>
<td>95 (87 to 98)</td>
<td>79 (73 to 84)</td>
<td>83%</td>
</tr>
</tbody>
</table>

### 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 Summary of evidence statements

Studies reported on the diagnostic accuracy of natriuretic peptides compared to the diagnostic accuracy of a variety of commonly used echo measures\(^37,38,41\). One study compared results with healthy controls\(^43\). The sensitivity of NT-BNP for diagnosing diastolic dysfunction ranged from 65.6% (NT-pro BNP >11.1 pmol/l) to 87.5% (NT-proBNP >854pg/ml). The specificity of NT-proBNP (>854pg/ml) ranged from 55% to 91% (NT-pro BNP cut off point of 120pg/ml). Only one study reported the positive and negative predictive values of NT-pro BNP (at a cut off point of 120pg/ml) as 63 and 93% respectively.

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\(^39,40,42-44\). Sensitivity ranged from 62% (BNP point off of 130 pg/mL) to 100% (cut off point NT-proBNP 550pg/ml). Specificity ranged from 45% (cut off point BNP 17.5 pg/mL) to 98% (cut off point BNP 130 pg/mL). The positive predictive values of BNP ranged from 54% with a cut off point of 17.5 pg/ml to 96% with a cut off point of 92 pg/ml. Negative predictive values for NT-proBNP ranged from 79% (cut off point 130 pg/mL) to 95% (cut off point 17.5 pg/ml).

### 4.2.3.5 From evidence to recommendations

The GDG considered the evidence from the eight reviewed papers\(^37-44\). The most important reservation was that with the exception of one study\(^41\), 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’. However, 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, therefore making a general conclusion from the studies that could cover all the echo parameters was not possible.

The GDG members, however, were most interested in the paper of Tschope \textit{et al}\(^41\) 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. Interestingly, however, 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) 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, 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: rules out all forms of heart failure.

Therefore, 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.

4.2.3.6 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 Efforts should be made to try to exclude other disorders that may present in a similar manner. [2003, R3]

R3 Consider the following tests to evaluate possible aggravating factors and/or alternative diagnoses:

- ECG [new 2010]
- chest X-ray
- blood tests:
  - biochemical profile including electrolytes, urea and creatinine
  - full blood count
  - thyroid function tests
  - liver function tests
  - fasting lipids
  - fasting glucose
- urinalysis
- peak flow or spirometry [2003, R4]

R4 Refer patients with suspected heart failure and previous myocardial infarction (MI) urgently, to have echocardiography and specialist assessment within 2 weeks. [new 2010]

R5 Measure serum natriuretic peptides in patients with suspected heart failure without previous MI. [new 2010]

R6 Refer patients with suspected heart failure and very high levels of serum natriuretic peptides urgently, to have echocardiography and specialist assessment within 2 weeks. [new 2010]

R7 Refer patients with suspected heart failure and raised levels of serum natriuretic peptides for echocardiography and specialist assessment. [new 2010]
R8 Be aware that very high levels of serum natriuretic peptides carry a poor prognosis. [new 2010]

R9 Determine cut-off levels of serum natriuretic peptides for referral and urgent referral locally, following discussions with local cardiac networks. When determining cut-off levels consider clinical features and the assay used. [new 2010]

R10 Perform Trans-thoracic Doppler 2D echocardiography examination should be performed to exclude important valve disease, assess the systolic (and diastolic) function of the (left) ventricle, and detect intracardiac shunts [2003, R5]

R11 Trans-thoracic Doppler 2D echocardiography studies 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, R6]

R12 The reporting of echocardiography should be performed by experienced operators trained to the relevant professional standards. Need and demand for these studies should not compromise quality [2003, R6]

R13 Consider alternative methods of imaging the heart should be considered (for example, radionuclide angiography, cardiac magnetic resonance imaging or transoesophageal Doppler 2D echocardiography) when a poor image is produced by echocardiography [2003, R8]

R14 Offer a serum natriuretic peptide test to patients in whom heart failure is still suspected after echocardiography has shown a preserved left ventricular ejection fraction. [new 2010]

R15 Be aware that a normal level of serum natriuretic peptide in an untreated patient makes a diagnosis of heart failure unlikely. [new 2010]

R16 Be aware that the level of serum natriuretic peptide does not differentiate between heart failure due to systolic left ventricular dysfunction, and heart failure with preserved left ventricular ejection fraction. [new 2010]

R17 If the diagnosis is unclear or if a diagnosis of diastolic heart failure with preserved ejection fraction is being considered, refer the patient for more further specialist assessment. [2003, R9]

R18 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, R10]

R19 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, R11]

4.4 Recommendation to be deleted

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 [2003, R2]
Draft for consultation

4.5 Diagnostic algorithm

Suspected heart failure (HF)
history, symptoms and signs?

No previous MI
Measure natriuretic peptides (NP)

NP is very high
Refer urgently
Patient has an echocardiogram and assessment by specialist within 2 weeks
(Where LVEF is normal and suspicion of HF persists, the specialist checks NP)

Abnormality consistent with HF (6a)

No abnormality consistent with HF
HF unlikely

NP above cut off point
Refer for echocardiogram and assessment by specialist

No abnormality consistent with HF
HF unlikely

NP below cut off point
HF unlikely

*Other recommended tests:

- ECG
- chest X-ray
- blood tests: U&Es, creatinine, FBC, TFTs, glucose, and lipids
- urinalysis,
- peak flow or spirometry

** Non-HF causes of rises of NP:
LVH, ischaemia, tachycardia, RV overload, hypoxaemia, renal dysfunction, infection, sepsis, advanced age, cirrhosis of the liver.

***Factors lowering NP:
Obesity and diuretics

α: assess HF severity, aetiology, precipitating and exacerbating factors and type of cardiac dysfunction. Correctable causes must be identified.

δ: Heart failure specialist
The secondary care consultant with a subspecialty interest in heart failure, who is usually a cardiologist, and who will work in a multi-disciplinary team.
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 the patients’ poor prognosis. Since then several hypotheses into the management of heart failure were introduced, and these include: the haemodynamic, the neuro-endocrine and the inflammatory hypotheses. Several classes of drugs were 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 patients’ symptoms, improving their exercise tolerance, reducing their hospitalisation rate and improving their quality of life.

2. Improving the patients’ 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 varying perspectives that the patient 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 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 multidisciplinary team in the continuing management of heart failure patients is pivotal.

The partial update include 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
5.2 Pharmacological treatment of heart failure
5.3 Other causes of heart failure
5.4 Invasive procedures
5.5 Treatment algorithm
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\(^{19}\):

- 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

Smoking

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


R20 Patients must be strongly advised not to smoke. Referral to smoking cessation services should be considered. [2003, R13].

Alcohol

R21 Patients with alcohol-related heart failure should abstain from drinking alcohol [2003, R14]

R22 Healthcare professionals should discuss alcohol consumption with the patient and tailor their advice appropriately to the clinical circumstances. [2003, R15]

Sexual activity

R23 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, R16]

Vaccination

R24 Patients with heart failure should be offered an annual vaccination against influenza [2003, R17]

R25 Patients with heart failure should be offered vaccination against pneumococcal disease (only required once).[2003, R18]

Air travel

R26 Air travel will be possible for the majority of patients with heart failure, depending on their clinical condition at the time of travel. [2003, R19]
Driving regulations

R27. **Large Goods Vehicle and Passenger Carrying Vehicle licence**: physicians should be up to date with the latest Driver and Vehicle Licencing Agency guidelines. Check the website for regular updates: [www.dft.gov.uk/dvla/](http://www.dft.gov.uk/dvla/) [2003, R20]

5.1.2 **Recommendations on lifestyle to be deleted**

**Exercise training**

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. [2003, R12]

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 the neuro-endocrine over-activity. Since the latter started in 1986, major advances have been achieved 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, β-blockers, aldosterone antagonists, combined arterial and venous dilators (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. Most of what we know on this topic is derived from studies that recruited patients with HF with LVSD.

Since the late 1990’s, it has been increasingly realised that the other half of the picture of heart failure is comprised of patients with heart failure who have either a normal left ventricular ejection fraction, or no significant reduction of the 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 detecting of HFPEF and a better understanding of the pathophysiological processes. This may lead to more successful therapeutic interventions. Until then, attempts were made to treat patients with HFPEF using some of the agents that were successfully used in the treatment of HF with LVSD.

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

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:

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

Drugs reviewed in partial update

5.2.1 Angiotensin converting enzyme (ACE) inhibitors

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. ACEI doses should be up-titrated slowly up to the target doses used in randomised controlled trials (RCT).

The GDG considered the impact of the new evidence looking at the sequence of therapy in relation to ACEI and β blockers, within the section on β 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, hypertension and in reducing adverse cardiovascular events in patients with ischaemic heart disease and diabetes mellitus. 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 or ischaemic heart disease. These are some of the justifications for investigating the role of ACEI in the management of HFPEF.

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 (ACE) inhibitor vs. Placebo

Population: heart failure with preserved ejection fraction (HFPEF)

Intervention: angiotensin converting enzyme inhibitors

Comparison: placebo

Outcomes: all cause mortality up to 5 years, unplanned hospitalization, quality of life, side effects/adverse events, New York Heart Association (NYHA) class.

Populations:
- LVEF ≥ 40% 
- Mean age range: 75-78 years
- >50% female

Background medication:
- BB >60%
- BB <20%

Intervention:
- Quinapril (up to 40mg)
- Perindopril (4mg)

Comparison:
- Placebo

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

Data were reported on the following outcomes:
- All cause mortality or unplanned hospitalisation (follow-up 12 months and 12 to 54 months)
- All cause mortality (follow-up 6 to 12 months and 12 months to 54 months)
- CV mortality (follow-up 12 months and 12 to 54 months)
- HF hospitalisation (follow-up 12 months and 12 to 54 months)
- Quality of Life (follow-up 6 months) (McMaster questionnaire; range of scores: 16-112; Better indicated by more)
- Improvement in NYHA class from III to II (follow-up 6 months)
- Total adverse events (follow up 6 to 54 months)
5.2.1.3 Clinical evidence statements

Compared with placebo, ACE inhibitors significantly reduced:

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

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

- 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 hospitalization (follow-up 12 to 54 months) [moderate quality]
- Total side effects (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) \(^{48,49}\) comparing **ACE inhibitors vs. placebo in HFPEF.**
**Evidence Profile: ACE inhibitors vs placebo in HFPEF**

**Date:** 2009-06-09  
**Question:** Should ACE inhibitors vs placebo be used for CHF?


<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of patients</td>
<td>Effect</td>
</tr>
<tr>
<td>All cause mortality or unplanned hospitalisation (no. of patients) (follow-up 12 months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 PEP-CHF randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
</tr>
</tbody>
</table>

| All cause mortality or unplanned hospitalisation (no. of patients) (follow-up 12-54 months) | | | |
| 1 PEP-CHF randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious\(^1\) none | 100/420 (23.8%) | 107/426 (25.1%) | RR 0.95 (0.75 to 1.2) | 13 fewer per 1000 (from 63 fewer to 50 more) | ⬤⬤⬤⬤ O MODERATE |

| All cause mortality (no. of patients) (follow-up 6-12 months) | | | |
| 2 PEP-CHF randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious\(^1\) none | 18/456 (3.9%) | 20/464 (1%) | RR 0.91 (0.49 to 1.71) | 0 fewer per 1,000 | ⬤⬤⬤⬤ O MODERATE |

| 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%) | RR 1.06 (0.73 to 1.53) | 2 more per 1000 (from 10 fewer to 20 more) | ⬤⬤⬤⬤ O MODERATE |

| CV mortality (no. of patients) (follow-up 1 years) | | | |
| 1 PEP-CHF randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious\(^1\) none | 10/420 (2.4%) | 17/426 (4%) | RR 0.60 (0.28 to 1.29) | 16 fewer per 1000 (from 29 fewer to 12 more) | ⬤⬤⬤⬤ O MODERATE |

| 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 1.48) | 1 fewer per 1000 (from 1000 to 50 more) | ⬤⬤⬤⬤ O MODERATE |
1.47) 11 fewer to 13 more) MODERATE

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

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

< 300 events
5.2.1.4 Health Economic Methodological introduction

The 2003 Guideline 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 Summary of evidence statements

In HFPEF, the use of ACEI was considered through the evidence derived from two randomised controlled trials (RCT’s) by Zi et al and Cleland et al. Both studies compared ACEI (Quinapril and Perindopril, respectively) to placebo in patients with heart failure and LVEF of over 40%. The patients enrolled in the two studies were elderly patients with a mean age of 75-78 years. The studies showed significant reduction (35%) in heart failure hospitalisation. However, no difference was found between placebo-treated and ACEI-treated groups, in terms of all cause mortality, cardiovascular mortality, side-effects, quality of life and the New York Heart Association functional class.

There is no published cost-effectiveness analysis associated with these trials.

5.2.1.7 From evidence to recommendations

Relative value placed on the outcomes considered

In the two appraised trials: 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, 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, 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
Net resource use would be likely to be low given that hospital admissions might be reduced, and ACEI therapy is relatively low cost. However, the GDG noted that the pre-specified hospitalisation endpoint was non-significant and therefore did not attach weight to the reduction of hospitalisation at one year.

5.2.1.8 Recommendations
The GDG decided there was inadequate evidence to support the use of ACEI in HFPEF.

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 β 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 β blockers at low doses. These should be up-titrated slowly. The introduction of β 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 the 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).

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?

POPULATION: all chronic heart failure and older adults

INTERVENTION: Beta blockers, selective beta blockers, beta blockers then ACEI

COMPARISON: Placebo, non-selective beta blockers, ACEI then beta blockers

OUTCOMES: all cause death up to 5 yrs, all cause hospitalization, composite score, sudden death, quality of life, adverse event

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. Two of these papers were in a sub-population derived from RCT’s carried out on all patients with chronic heart failure. Table 5.1 below summarises the patient population and intervention for each study. Patients with COPD were excluded in all studies except one study.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEEDWANIA</td>
<td>Patients ≥ 65 yrs with EF ≤ 30% and NYHA II to IV</td>
<td>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</td>
</tr>
<tr>
<td>EDES</td>
<td>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</td>
<td>Nebivolol Titration period of 8 weeks. 1.25 mg double every 14 days until highest tolerated or maximum of 10 mg/day</td>
</tr>
<tr>
<td>ERDMANN</td>
<td>Patients ≥ 71 yrs with chronic heart failure Inclusion criteria: NYHA II, IV EF ≤35% Concomitant medication diuretics and ACEI</td>
<td>Bisoprolol 1.25 mg to a maximum of 10 mg/day</td>
</tr>
</tbody>
</table>
| FLATHER   | 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 | 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
The outcomes reported were

- Death – all cause up to 27 months
- Sudden death – up to 24 months
- All cause hospitalisation – up to 27 months
- Quality of life – Minnesota Living with Heart Failure at 40 weeks
- Adverse events – no. of patients at 40 weeks
- Adverse events – no. of patients (leading to withdrawal of study medication) at 12 months

b) Evidence profile: Beta blockers versus placebo for patients with preserved left ventricular systolic dysfunction

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%

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Veldhuisen N=2111</td>
<td>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.</td>
<td>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</td>
</tr>
</tbody>
</table>

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%
The following outcomes were reported:

- All cause mortality or CV hospitalisation – 21 months
- All cause mortality – 21 months
- All cause mortality or HF hospitalisation – 21 months
- All cause hospitalisation – 21 months

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

Three papers were identified comparing selective with non-selective beta blockers for chronic heart failure. One of the papers reported on additional data from the main study. 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**

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

The outcomes reported were:

- Mortality and hospitalisation – all cause mean follow-up 58 months
- Mortality – all cause mean follow-up 58 months
- Sudden death = mean follow-up 58 months
- Quality of life – Minnesota Living with Heart Failure follow-up 12 weeks
- Adverse events – no. of patients experiencing mean follow-up 58 months

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

One study was identified comparing beta blockers then ACEI with ACEI then beta blockers. 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population</th>
<th>BB then ACEI</th>
<th>ACEI then BB</th>
</tr>
</thead>
<tbody>
<tr>
<td>WILLHEIMER</td>
<td>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</td>
<td>Beta 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</td>
<td>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 beta blockerm Combination therapy: beta-blocker introduced as for intervention</td>
</tr>
</tbody>
</table>

The outcomes reported were:

- Mortality and hospitalisation – all cause mean follow-up 1.22 years
- Mortality – all cause mean follow-up 1.22 years
- Hospitalisation – all cause mean follow-up 1.22 years
- Sudden death = mean follow-up 1.22 years

Adverse events – no. of patients experiencing mean follow-up 58 months

#### 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 [moderate quality]
- Sudden death – up to 24 months [moderate quality]
Compared with placebo, beta blockers were associated with no significant differences for:

- All cause hospitalisation – up to 27 months [high 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]

Below is the evidence profile for the comparison of beta-blockers compared with placebo in the elderly.

The evidence profile below summarises the quality of evidence and outcome data from five papers comparing beta blockers with placebo in older adults with chronic heart failure.
Evidence profile for comparison of beta-blockers with placebo in older adults

<table>
<thead>
<tr>
<th>No. of patients experiencing adverse event (follow-up 40 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Beta blockers</strong></td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Mortality - all cause (follow-up 8-27 months)</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>All cause hospitalisation (follow-up 21 to 27 months)</td>
</tr>
<tr>
<td>8</td>
</tr>
<tr>
<td>9</td>
</tr>
<tr>
<td>Quality of Life (follow-up 40 weeks; measured with: Minnesota Living with Heart Failure; range of scores: 0-105; Better indicated by less)</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>No. of patients experiencing adverse event (follow-up 40 weeks)</td>
</tr>
<tr>
<td>Adverse events - leading to withdrawal of medication (follow-up mean 12 months)</td>
</tr>
<tr>
<td>11</td>
</tr>
</tbody>
</table>

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 or harm
7. Allocation concealment poor; drop out rate > 20%
8. Allocation concealment unclear; unclear drop-out rates - sub-population
Draft for consultation

1 b) **Beta blockers versus placebo for patients with preserved left ventricular systolic dysfunction**

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

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>No of patients</th>
<th>Summary of findings</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of studies</td>
<td>Design</td>
<td>Limitations</td>
<td>Inconsistency</td>
<td>Indirectness</td>
<td>Imprecision</td>
</tr>
<tr>
<td>All cause mortality or CV hospitalisation (no of patients) - LVEF &gt; 35% (follow-up 21 months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Van Veldhuisen 2009</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious’</td>
</tr>
<tr>
<td>All cause mortality - LVEF &gt; 35% (follow-up 21 months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Veldhuisen 2009</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious’</td>
</tr>
<tr>
<td>All cause mortality or HF hospitalisation - LVEF &gt; 35% (follow-up 21 months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Veldhuisen 2009</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious’</td>
</tr>
<tr>
<td>All cause hospitalisation (no of patients) - LVEF &gt; 35% (follow-up 21 months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Veldhuisen 2009</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious’</td>
</tr>
</tbody>
</table>

* < 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 \(^{55, 56, 57}\).
### 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?

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>No of patients</th>
<th>Summary of findings</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of studies</td>
<td>Design</td>
<td>Limitations</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td><strong>Mortality and hospitalisation - all cause (follow-up mean 58 months)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Poole-Wilson</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
</tr>
<tr>
<td><strong>Mortality - all cause (follow-up mean 58 months)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Poole-Wilson</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious ¹</td>
</tr>
<tr>
<td><strong>Sudden death (follow-up mean 58 months)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Poole-Wilson</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious ¹</td>
</tr>
<tr>
<td><strong>Quality of Life (follow-up 12 weeks; measured with: Minnesota Living with Heart Failure; range of scores: 0-105; Better indicated by less)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Sanderson</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious ¹</td>
</tr>
<tr>
<td><strong>Adverse events - no. of patients (follow-up mean 58 months)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Poole-Wilson</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
</tr>
</tbody>
</table>

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 [moderate quality]
- Mortality – all cause mean follow-up 1.22 years [high 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.\(^68\)
### 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 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

#### Quality assessment

<table>
<thead>
<tr>
<th>No of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>No of patients BB plus ACEI</th>
<th>ACEI plus BB</th>
<th>Summary of findings</th>
<th>Effect Absolute</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality and hospitalisation - all cause</strong> (follow-up mean 1.22 years)</td>
<td>1</td>
<td>Willenheimer randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>none</td>
<td>178/505 (35.2%)</td>
<td>186/505 (36.8%)</td>
<td>RR 0.96 (0.81 to 1.13)</td>
<td>15 fewer per 1000 (from 70 fewer to 48 more)</td>
<td>@@@@ HIGH</td>
<td></td>
</tr>
<tr>
<td><strong>Mortality - all cause (follow-up mean 1.22 years)</strong></td>
<td>1</td>
<td>Willenheimer randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious</td>
<td>65/505 (12.9%)</td>
<td>73/505 (14.5%)</td>
<td>RR 0.89 (0.65 to 1.21)</td>
<td>16 fewer per 1000 (from 51 fewer to 30 more)</td>
<td>@@@O MODERATE</td>
<td></td>
</tr>
<tr>
<td><strong>Hospitalisation - all cause (follow-up mean 1.22 years)</strong></td>
<td>1</td>
<td>Willenheimer randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>none</td>
<td>151/505 (29.9%)</td>
<td>157/505 (31.1%)</td>
<td>RR 0.96 (0.8 to 1.16)</td>
<td>12 fewer per 1000 (from 62 fewer to 50 more)</td>
<td>@@@@ HIGH</td>
<td></td>
</tr>
<tr>
<td><strong>Sudden death (follow-up mean 1.22 years)</strong></td>
<td>1</td>
<td>Willenheimer randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious</td>
<td>29/505 (5.7%)</td>
<td>34/505 (6.7%)</td>
<td>RR 0.85 (0.53 to 1.38)</td>
<td>10 fewer per 1000 (from 31 fewer to 25 more)</td>
<td>@@@O MODERATE</td>
<td></td>
</tr>
<tr>
<td><strong>Adverse event - serious (follow-up mean 1.22 years)</strong></td>
<td>1</td>
<td>Willenheimer randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious</td>
<td>113/505 (22.4%)</td>
<td>111/505 (22%)</td>
<td>RR 1.02 (0.76 to 1.38)</td>
<td>4 more per 1000 (from 53 fewer to 84 more)</td>
<td>@@@@ HIGH</td>
<td></td>
</tr>
</tbody>
</table>

1. Single blind
2. < 300 events
5.2.2.4 Health Economic Methodological introduction

From the 2003 Guideline, 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) 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. 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.

Yao et al. (2008) 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. 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Study quality*</th>
<th>Study applicability**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yao 2008^59</td>
<td>Minor limitations</td>
<td>Directly applicable</td>
</tr>
</tbody>
</table>

5.2.2.5 Health economic evidence statements

Results of the Yao et al. (2008) analysis 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 mentioned 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

<table>
<thead>
<tr>
<th>Incremental cost (£)</th>
<th>Incremental effects</th>
<th>ICER</th>
<th>Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>£1724</td>
<td>0.649 QALYs</td>
<td>Base-case analysis: £2656 per QALY gained</td>
<td>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;</td>
</tr>
</tbody>
</table>

### 5.2.2.6 Summary of evidence statements

The evidence that was considered revolved around four topics on the use of beta-blockers in the treatment of heart failure: treatment of older adults with heart failure, the treatment of heart failure with preserved left ventricular ejection fraction, the comparison between selective and non-selective beta-blockers and comparison between two different sequences of beta-blockers and ACE inhibitors.

For the first question, four papers were considered\(^{50-53}\). Two of which were post-hoc analysis of randomised controlled trials\(^{50,51}\). These trials used Nebivolol, Metoprolol CR/XL or Bisoprolol. In older adults with heart failure treatment with beta-blockers resulted in a significant reduction of all cause mortality and of sudden death at 27 months and 24 months, respectively. There was, however, no significant reduction of hospitalisation and no significant improvement in the Minnesota Living with Heart Failure Quality of Life Score. Another paper was published based on the results of the SENIORS study\(^{54}\). The impact of Nebivolol therapy was compared in older adults with either heart failure due to left ventricular systolic dysfunction or heart failure and preserved left ventricular ejection fraction. There were no significant differences between the two groups in the primary and secondary end-points.

No study specifically looked at using beta-blockers in the treatment of heart failure with preserved left ventricular ejection fraction.

In comparing non-selective to selective beta-blockers in the treatment of heart failure, there were three papers that compared carvedilol to metoprolol\(^{55-57}\). One of the papers was from a small study that looked at the quality of life\(^{57}\). The other two were from one large randomised controlled trial. These trials suggest that treating heart failure with Carvedilol rather than Metoprolol resulted in reduced all cause mortality and reduced sudden death. However, it did not alter the combined outcome of all cause mortality and hospitalisation.

There was one trial that studied the sequencing of therapeutics used in the treatment of heart failure\(^{58}\). This found no difference between the outcome of heart failure patients treated with beta-blockers followed by ACEI, and the outcome of heart failure patients treated as per the usual sequence of ACEI followed by beta-blockers.

From the health economic review, there was one UK study\(^{59}\) based on the use of Nebivolol in the treatment of heart failure in old adults. This analysis concluded that beta-blockers are cost-effective in this population.
5.2.2.7 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, 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. The GDG reviewed the post-hoc analyses of two randomised controlled studies of the older adults population using Bisoprolol or Metoprolol CR/XL. 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 were patients with a left ventricular ejection fraction >40%. While the size of effect in the sub-group with an ejection fraction >40% was of similar magnitude to that seen in patients with LVSD, the effect in the sub-group with higher ejection fraction was non-significant. Therefore, the GDG did not feel that there was yet sufficient evidence to recommend using beta-blockers in the treatment of HFPEF and that further research on the effectiveness of beta blockers in HFPEF was required.

The GDG reviewed the COMET trial comparing the impact of the non-selective beta-blocker Carvedilol to the selective beta-blocker Metoprolol 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 was necessarily applicable to other beta-blockers. The GDG recognised that other selective beta-blockers licensed for use in heart failure had given similar results in randomised controlled trials to carvedilol.

The GDG considered the CIBIS III trial, 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 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.

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 were excluded from the trials using selective beta-blockers such as bisoprolol (CIBIS II) and Metoprolol CR/XL (MERIT-HF). 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.
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 β blocker licensed for heart failure could be considered.

The GDG then 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.

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

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

### 5.2.2.8 Recommendations

- **R29** 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]

- **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 and electrolytes after initiation of an ACE inhibitor and at each dose increment. [2010]

- **R32** Offer beta-blockers licensed for heart failure to all patients with heart failure due to left ventricular systolic dysfunction, including those with:
  - peripheral vascular disease
  - erectile dysfunction
  - diabetes mellitus
  - interstitial pulmonary disease and
  - chronic obstructive pulmonary disease (COPD) without reversibility.

There is no upper age limit. [new 2010]

- **R33** Introduce beta-blockers for heart failure 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]

### 5.2.3 Aldosterone antagonists

**Clinical 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?
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 in 1999 of the RALES study. This was reviewed in the 2003 guidance. The latter document confirmed that moderately to severely symptomatic patients with heart failure despite optimal medical therapy would attain lower hospitalisation rate and higher survival rate 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. 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

ALDO: aldosterone antagonist + optimal medical management vs. placebo + optimal medical management

Population: all chronic heart failure, including heart failure post myocardial infarction (MI).

Intervention: aldosterone antagonists (eplerenone and spironolactone) plus optimal medical management.

Comparison: placebo plus optimal medical management

Outcomes: all cause death, hospitalization, sudden cardiac death, renal failure (creatinine), hyperkalaemia, quality of life (Minnesota Living with Heart Failure Questionnaire) and gynecomastia.

Three studies were identified comparing aldosterone antagonists plus optimal medical management with placebo plus optimal medical management in patients with heart failure post-MI.

All included studies were from the original EPHESUS trial. 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 HF (LVEF <30%).

The outcomes reported were

- Mortality all cause at 30 days
- Mortality all cause at 16 months
- Sudden death at 30 days
- Sudden death at 16 months
• Heart failure hospitalization at 30 days
• All cause hospitalization at 16 months
• Hyperkalaemia at 16 months

Subgroup: with severe heart failure, LVEF <35%
• Death- all cause at 16 months
• Sudden death at 16 months
• Nonfatal heart failure hospitalization at 16 months

Two studies were identified comparing aldosterone antagonists plus optimal medical management with placebo plus optimal medical management in patients with severe chronic heart failure defined as LVEF <35% 64,65.

PITT 1999 was a part of the RALES study comparing spironolactone with placebo in patients with severe heart failure defined as LVEF <35%. ANON 1996 was performed by the RALES investigators, this trial preceded PITT 1999 and was intended as a dose finding trial for spironolactone in patients with severe HF defined as 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 hospitalization, this may have been caused by the slightly different populations (heart failure vs. heart failure post-MI), the different type of aldosterone antagonist used (spironolactone vs. eplerenone) or the slight difference in outcome (nonfatal HF hospitalization vs. HF hospitalization).

The outcomes reported were
• Mortality all cause at 24 months
• Heart failure hospitalization at 24 months
• Hyperkalaemia at 3 to 24 months
• Gynecomastia in men at 24 months

Three studies were identified comparing aldosterone antagonists plus optimal medical management with placebo plus optimal medical management in patients with chronic heart failure 66-68.

Barr (1995) 68 compared spironolactone with placebo in a population with chronic heart failure (CHF) secondary to coronary heart disease. Macdonald (2004) 67 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 patients substantially into a stable, less symptomatic. Agostoni (2005) 66 compared spironolactone with placebo in a population with CHF and reduced lung diffusion.

Intervention:
• Spironolactone

The outcomes reported were
• Quality of life- Minnesota Living with Heart Failure Questionnaire (MLWHFQ) at 6 months
• Hyperkalaemia >5.5 mmol/l at 2 months
• Raised creatinine >300 umol/l at 8 weeks
• Creatinine mean change at 6 months
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 HF/ LVEF <35% [moderate quality]
- Sudden death at 16 months [moderate quality]
- Sudden death at 16 months – subgroup: severe HF/ 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 hospitalization at 30 days [moderate quality]
- Nonfatal HF hospitalization at 16 months – subgroup: severe HF/ LVEF <35% [moderate quality]
- All hospitalization at 16 months [high quality]

The evidence profile below summarises the quality of the evidence and outcome data from 3 studies 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.

Date: 2009-04-03

Question: Should aldosterone antagonist vs placebo be used for chronic heart failure post-MI?


## Quality assessment

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
<th>Imprisonment</th>
<th>Other considerations</th>
<th>Indirectness</th>
<th>Inconsistency</th>
<th>Limitations</th>
<th>Design</th>
<th>No of patients</th>
<th>Effect Relative (95% CI)</th>
<th>Absolute Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 EPHESUS (2005) randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious¹</td>
<td>None</td>
<td>107/3319 (3.2%)</td>
<td>153/3313 (4.6%)</td>
<td>RR 0.70 (0.55 to 0.89)</td>
<td>14 fewer per 1000 (from 5 fewer to 21 fewer)</td>
<td>MODERATE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cause mortality (follow-up 30 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 EPHESUS (2005) randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
</tr>
<tr>
<td>All cause mortality (follow-up 16 months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 EPHESUS (2005) randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>no serious imprecision¹</td>
</tr>
<tr>
<td>sudden death (follow-up 30 days)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>1 EPHESUS (2005) randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>no serious imprecision²</td>
</tr>
<tr>
<td>sudden death (follow-up 16 months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 EPHESUS (2005) randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>no serious imprecision³</td>
</tr>
<tr>
<td>HF hospitalization (follow-up 30 days)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 EPHESUS (2005) randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
</tr>
<tr>
<td>Event</td>
<td>Clinical setting</td>
<td>Mortality &amp; cause</td>
<td>Follow-up (months)</td>
<td>1 EPHESUS (2003)</td>
<td>Randomised trial</td>
<td>No serious limitations</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious</td>
<td>None</td>
<td>Number of events</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>-------</td>
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</tr>
<tr>
<td>Hyperkalaemia</td>
<td>(follow-up 16 months)</td>
<td></td>
<td></td>
<td></td>
<td>Randomised trial</td>
<td>No serious limitations</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious</td>
<td>None</td>
<td>113/3307 (3.4%)</td>
<td>66/3301 (2%)</td>
</tr>
<tr>
<td>Subgroup: severe HF/LVEF&lt;35%</td>
<td></td>
<td></td>
<td></td>
<td>1 EPHESUS (2006)</td>
<td>Randomised trial</td>
<td>No serious limitations</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious</td>
<td>None</td>
<td>205/1048 (19.6%)</td>
<td>254/1058 (24%)</td>
</tr>
<tr>
<td>Sudden death</td>
<td>(follow-up 16 months)</td>
<td></td>
<td></td>
<td>1 EPHESUS (2006)</td>
<td>Randomised trial</td>
<td>No serious limitations</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious</td>
<td>None</td>
<td>71/1048 (6.8%)</td>
<td>103/1058 (9.7%)</td>
</tr>
<tr>
<td>Hospitalisation non-fatal HF</td>
<td>(follow-up 16 months)</td>
<td></td>
<td></td>
<td>1 EPHESUS (2006)</td>
<td>Randomised trial</td>
<td>No serious limitations</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious</td>
<td>None</td>
<td>152/1048 (14.5%)</td>
<td>181/1058 (17.1%)</td>
</tr>
</tbody>
</table>

1. Total number of events is less than 300.
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. 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect includes both negligible effect and appreciable benefit.
4. Total number of events is less than 300.
a) Aldosterone antagonists plus optimal medical management vs. placebo plus optimal medical management in patients with severe chronic heart failure defined as LVEF <35%.

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

- Mortality all cause at 24 months [moderate quality]
- HF hospitalization 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 comparing aldosterone antagonists plus optimal medical management with placebo plus optimal medical management in patients with severe chronic heart failure defined as LVEF <35%.
Evidence profile: Aldosterone antagonists plus optimal medical management vs. placebo plus optimal medical management in patients with severe chronic heart failure defined as LVEF <35%.

Date: 2009-04-03

Question: Should aldosterone antagonist vs placebo be used for severe heart failure LVEF<35%?


<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of studies</td>
<td>Design</td>
<td>Limitations</td>
<td>Inconsistency</td>
<td>Indirectness</td>
<td>Imprecision</td>
</tr>
<tr>
<td>All cause mortality (follow-up 24 months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 PITT (RALES) 1999 randomised trial no serious limitations no serious inconsistency no serious indirectness serious¹ none</td>
<td>284/822 (34.5%)</td>
<td>386/841 (45.9%)</td>
<td>RR 0.75 (0.67 to 0.85)</td>
<td>138 fewer per 1000 (from 83 fewer to 184 fewer)</td>
<td>⚫⚫⚫⚫ MODERATE</td>
</tr>
<tr>
<td>HF hospitalization a (follow-up 24 months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 PITT (RALES) 1999 randomised trial no serious limitations no serious inconsistency no serious indirectness</td>
<td>215/822 (26.2%)</td>
<td>300/841 (35.7%)</td>
<td>RR 0.73 (0.63 to 0.85)</td>
<td>107 fewer per 1000 (from 64 fewer to 146 fewer)</td>
<td>⚫⚫⚫⚫ MODERATE</td>
</tr>
<tr>
<td>hyperkalaemia (follow-up 3-24 months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 2 PITT (RALES) 1999 + PITT 1996 randomised trial serious¹ no serious inconsistency no serious indirectness serious¹ none</td>
<td>21/869 (2.4%)</td>
<td>11/881 (1.2%)</td>
<td>RR 1.88 (0.91 to 3.9)</td>
<td>11 more per 1000 (from 1 fewer to 35 more)</td>
<td>⚫⚫⚫⚫ LOW</td>
</tr>
<tr>
<td>gynecomastia in men (follow-up 24 months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 PITT (RALES) 1999 randomised trial no serious limitations no serious inconsistency no serious indirectness no serious imprecision none</td>
<td>55/603 (9.1%)</td>
<td>8/614 (1.3%)</td>
<td>RR 7.00 (3.36 to 14.57)</td>
<td>78 more per 1000 (from 31 more to 176 more)</td>
<td>⚫⚫⚫⚫ HIGH</td>
</tr>
</tbody>
</table>

¹ 95% confidence interval around the pooled or best estimate of effect includes both negligible effect and appreciable benefit
² unclear 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
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\(^{66-68}\) 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.

**Date:** 2009-04-03  
**Question:** Should aldosterone antagonist vs placebo be used for all chronic heart failure?  

<table>
<thead>
<tr>
<th>No of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>No of patients</th>
<th>Summary of findings</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>aldosterone antagonist</td>
<td>placebo</td>
<td>Relative (95% CI)</td>
<td>Effect Absolute</td>
</tr>
<tr>
<td>2</td>
<td>AGOSTONI (2005) MACDONALD (2004)</td>
<td>randomised trial</td>
<td>serious¹</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious²</td>
<td>none</td>
<td>58</td>
<td>58</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>BARR (1995)</td>
<td>randomised trial</td>
<td>serious³</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious²</td>
<td>none</td>
<td>4/28 (14.3%)</td>
<td>0/14 (0%)</td>
<td>RR 4.66 (0.27 to 80.84)</td>
</tr>
<tr>
<td>1</td>
<td>BARR (1995)</td>
<td>randomised trial</td>
<td>serious³</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious²</td>
<td>none</td>
<td>4/28 (14.3%)</td>
<td>0/14 (0%)</td>
<td>RR 4.66 (0.27 to 80.84)</td>
</tr>
<tr>
<td>1</td>
<td>AGOSTONI (2005)</td>
<td>randomised trial</td>
<td>serious³</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious²</td>
<td>none</td>
<td>15</td>
<td>15</td>
<td>-</td>
</tr>
</tbody>
</table>

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, 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, and the other was an Irish study assessing spironolactone. We believe the healthcare system in Ireland is reasonably comparable to the UK’s NHS.

Furthermore, we developed a health economic assessment comparing the use of aldosterone antagonists or ARBs in addition to optimal medical treatment in patients with heart failure, for which there is no direct published clinical or cost-effectiveness evidence.

**UK study assessing eplerenone**

Duerden et al. (2008) 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. 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). 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 hospitalization 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 presents the quality and applicability assessment of this economic analysis.

**Irish study assessing spironolactone**

Tilson et al. (2003) 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 to 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 presents the quality and applicability assessment of this economic analysis.
Table 5.7: Economic study assessment

<table>
<thead>
<tr>
<th>Study</th>
<th>Study quality*</th>
<th>Study applicability**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duerden et al. (2008)**</td>
<td>Potentially serious limitations (a)</td>
<td>Directly applicable</td>
</tr>
<tr>
<td>Tilson et al. (2003)**</td>
<td>Potentially serious limitations (b)</td>
<td>Partially applicable (c)</td>
</tr>
</tbody>
</table>

*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 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 economic analysis

<table>
<thead>
<tr>
<th>Incremental cost (£)</th>
<th>Incremental effects</th>
<th>Results (base-case analysis and sensitivity analysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incremental cost per patient not reported</td>
<td>Incremental effect per patient not reported</td>
</tr>
<tr>
<td>Analysis</td>
<td>Cost per life-year gained</td>
<td>Cost per QALY gained*</td>
</tr>
<tr>
<td>Base case</td>
<td>£6,730 per LYG</td>
<td>£10,045 per QALY</td>
</tr>
<tr>
<td>10% Reduction in mortality</td>
<td>£2,771 per LYG</td>
<td>£4,136 per QALY</td>
</tr>
<tr>
<td>15% Reduction in mortality</td>
<td>£2,180 per LYG</td>
<td>£3,254 per QALY</td>
</tr>
<tr>
<td>20% Reduction in mortality</td>
<td>£1,812 per LYG</td>
<td>£2,704 per QALY</td>
</tr>
</tbody>
</table>

* Calculated assuming a utility score of 0.67 (quality of life measure on a 0-1 scale) for patients with heart failure and left ventricular systolic dysfunction post acute myocardial infarction: the EQ-5D questionnaire was administered to a subset of patients in EPHESUS. We estimated the utility score for the population of patients in EPHESUS from results of a cost-effectiveness analysis by Szucs et al. (2006) based on EPHESUS and developed from a Swiss perspective.

Irish study assessing spironolactone

Results of the cost-effectiveness analysis by Tilson et al. (2003) are presented in Table 5.9. Considering a cost-effectiveness threshold of £13,400 per life-year gained (calculated assuming a utility score of 0.67 and considering the NICE threshold of £20,000 per QALY 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 200371 economic analysis

<table>
<thead>
<tr>
<th>Base-case analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Incremental cost (£) Not reported</td>
<td></td>
</tr>
<tr>
<td>Incremental effect Not reported</td>
<td></td>
</tr>
<tr>
<td>Result (pDeath = 0.18; pHosp = 0.25; 1 additional outpatient visit for spironolactone cohort; hosp cost = €3,019)</td>
<td>£417/ Life-Year Gained (LYG)</td>
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</table>

<table>
<thead>
<tr>
<th>Sensitivity analysis - Result</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Two-way sensitivity analysis – variation of probabilities of death (0.16, 0.21) and hospitalisation (0.21, 0.29)</td>
<td>from £277/LYG to £558/LYG</td>
</tr>
<tr>
<td>One-way sensitivity analysis – additional outpatient visits required to initiate medication for spironolactone group (1, 2, 4)</td>
<td>from £417/LYG to £1,016/LYG</td>
</tr>
<tr>
<td>One-way sensitivity analysis – cost of hospitalisation varied (€1,060; €9,319)</td>
<td>from £651/LYG to spinorolactone cohort dominates* the placebo cohort</td>
</tr>
</tbody>
</table>

* It was more effective and less costly.

Health economic assessment comparing the addition of an aldosterone antagonist
or an ARB to optimal medical treatment

The aldosterone antagonist spironolactone is recommended in the UK for treating
patients with moderate to severe heart failure who are already taking an ACEI and a
beta-blocker73. The 2003 guideline19 recommended the following treatment pathway
when a new diagnosis of CHF is confirmed:

1. Start ACEI and titrate upwards (or ARBs if intolerant to ACEI);
2. Add beta-blocker and titrate upwards (regardless of whether or not symptoms
   persist);
3. Add spironolactone (if patient remains moderately to severely symptomatic
   despite optimal drug therapy listed above).

Spironolactone added to optimal medical treatment was assessed by the RALES
study64,65 conducted on patients with severe heart failure and LVEF <35%. This study
showed that spironolactone significantly reduced all-cause mortality at 24 months
(RR 0.70 [95% CI 0.6 to 0.82]) and significantly reduced heart failure-related
hospitalisations at 24 months (RR 0.70 [95% CI 0.59 to 0.82]). In the UK,
spironolactone is a low-cost drug (28-pack (25mg) = £1.7673). A cost-effectiveness
study based on the RALES trial and conducted from a Republic of Ireland
perspective concluded that spironolactone is highly cost-effective (Tilson 200371).

Eplerenone is an aldosterone antagonist recommended in the UK for the
management of patients with heart failure after an acute myocardial infarction with
evidence of left ventricular dysfunction73. This therapy added to optimal medical
treatment was assessed by the EPHEBUS trial69 on patients with heart failure and
LVEF <40% post myocardial infarction. Results of this trial showed that the therapy
significantly reduced all-cause mortality at 16 months (RR 0.85 [95% CI 0.75 to 0.96])
and non-significantly reduced heart failure-related hospitalisations at 16 months (RR
0.91 [95% CI 0.81 to 1.01]). In the UK, eplerenone 25mg and 50mg tablets cost
£1.53 per tablet73. A cost-effectiveness analysis conducted from a UK perspective
and based on the EPHEBUS trial concluded that eplerenone is cost-effective in this
context (Duerden 200870).
The addition of an ARB to ACEi and BB (optimal medical treatment) was a treatment strategy assessed in several clinical trials such as CHARM-Added\textsuperscript{74}, Val-HeFT\textsuperscript{75}, and VALIANT\textsuperscript{76}. CHARM-Added\textsuperscript{74} and Val-HeFT\textsuperscript{75} were conducted on patients with heart failure and LVEF $<40\%$. VALIANT\textsuperscript{76} was conducted on patients with heart failure and LVEF $<35\%-40\%$ following myocardial infarction. Meta-analysing results of these trials showed a non-significant marginal reduction of all-cause mortality (follow-up of 23 to 41 months; RR 0.98 [95\% CI 0.92 to 1.04]), and a significant reduction of heart failure-related hospitalisations (follow-up of 23 to 41 months; RR 0.84 [95\% CI 0.76 to 0.92]). A cost-effectiveness analysis based on CHARM-Added and developed from a UK perspective concluded that this therapy is cost-effective (McMurray 2006\textsuperscript{77}).

There is no published clinical or cost-effectiveness evidence directly comparing the addition of ARB to optimal medical treatment with the addition of aldosterone antagonist. It is possible to assess the cost-effectiveness of this comparison indirectly using outcomes from EPHESUS\textsuperscript{69} (eplerenone) and VALIANT\textsuperscript{76} (valsartan) trials, which are conducted on similar populations of patients (heart failure patients with left ventricular systolic dysfunction post myocardial infarction).

Table 5.10 shows comparative survival and hospitalisation outcomes from EPHESUS\textsuperscript{69} and VALIANT\textsuperscript{76} trials, and cost components related to drug treatments.

<table>
<thead>
<tr>
<th></th>
<th>EPHESUS\textsuperscript{69} (eplerenone)</th>
<th>VALIANT\textsuperscript{76} (valsartan)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>0.85 (0.75 to 0.96)*</td>
<td>0.99 (0.91 to 1.07)</td>
</tr>
<tr>
<td>HF hospitalisations</td>
<td>0.91 (0.81 to 1.01)</td>
<td>0.89 (0.82 to 0.96)</td>
</tr>
<tr>
<td>All-Cause hospitalisations</td>
<td>0.95 (0.89 to 1.02)</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

* RR (95\% CI)  
** BNF No. 57, March 2009\textsuperscript{73}  
\*/2 GP visits according to the clinical trial\textsuperscript{69}; can be up to 4 visits according to UK current practice  
\/*\*/4 GP visits according to the clinical trial\textsuperscript{76}; can be up to 7 visits according to UK current practice

By looking at Table 5.10, and assuming that the relative risk estimates are constant over time, it is clear that adding eplerenone to optimal medical treatment in patients with heart failure and left ventricular systolic dysfunction post myocardial infarction is more cost-effective than adding valsartan. Furthermore, side effects from these treatments leading to additional resource use (GP visits and biochemistry tests) are presented in Table 5.11. These figures once more seem to favour eplerenone.

Table 5.10: Outcomes for eplerenone and valsartan

<table>
<thead>
<tr>
<th></th>
<th>Drug price per day (GP visits)</th>
<th>Up-titration costs (GP visits)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPHESUS\textsuperscript{69} (eplerenone)</td>
<td>25mg or 50mg = £1.53**</td>
<td>2-4*</td>
</tr>
<tr>
<td>VALIANT\textsuperscript{76} (valsartan)</td>
<td>160mg (cap) x2 = £1.55**</td>
<td>4-7**</td>
</tr>
</tbody>
</table>

\* RR (95\% CI)  
** BNF No. 57, March 2009\textsuperscript{73}  
\*/2 GP visits according to the clinical trial\textsuperscript{69}; can be up to 4 visits according to UK current practice  
\/*\*/4 GP visits according to the clinical trial\textsuperscript{76}; can be up to 7 visits according to UK current practice

By looking at Table 5.10, and assuming that the relative risk estimates are constant over time, it is clear that adding eplerenone to optimal medical treatment in patients with heart failure and left ventricular systolic dysfunction post myocardial infarction is more cost-effective than adding valsartan. Furthermore, side effects from these treatments leading to additional resource use (GP visits and biochemistry tests) are presented in Table 5.11. These figures once more seem to favour eplerenone.

Table 5.11: Side-effect outcomes

<table>
<thead>
<tr>
<th></th>
<th>EPHESUS\textsuperscript{69} (follow-up at 16 months)</th>
<th>VALIANT\textsuperscript{76} (follow-up at 24.7 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperkalaemia</td>
<td>1.71 (1.27 to 2.31)*</td>
<td>1.43 (1.14 to 1.78)</td>
</tr>
<tr>
<td>Serious Hyperkalaemia (serum potassium ≥6mmol/liter)</td>
<td>1.52 (1.38 to 1.68)</td>
<td>2.20 (1.53 to 3.18)</td>
</tr>
</tbody>
</table>

* RR (95\% CI)
In summary, adding eplerenone to optimal medical treatment is clearly more cost-effective than adding valsartan (ARB), especially considering the large difference in mortality estimates and the marginal difference in hospitalisation estimates between EPHESUS\(^69\) and VALIANT\(^76\) trials. Detailed cost-effectiveness modelling would not add information that could alter this conclusion.

The population of patients assessed in the RALES\(^64,65\) (patients with severe heart failure and LVEF <35%) and in the EPHESUS trials\(^69\) (patients with heart failure and LVEF <40% post myocardial infarction) are not comparable. Table 5.12 compares the evidence for eplerenone and spironolactone. If the relative risks are constant across different populations, spironolactone looks to be highly cost-effective compared to eplerenone.

### Table 5.12: Outcomes for eplerenone and spironolactone

<table>
<thead>
<tr>
<th></th>
<th>EPHESUS(^69) (eplerenone)</th>
<th>RALES(^64,65) (spironolactone)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Outcomes at 16 months</td>
<td>Outcomes at 24 months</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.85 (0.75 to 0.96)*</td>
<td>RR 0.70 (0.6 to 0.82)</td>
</tr>
<tr>
<td>HF hospitalisations</td>
<td>0.91 (0.81 to 1.01)</td>
<td>RR 0.70 (0.59 to 0.82)</td>
</tr>
<tr>
<td>All-Cause hospitalisations</td>
<td>0.95 (0.89 to 1.02)</td>
<td>Not reported</td>
</tr>
<tr>
<td>** Eplerenone as an adjunct to optimal medical treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>** Spironolactone as an adjunct to optimal medical treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug price per day</td>
<td>50mg = £1.53**</td>
<td>25mg to 50mg = £0.06 to £0.09**</td>
</tr>
</tbody>
</table>

* RR (95% CI)
** BNF No. 57, March 2009\(^73\)

### 5.2.3.6 Summary of evidence statements

Since 2003, there has been one large randomised clinical trial and two post-hoc analyses of the same trial (EPHESUS)\(^62,63,69\) into the use of the aldosterone antagonist eplerenone (12.5 – 50 mg/day) or placebo, in the treatment of symptomatic heart failure after myocardial infarction, or asymptomatic diabetic patients with left ventricular systolic dysfunction (LVEF<40%) after myocardial infarction. The treatment with eplerenone or placebo was added to optimal medical therapy at 3-14 days after myocardial infarction. Treatment with aldosterone antagonist significantly reduced all cause mortality for the whole cohort at 30 days and at 16 months. It also reduced the all cause mortality and the risk of sudden death at 16 months for those with severe heart failure (LVEF<30%).

However, this therapy resulted in a significant increase in the risk of hyperkalaemia. At 30 days, aldosterone antagonists did not have significant impact on the risk of sudden death or of heart failure hospitalisation. At 16 months, the treatment did not have an impact on non-fatal heart failure hospitalisation or on all-cause hospitalisations.

Prior to 2003, the aldosterone antagonist spironolactone (25-50 mg/day) was compared to placebo in addition to optimal medical therapy for the treatment of severe chronic heart failure, with left ventricular ejection fraction <35%. The treatment with the aldosterone antagonist resulted in a statistically significant reduction in both mortality and heart failure hospitalisations at 24 months. However, there was a significant increase in gynaecomastia amongst men. There was no significant increase in hyperkalaemia.
No significant effects on hyperkalaemia or renal failure were found in the small studies of aldosterone antagonists or placebo in patients with heart failure. However, one of the studies suggested worsening quality of life while on spironolactone.

In the health economic review, eplerenone and spironolactone were seen as cost-effective treatments for heart failure\textsuperscript{70, 71}. Our health economic assessment comparing the addition of an ARB or an aldosterone antagonist to optimal medical treatment in heart failure, based on EPHESUS\textsuperscript{69} and VALLIANT\textsuperscript{76} trials, concluded that adding an aldosterone antagonist to optimal medical treatment is more cost-effective than adding an ARB.

### 5.2.3.7 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.

The aldosterone antagonist spironolactone was added to loop diuretics and an ACEI in patients with chronic heart failure 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. Only 10-11\% of the patients thus treated were on beta-blockers.

The aldosterone antagonist eplerenone was used in the treatment of symptomatic heart failure (LVEF<40\%) after myocardial infarction, or in asymptomatic heart failure (LVEF<40\%) after myocardial infarction in diabetic patients. The aldosterone antagonist 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 treatment of chronic heart failure. While the heart failure resulted from acute myocardial infarction, it continued beyond the acute initial phase of the infarction. The patients continued to display evidence of left ventricular systolic dysfunction (LVEF<40\%, with symptoms unless diabetic) some 3-14 days after myocardial infarction. The GDG decided that the evidence from this group of trials was relevant for patients with chronic heart failure. Eplerenone therapy resulted in 15\%, and 11\% reductions of all cause mortality and sudden death, respectively, at 16 months. 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 variable weight to be given to results of randomised controlled trials as opposed to post-hoc analyses of randomised controlled trials. The GDG did not feel it was appropriate to combine the post-hoc analysis of the outcomes in the sub-group of patients with LVEF<30\% treated with eplerenone\textsuperscript{63}, with the study of patients with LVEF<35\% treated with spironolactone\textsuperscript{64} 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 the class are hyperkalaemia and renal impairment. When serious renal dysfunction or hyperkalaemia occur, the aldosterone antagonist needs to be discontinued. In less serious situations, the dose should be reduced (for example to 12.5 mg daily, or 25 mg on alternate days).

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 assessing eplerenone based on the EPHESUS trial. 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, the use of spironolactone was also cost effective (ICER just above £400 per life-year gained).

In the absence of a 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. Thus it may be justifiable to use spironolactone both in chronic heart failure and in heart failure after myocardial infarction, unless there is intolerance. However, the GDG accepts the guidance of NICE on the management of myocardial infarction complicated by heart failure that an aldosterone antagonist licensed for use after myocardial infarction should be used. In the EPHESUS trial the treatment was continued for a mean of 16 months (range 0-33 months). The GDG agreed with the 2003 recommendation that initiation of spironolactone should be decided by a specialist.

There is no direct evidence comparing aldosterone antagonists (AA) to angiotensin receptor blockers (ARB) as third line agents in the treatment of heart failure, following angiotensin enzyme inhibitors (ACEI) and β blockers (BB). Our health economic analysis suggested that the addition of an aldosterone antagonist is more cost-effective than the addition of an angiotensin receptor blocker.

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.

**5.2.3.8 Recommendations**

R35 Offer an aldosterone antagonist to patients with heart failure due to left ventricular systolic dysfunction if moderate to severe symptoms persist despite optimal therapy with an ACE inhibitor and beta-blocker. [new 2010]

R36 Seek specialist advice before offering aldosterone antagonists to patients with heart failure due to left systolic dysfunction. [new 2010]

R37 In patients with heart failure due to left ventricular systolic dysfunction, who are taking aldosterone antagonists, monitor potassium and creatinine levels for signs of hyperkalaemia and/or deteriorating renal function. Halve the dose of aldosterone antagonist and recheck the potassium and creatinine levels if the patient develops hyperkalaemia or renal impairment. [new 2010]

R38 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]).

R39 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 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]).

5.2.4 Isosorbide Dinitrate/Hydralazine combination

Clinical Question:
ISO: 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 shortly 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 compared to the 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 according to the ethnic origin of the patient 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 / hydralazine versus placebo in addition to optimal medical management in the black population (patients self-identified as black (defined as of African descent)78-81). Two of the studies reported on different outcomes from the main RCT study78,80. Table 5.13 below present a summary of the patient population and interventions for each study.

Table 5.13: Population and interventions for studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population</th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARSON</td>
<td>male patients with a history of heart failure or</td>
<td>VHEFT I:</td>
<td>VHEFT I:</td>
</tr>
<tr>
<td>VHEFT I:</td>
<td></td>
<td>- prazosin 5mg 4xday OR</td>
<td>- placebo</td>
</tr>
<tr>
<td>N=642</td>
<td></td>
<td></td>
<td>VHEFT II:</td>
</tr>
</tbody>
</table>

Chronic heart failure_Full_Guideline_for consultationDRAFT (January 2010) 106
### VHEFT II: N=804

**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.

- combination of hydralazine 75mg + isosorbide dinitrate 40mg 4× day.

### VHEFT II: - combination of hydralazine 75mg + isosorbide dinitrate 40mg 4× 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, spironolactone and diuretics.

**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.**

- enalapril 10mg 2×day

### 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 tablets 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
The outcomes reported were:

- Composite score (weighted values for all cause death, first hospitalization for HF during 18 month follow-up and change in quality of life at 6 months)
- All cause mortality rate up to 5.5 yrs
- Cardiovascular death up to 18 months
- Hospitalization for CHF up to 5.5 yrs
- Quality of life measure-Minnesota Living with Heart Failure Questionnaire at 6 months
- Adverse events- head ache and dizziness, range 0 to 18 months

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.

The outcomes reported were:

- All cause mortality rate up to 66 months (5.5 years)
- Hospitalization for CHF up to 66 months (5.5 years)

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

One RCT was identified comparing isosorbide dinitrate + hydralazine versus placebo in addition to optimal medical management in different age groups.

**Table 5.14: Population and interventions for RCT (Cohn et al.)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>COHN</td>
<td>Men between the ages of 18 to 75 yrs with chronic heart failure. Inclusion criteria: evidence of cardiac dysfunction.</td>
<td>Hydralazine 75 mg plus isosorbide dinitrate 40 mg</td>
</tr>
</tbody>
</table>

The outcomes reported were:

- all cause mortality rate (per annum) in <60yrs
- all cause mortality rate (per annum) in >60 yrs

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

One RCT was identified comparing isosorbide dinitrate + hydralazine versus ACE I in different age groups.

**Table 5.15: Population and intervention RCT (Johnson et al.)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population</th>
<th>Intervention</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>JOHNSON</td>
<td>Male patients between 18-75 yrs old with chronic CHF. Patients had to have demonstrable cardiac</td>
<td>Hydralazine 300mg + isosorbide dinitrate 160mg + one placebo</td>
<td>Enalapril 20mg plus 2 placebos</td>
</tr>
<tr>
<td>dysfunction confirmed by radionuclide ejection fraction &lt;45%, a cardiothoracic ratio ≥ 0.55, or a left ventricular internal diameter at end diastole (LVIDD) &gt;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 &lt;25 mL·kg⁻¹·min⁻¹ at termination of the test for dyspnoea or fatigue.)</td>
<td>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.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 The outcomes reported were:

2 • all cause mortality at 2 years in <60yrs

3 • all cause mortality at 2 yrs in >60 yrs
5.2.4.3 Clinical evidence statements

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

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

- All cause mortality up to 5.5 yrs [moderate quality]
- Hospitalisation for heart failure 12.8 to 66 months [high 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 [moderate 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 ER 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) 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 patients of African descent

Author(s):

Date: 2009-03-11

Question: Should isosorbide dinitrate and hydralazine (vs. placebo) be used in addition to optimal medical therapy in black patients?

Settings:


Quality assessment

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
<th>No of patients</th>
<th>Effect</th>
<th>Absolute</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of studies</td>
<td>Design</td>
<td>Limitations</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td>1</td>
<td>TAYLOR 2004</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
</tr>
<tr>
<td>2</td>
<td>TAYLOR 2004 CARSON 1999</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
</tr>
<tr>
<td>1</td>
<td>TAYLOR 2007</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
</tr>
<tr>
<td>2</td>
<td>ANGUS 2005 CARSON 1999</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
</tr>
<tr>
<td>Total no. of ER and unscheduled office visits (follow-up mean 12.8 months)</td>
<td>1</td>
<td>randomised</td>
<td>no serious</td>
<td>no serious</td>
</tr>
</tbody>
</table>

Chronic heart failure_Full_Guideline_for consultationDRAFT (January 2010) 111
**ANGUS 2005**

<table>
<thead>
<tr>
<th>trial</th>
<th>limitations</th>
<th>inconsistency</th>
<th>indirectness</th>
<th>quality of life (follow-up mean 6 months; range of scores: 0-105; Better indicated by less)</th>
<th>(8.1%)</th>
<th>(0.49 to 1.19)</th>
<th>(from 41 fewer to 15 more)</th>
<th>MODERATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>randomised</td>
<td>no serious</td>
<td>no serious</td>
<td>no serious</td>
<td>Serious&lt;sup&gt;2&lt;/sup&gt; none</td>
<td>518</td>
<td>532</td>
<td>-</td>
<td>MD -2.9 (-5.42 to -0.38)</td>
</tr>
<tr>
<td>TAYLOR 2004</td>
<td>limitations</td>
<td>inconsistency</td>
<td>indirectness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**adverse events- headache (follow-up 0-18 months)**

<table>
<thead>
<tr>
<th>trial</th>
<th>limitations</th>
<th>inconsistency</th>
<th>indirectness</th>
<th>adverse events- headache (follow-up 0-18 months)</th>
<th>none</th>
<th>243/518 (46.9%)</th>
<th>102/532 (19.2%)</th>
<th>RR 2.45 (2.01 to 2.98)</th>
<th>278 more per 1000 (from 194 more to 380 more)</th>
<th>MODERATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>randomised</td>
<td>no serious</td>
<td>no serious</td>
<td>no serious</td>
<td>no serious indirectness no serious imprecision</td>
<td>none</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAYLOR 2004</td>
<td>limitations</td>
<td>inconsistency</td>
<td>indirectness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**adverse events-dizziness (follow-up 0-18 months)**

<table>
<thead>
<tr>
<th>trial</th>
<th>limitations</th>
<th>inconsistency</th>
<th>indirectness</th>
<th>adverse events-dizziness (follow-up 0-18 months)</th>
<th>none</th>
<th>152/518 (29.3%)</th>
<th>65/532 (12.2%)</th>
<th>RR 2.40 (1.84 to 3.13)</th>
<th>171 more per 1000 (from 102 more to 260 more)</th>
<th>MODERATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>randomised</td>
<td>no serious</td>
<td>no serious</td>
<td>no serious</td>
<td>no serious indirectness</td>
<td>none</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAYLOR 2004</td>
<td>limitations</td>
<td>inconsistency</td>
<td>indirectness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup> < 300 events; pooled or best estimate of effect includes both negligible effect and appreciable benefit

<sup>2</sup> 95% confidence interval includes no effect and the upper or lower confidence limit crosses the minimal important difference (MID), either for benefit or harm

<sup>3</sup> < 300 events
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 comparing isosorbide + hydralazine versus ACE I in the black population.
**EVIDENCE PROFILE: isosorbide dinitrate + hydralazine versus ACE I in the black population**

<table>
<thead>
<tr>
<th>No of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>No of patients</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>isosorbide + hydralazine</td>
<td>ACE I</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>39/109 (35.8%)</td>
<td>RR 0.97 (0.68 to 1.39)</td>
</tr>
<tr>
<td>all cause mortality (follow-up 0-66 months)</td>
<td>CARSON 1999</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>serious¹</td>
<td>none</td>
<td>39/106 (36.8%)</td>
<td></td>
</tr>
<tr>
<td>hospitalization for CHF (follow-up 0-66 months)</td>
<td>CARSON 1999</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>serious¹</td>
<td>none</td>
<td>23/109 (21.1%)</td>
<td>RR 0.93 (0.56 to 1.55)</td>
</tr>
</tbody>
</table>

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) 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

<table>
<thead>
<tr>
<th></th>
<th>Quality assessment</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of studies</td>
<td>Design</td>
</tr>
<tr>
<td>all cause mortality rate in &lt;60yrs (per annum)</td>
<td>1</td>
<td>COHN 1987</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>COHN 1987</td>
</tr>
<tr>
<td>all cause annual mortality &gt; 60 yrs (per annum)</td>
<td>2</td>
<td>Post-hoc sub group analysis</td>
</tr>
</tbody>
</table>

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) 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 in the < 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

<table>
<thead>
<tr>
<th>Author(s):</th>
<th>Date: 2009-03-11</th>
<th>Question: Should isosorbide dinitrate + hydralazine vs ACE I be used for chronic heart failure in different ages?</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>No of patients</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of studies</td>
<td>Design</td>
</tr>
<tr>
<td>all cause mortality at 2 years &lt;60 yrs (follow-up 2 years)</td>
<td>1</td>
</tr>
<tr>
<td>all cause mortality at 2 years &gt;60 yrs (follow-up 2 years)</td>
<td>1</td>
</tr>
</tbody>
</table>

<sup>1</sup> post-hoc subgroup analysis

<sup>2</sup> 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\(^{19}\), 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 II 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)\(^{80}\) 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 were 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 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.\(^{84}\) (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), ER visits, unscheduled physician visits, scheduled physician visits, ISDN/HYD therapy, concomitant medication, and other cares. Table 5.16 presents the quality and applicability assessment of this economic analysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study quality*</th>
<th>Study applicability**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angus et al. (2005)(^{80})</td>
<td>Minor limitations (a)</td>
<td>Partially applicable (b)</td>
</tr>
</tbody>
</table>

*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\(^{80}\) are presented in Table 5.17. 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 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 5.17: Results - Angus 2005\textsuperscript{80} economic analysis

<table>
<thead>
<tr>
<th></th>
<th>18 months time horizon (A-HeFT follow-up)</th>
<th>Lifetime horizon</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Main analysis</td>
<td>Bootstrap simulation sampling</td>
</tr>
<tr>
<td>Heart failure-related cost</td>
<td>Dominant * (incremental cost: £1899)**</td>
<td>49% dominant; 66% better than ~£6000 per Life-Year Gain (LYG)</td>
</tr>
<tr>
<td>All healthcare-related cost</td>
<td>Dominant * (incremental cost: £2623)**</td>
<td>71% dominant; 82% better than ~£6000 per LYG</td>
</tr>
</tbody>
</table>

* Improved survival and saved cost
** Incremental effect not reported

5.2.4.6 Summary of evidence statements

Both ethnicity and age subgroups were considered.

Prior to 2003, there were studies of the use of the combination with a background treatment with diuretics and digoxin (VHEFT-I; 1986)\textsuperscript{85} or in comparison with ACEI (VHEFT-II; 1991)\textsuperscript{86}. In the first trial there was significant reduction of mortality in black patients, with no impact on hospitalisation, when black and non-black patients were considered separately. In the second study, the combination was inferior to ACEI, especially in the white population.

New clinical evidence since the publication of the 2003 heart failure guidelines revolves around the effect of adding the combination of Hydralazine and nitrates as combined arterial and venous dilators, respectively in black patients with heart failure (AHEFT)\textsuperscript{79, 76, 80, 81}. This was in addition to optimal medical therapy. The appraised were four related publications. The combination significantly reduced all cause mortality (evidence was of moderate quality), and heart failure hospitalisation at 12.8-66 months (high-quality evidence). In addition, the combination significantly improved the quality of life (moderate-quality evidence) and the composite score (all cause mortality, first heart failure hospitalisation and change in quality of life), but the combination was associated with significant increase in the incidence of headache and dizziness. The combination did not reduce unplanned admissions to the accident and emergency department, or the clinic visits of the treated patients.

The reviewed health economic analysis\textsuperscript{80} was developed from a US perspective, and was based on the AHEFT trial conducted in the Black population. Treatment with a combination of hydralazine and nitrates, in addition to optimal therapy that included ACEI and beta-blockers, was cost-saving with 18-month time horizon. It is likely to be cost-effective over the lifetime as long as the effects observed in the trials persist for some months beyond 18 months.
5.2.4.7 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. The GDG noted that the main studies related to this subject 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) \(^79, \, 78, \, 80 \, 81\); The GDG noted the positive effects the combination has on reducing morbidity and mortality of heart failure patients.

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.

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 \(^82,83\).

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 \(^79\) were already treated with ACEI and beta-blockers (BB), 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 could not be used, and 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 \(^87\).

There is no evidence on the use of this combination in non-black patients who remain symptomatic after treatment with ACEI and β 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 of 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 β blockers could benefit from the introduction of this combination. In the absence of firm evidence to support this, the GDG suggested this topic as a research recommendation.

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 β 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 however, that this cost-effectiveness analysis 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 β blockers.

5.2.4.8 Recommendation
R40 Offer isosorbide in combination with hydralazine to black patients who remain symptomatic with ACE inhibitors and beta-blockers. [new 2010]

5.2.5 Angiotensin-II receptor antagonists vs placebo
Clinical question:
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?

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 particularly true when one considers ACEI and Aldosterone antagonists. Angiotensin receptor blockers (Antagonists of type I receptor of Angiotensin II) are a group of agents that proved to be effective 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 at the time the existing guidelines were published, however no firm recommendation was possible with regards to the use of ARB in combination with other agents particularly the ACEI.

Reasons for Review
New randomised clinical trials have reported on the use of ARB’s in the treatment of heart failure due to left ventricular systolic dysfunction as an add-on to ACEI, 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 non-concordant results. Thus the 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 ARB’s exert the same effect as ACEI. In addition, another question is whether all ARB’s exert the same effect. Clarification is needed on the potential risks from combining ACEI, ARB and beta-blockers. One issue is whether patients who remain symptomatic despite therapy with ACEI and beta blockers should be additionally treated with ARB’s or aldosterone antagonists.

5.2.5.2 Clinical Methodological introduction
ARB1: Angiotensin-II receptor antagonists (ARBS) vs. placebo

4 Black patients are those of African or Caribbean descent, and not mixed-race, Asian or Chinese patients.
1 **Population:** all chronic heart failure

2 **Intervention:** angiotensin-II receptor antagonists

3 **Comparison:** placebo

4 **Outcomes:** all cause death, hospitalization, composite score (cardiovascular (CV) death and heart failure hospitalization), renal failure (creatinine), hyperkalaemia, quality of life (Minnesota Living with Heart Failure Questionnaire), New York Heart Association (NYHA) class and hypotension.

(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) \(^{88-92}\).

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

**Outcomes reported:**

- All cause mortality
- All cause mortality- post hoc subgroup
- HF hospitalization
- Composite score (CV death and HF hospitalization)
- Hyperkalaemia
- Raised creatinine
- Mean increase in creatinine
- Hypotension\(^5\)
- Hypotension- post hoc subgroup\(^6\)
- Quality of life- Minnesota Living With Heart Failure Questionnaire (MLWHFQ)

(b) In patients with HFPEF:

In I-PRESERVE \(^{93}\) 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 \(^{94}\) initially ACE inhibitors were not allowed as concomitant therapy, however with the publication of new trials, their use was permitted in

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\(^5\) Hypotension was reported as either an adverse event or a cause of discontinuation.

\(^6\) Hypotension was reported as a persistent standing systolic blood pressure <80 mm Hg or symptoms of hypotension and a cause of treatment discontinuation.
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)

Outcomes reported:

- All cause mortality
- CV mortality
- HF hospitalization
- Composite score (CV death and HF hospitalization)
- Hyperkalaemia
- Raised creatinine
- Mean increase in creatinine
- Hypotension

---

7 Hypotension was reported as either a serious adverse event or a cause of 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 hospitalization [moderate quality]
- Composite score (CV mortality and HF hospitalization) [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:

- 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 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).

**Date:** 2009-05-13  
**Question:** Should angiotensin II receptor blockers (ARBs) vs. placebo be used for chronic heart failure?


<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of patients</td>
</tr>
<tr>
<td></td>
<td>angiotensin II</td>
</tr>
<tr>
<td></td>
<td>receptor blockers</td>
</tr>
<tr>
<td></td>
<td>(ARBs)</td>
</tr>
<tr>
<td></td>
<td>placebo</td>
</tr>
<tr>
<td>All cause mortality (follow-up 1-24 months)</td>
<td>4 Mazayez, STRETCH, CHARM-alternative, ARCH-J</td>
</tr>
<tr>
<td>All cause mortality (follow-up 7.5-24 months)</td>
<td>1 Val-HeFT- post-hoc analysis</td>
</tr>
<tr>
<td>HF hospitalization (follow-up 7.5-24 months)</td>
<td>2 CHARM-alternative, ARCH-J</td>
</tr>
<tr>
<td>Composite score: CV death and HF hospitalization (follow-up median 33.7 months)</td>
<td>1 CHARM-alternative</td>
</tr>
<tr>
<td>Hyperkalaemia (follow-up median 33.7 months)</td>
<td>1 CHARM-alternative</td>
</tr>
<tr>
<td>Raised creatinine (follow-up 3-24 months)</td>
<td>2 CHARM-</td>
</tr>
</tbody>
</table>
### Mean increase in creatinine- post hoc subgroup (follow-up 24 months; measured with: mg/dl; range of scores: -; Better indicated by less)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Post hoc analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Val-HeFT- post-hoc analysis</td>
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<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>none</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>185</td>
</tr>
<tr>
<td>Mean increase in creatinine</td>
<td></td>
<td></td>
<td></td>
<td>3%</td>
</tr>
</tbody>
</table>

### Hypotension (follow-up 1-24 months)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Post hoc analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 CHARM- alternative, STRETCH,</td>
<td>randomised</td>
<td>no serious</td>
<td>no serious indirectness</td>
<td>none</td>
</tr>
<tr>
<td>Mazayev</td>
<td></td>
<td>limitations</td>
<td></td>
<td>48/1239 (3.9%)</td>
</tr>
<tr>
<td>Mean increase in creatinine</td>
<td></td>
<td>1.3%</td>
<td></td>
<td>0 more per 1,000</td>
</tr>
</tbody>
</table>

### Hypotension- post hoc subgroup (follow-up 24 months)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Post hoc analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Val-HeFT- post-hoc</td>
<td>randomised</td>
<td>no serious</td>
<td>no serious indirectness</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td></td>
<td>limitations</td>
<td></td>
<td>1/185 (0.5%)</td>
</tr>
<tr>
<td>Mean increase in creatinine</td>
<td></td>
<td>1.3%</td>
<td></td>
<td>0 fewer per 1000 (from 6 fewer to 87 more)</td>
</tr>
</tbody>
</table>

### 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)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Post hoc analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Val-HeFT- post-hoc analysis</td>
<td>randomised</td>
<td>no serious</td>
<td>no serious indirectness</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td></td>
<td>limitations</td>
<td></td>
<td>185</td>
</tr>
</tbody>
</table>

---

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 EF.

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

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

Compared with placebo, angiotensin-II receptor antagonists non-significant affect 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 hospitalization [high quality]
- Composite score (CV mortality and HF hospitalization) [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 comparing ARBs vs. placebo in heart failure with preserved EF.
## Evidence profile: ARBs vs. placebo in heart failure with preserved EF

**Date:** 2009-05-13  
**Question:** Should angiotensin II receptor blockers (ARBs) vs. Placebo be used for HFPEF?  

### No of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | No of patients | Effect | Absolute | Quality | Importance |
<table>
<thead>
<tr>
<th></th>
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<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All cause mortality (follow-up 24-49 months)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>I-PRESERVE, CHARM PRESERVED</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
<td>none</td>
<td>682/3581 (19%)</td>
<td>RR 1.00 (0.91 to 1.10)</td>
<td>0 fewer per 1,000</td>
<td>☑️</td>
</tr>
<tr>
<td><strong>CV mortality (follow-up 24-49 months)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>I-PRESERVE, CHARM PRESERVED</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
<td>none</td>
<td>481/3581 (13.4%)</td>
<td>RR 1.02 (0.9 to 1.14)</td>
<td>2 more per 1,000</td>
<td>☑️</td>
</tr>
<tr>
<td><strong>HF hospitalization (follow-up 24-49 months)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>I-PRESERVE, CHARM PRESERVED</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
<td>none</td>
<td>566/3581 (15.8%)</td>
<td>RR 0.92 (0.83 to 1.02)</td>
<td>12 fewer per 1,000</td>
<td>☑️</td>
</tr>
<tr>
<td><strong>Composite score: CV death and HF hospitalization (follow-up 24-49 months)</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>I-PRESERVE, CHARM PRESERVED</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>no serious imprecision</td>
<td>none</td>
<td>761/3581 (21.3%)</td>
<td>RR 0.94 (0.86 to 1.03)</td>
<td>14 fewer per 1,000</td>
<td>☑️</td>
</tr>
<tr>
<td><strong>Hyperkalaemia (follow-up 24-49 months)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>I-PRESERVE, CHARM PRESERVED</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious¹</td>
<td>none</td>
<td>34/3581 (0.9%)</td>
<td>RR 1.88 (1.07 to 3.33)</td>
<td>3 more per 1,000</td>
<td>☑️</td>
</tr>
<tr>
<td><strong>Raised creatinine (follow-up median 36.6 months)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>CHARM-PRESERVED</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious²</td>
<td>none</td>
<td>72/1514 (4.8%)</td>
<td>RR 1.99 (1.34 to 2.96)</td>
<td>24 more per 1,000 (from 8 more to 47 more)</td>
<td>☑️</td>
</tr>
</tbody>
</table>

**Summary of findings**

- **All cause mortality (follow-up 24-49 months)**
  - Relative Risk: 1.00 (0.91 to 1.10)
  - Absolute Risk: 0 fewer per 1,000
  - Quality: HIGH

- **CV mortality (follow-up 24-49 months)**
  - Relative Risk: 1.02 (0.9 to 1.14)
  - Absolute Risk: 2 more per 1,000
  - Quality: HIGH

- **HF hospitalization (follow-up 24-49 months)**
  - Relative Risk: 0.92 (0.83 to 1.02)
  - Absolute Risk: 12 fewer per 1,000
  - Quality: HIGH

- **Composite score: CV death and HF hospitalization (follow-up 24-49 months)**
  - Relative Risk: 0.94 (0.86 to 1.03)
  - Absolute Risk: 14 fewer per 1,000
  - Quality: HIGH

- **Hyperkalaemia (follow-up 24-49 months)**
  - Relative Risk: 1.88 (1.07 to 3.33)
  - Absolute Risk: 3 more per 1,000
  - Quality: MODERATE

- **Raised creatinine (follow-up median 36.6 months)**
  - Relative Risk: 1.99 (1.34 to 2.96)
  - Absolute Risk: 24 more per 1,000 (from 8 more to 47 more)
  - Quality: MODERATE
### Mean increase in creatinine (follow-up mean 49.5 months; measured with: mg/dl; range of scores: -; Better indicated by less)

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Events</th>
<th>RR (95% CI)</th>
<th>Additional Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 I-PRESERVE</td>
<td>Randomised</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>2067</td>
<td>0.04 (0.02 to 0.06)</td>
<td>HIGH</td>
</tr>
<tr>
<td>2 I-PRESERVE,</td>
<td>Randomised</td>
<td>Serious</td>
<td>None</td>
<td>None</td>
<td>97/3581(2.7%)</td>
<td>1.22 (0.91 to 1.64)</td>
<td>LOW</td>
</tr>
<tr>
<td>CHARM PRESERVED</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>79/3570(2.1%)</td>
<td>2 more per 1,000</td>
<td></td>
</tr>
</tbody>
</table>

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\textsuperscript{19}, 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\textsuperscript{95}. This analysis showed little difference between the cost-effectiveness ratios 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. Furthermore, we developed a health economic assessment comparing the use of aldosterone antagonists or ARBs in addition to optimal medical treatment in patients with heart failure, for which there is no direct published clinical or cost-effectiveness evidence (presented and discussed in Section 5.2.6.4).

McMurray et al. (2006)\textsuperscript{77} 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 (calculating 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 5.18 presents the quality and applicability assessment of this economic analysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study quality*</th>
<th>Study applicability**</th>
</tr>
</thead>
<tbody>
<tr>
<td>McMurray 2006\textsuperscript{77}</td>
<td>Potentially serious limitations (a)</td>
<td>Directly applicable</td>
</tr>
</tbody>
</table>

*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 5.19 presents UK results of the cost-effectiveness analyses developed by McMurray et al. (2006)\textsuperscript{77}. 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 5.19 Cost-effectiveness results - McMurray 200677 economic analysis

<table>
<thead>
<tr>
<th>CHARM Trial</th>
<th>Incremental cost (£)</th>
<th>Incremental effect - Life-year gained (LYG) (95%CI)</th>
<th>UK results – Cost/LYG (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternative</td>
<td>£68±£1035/year*</td>
<td>0.078 (0.003-0.15)</td>
<td>£2267 ** (dominant*; £942,752)</td>
</tr>
<tr>
<td>Added</td>
<td>£14±£283/year*</td>
<td>0.061 (-0.002-0.12)</td>
<td>Dominant*</td>
</tr>
</tbody>
</table>

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

**Using the utility score proposed by Mant 200934 of 0.65 for patients with heart failure, we estimated the threshold in cost per LYG related to £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, considering that seven GP visits and biochemistry tests is more appropriately reflecting 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 5.20). In addition, the length of stay per hospitalised patient was longer (non-significant) for the treatment arm77. These estimates indicate that the cost-effectiveness ratio for CHARM-Preserved is likely to indicate that adding an ARB is not cost-effective. However, modelling CHARM-Preserved using heart failure-related hospitalisations might lead to a cost-effective result.

Table 5.20 Outcomes from CHARM-Preserved77, 74, 88

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Hospital admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause</td>
<td>Heart failure-related</td>
</tr>
<tr>
<td>RR = 0.97 (95%CI 0.02, 1.14)</td>
<td>RR = 0.99, ns</td>
</tr>
</tbody>
</table>

Additional limitations of the McMurray et al. (2006) study77 were that a short time horizon was used, and quality of life was not considered.

5.2.5.6 Summary of evidence statements

There were 5 studies that compared treatment with ARB to placebo in the treatment of heart failure caused by left ventricular systolic dysfunction88-92. In those trials, the use of angiotensin converting enzyme inhibitors (ACEI) was not allowed. The ARB in three of the trials was candesartan88,91,92. Valsartan was the ARB used in the remaining two trials (VAL-HEFT-post-hoc analysis JACC 2002, and Mazayev et
The ARB’s led to a statistically significant reduction in the rate of heart failure hospitalisation and in the composite outcome of mortality and heart failure hospitalisation. Compared to placebo, ARB’s resulted in significant improvement in the quality of life as measured by the Minnesota Living with Heart Failure Questionnaire, and in a significant improvement in the New York Heart Association functional class. Treatment with these agents resulted in statistically significant increase in the incidence of hyperkalaemia, raised serum creatinine and hypotension. The latter was defined as either sustained systolic blood pressure of < 80 mmHg, or as symptomatic hypotension, that may result in discontinuation of the ARB. Meta-analysis of the data from ARCH-J, CHARM-Alternative, Mazayev et al and STRETCH resulted in no significant impact on all cause mortality.

In patients with heart failure and preserved left ventricular ejection fraction, there were two randomised controlled trials. These were the CHARM-Preserved trial using candesartan and the I-PRESERVE trial using irbesartan. In these two trials, ACEI were used in 20% and 25% of the patients, respectively. The patients recruited were heart failure patients with an NYHA class II-IV, with a left ventricular ejection fraction >40-45%. In this setting, treatment with the ARB resulted in statistically significant rise in the serum potassium and serum creatinine levels. They had no significant impact on mortality, hospitalisation or the combined score of mortality and hospitalisation.

From the health economic review, there was one study, based on the CHARM programme and it took a UK perspective. This study developed cost-effectiveness assessments based on CHARM-Added and CHARM-Alternative. No cost-effectiveness assessment was developed from the CHARM-Preserved trial. Results show that ARBs are cost-effective treatments based on CHARM-Added and CHARM-Alternative. Looking at outcomes from CHARM-Preserved, the likelihood of cost-effectiveness is not clear. Results are not likely to be cost-effective considering all-cause hospitalisation and length of stay data. However, it may be cost-effective modelling CHARM-Preserved using heart-failure related hospitalisations.

5.2.5.7 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). There was also a significant reduction of the composite end-point of cardiovascular mortality and heart failure hospitalisation (CHARM-alternative trial).

Only one trial (Val-HeFT post-hoc analysis) showed an improved quality of life score, and another trial (STRETCH) showed 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 felt that direct comparison between ACEI and ARB in heart failure with LVSD had not been considered. The GDG asked for two trials (ELITE II and OPTIMAAL) to be looked at. These trials studied the impact of using ARB in patients with heart failure due to left ventricular systolic dysfunction in comparison to ACEI. ELITE-II compared Losartan to Captopril in patients > 60 years with LVEF ≤ 40%. It found similar morbidity and mortality on either agent. OPTIMAAL compared Losartan to Captopril in patients with significant left ventricular systolic dysfunction following Q wave myocardial infarction. There was a trend in OPTIMAAL for Captopril superiority in reducing mortality, but no difference between the two agents in
Draft for consultation

Reducing morbidity. Taken together, ARB was not superior to ACEI in this context. All the ACEI trials except CONSENSUS-II (which was in a unique early AMI phase using intravenous ACEI), have consistently shown reduction of morbidity and mortality of heart failure due to left ventricular systolic dysfunction. Those trials were similar to the newer trials of ARB against placebo. Unlike ACEI, ARB did not reduce mortality, therefore ARB are not equivalent agents to ACEI in the treatment of heart failure caused by LVSD.

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 of ACEI that justifies switching treatment to ARB. Angio-oedema reflects true intolerance to ACEI, but is shared with ARB. The occurrence of renal impairment, hypotension or hyperkalaemia while on ACEI should call for reduction (when significant) of the dose of ACEI rather than switching to ARB (see Appendix J on practical recommendations). The GDG advised that every attempt is made not to stop ACEI in the presence of side-effects, and that education is provided for patient and carers.

In the presence of true intolerance of ACEI (other than angio-oedema, hypotension, hyperkalaemia and renal impairment: which are problems shared between ACEI and ARB), the ACEI could be discontinued and ARB could be commenced at a low dose to be up-titrated.

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

Two large randomised controlled trials were reviewed: 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).

**Quality of evidence**

In trials looking at the impact of ARB therapy of 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, 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 score, 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 the 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 of 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. Finally, the lack of significant increase in the incidence of hypotension was of low quality evidence.

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

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

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. However, treatment with these agents requires frequent monitoring of renal function and serum electrolytes 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. The breadth of the confidence interval reflects the uncertainty around the mortality reduction. In addition, the GDG was of the opinion that the resource use of the Candesartan arm in this analysis may have underestimated the number of visits to the general practitioner and the number of blood tests needed during the up-titration. However, additional GP visits for candesartan-related complications were included in the sensitivity analysis, and this did not affect the conclusion. Nevertheless, the GDG accepted conclusions of the cost-effectiveness analysis despite its limitations.

For the cost-effectiveness of the use 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.

### 5.2.5.8 Recommendations

- **R41** Do not substitute angiotensin II receptor antagonists (ARBs) for ACE inhibitors in patients with heart failure due to left ventricular systolic dysfunction unless there are intolerable side effects with ACE inhibitors. [new 2010]

- **R43** Monitor renal function and serum electrolytes for signs of renal impairment or hyperkalaemia in patients with heart failure who are taking an ARB. [new 2010]

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

**Clinical Question:**

ARB2: 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) ARB + ACEI + BB vs placebo + ACEI + BB

Four studies were identified comparing ARBs + ACEI + BB vs. placebo + ACEI + BB in heart failure with left ventricular systolic dysfunction (LVSD) 74,75,98, 76

NOTE: The VALIANT trial (Pfeffer et al)76 was designed differently to the other included trials. 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 BB.

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%
- VALIANT (Pfeffer et al): BB 70%

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.)
- Valsartan up to 160 mg/day 160mg bd vs Valsartan up to 80bd plus captopril up to 150 mg/day vs captopril up to 150 mg/day (VALIANT - Pfeffer et al.)

Outcomes reported:

- All cause mortality
- HF hospitalization
- Composite score (CV death and HF hospitalization)
- Hypotension
- Hyperkalaemia
- Increased creatinine (number of patients)
- Quality of life- Minnesota Living With Heart Failure Questionnaire (MLWHFQ)
- Improved NYHA class
- Worsened NYHA class
- Unchanged NYHA class

b) ARB + ACEI vs placebo + ACEI

Two studies were identified comparing ARB plus ACEI with placebo plus ACEI 99,100.

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 (160 bd) (Val-HeFT subgroup analysis - Krum et al)
- Losartan up to 50 mg/day (Houghton et al)

Comparison:

- Placebo

Outcomes reported:
Draft for consultation

1. Mortality
2. HF hospitalization
3. QoL
4. Mean increase in serum creatinine (µmol/L)
5.2.6.3 Clinical evidence statements

ARB + ACEI + BB vs placebo + ACEI + BB

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

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

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

- Worsened NYHA class [low quality]

Compared with placebo + ACEI + BB, ARB + ACEI + BB had no impact 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]

The evidence profile below summarises the quality of the evidence and outcome data from 4 studies comparing ARBs + ACEI + BB vs. placebo + ACEI + BB in heart failure with left ventricular systolic dysfunction (LVSD).
Evidence Profile: ARBs + ACEI + BB vs. placebo + ACEI + BB in heart failure with left ventricular systolic dysfunction (LVSD)

**Question:** Should ARB + ACEI + BB vs Placebo + ACEI + BB be used for CHF?

**Settings:** CHF

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>ARB + ACEI + BB</td>
<td>Placebo + ACEI + BB</td>
</tr>
<tr>
<td>All cause mortality (follow-up 23 to 41 months)</td>
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<tr>
<td>3</td>
<td>randomised trial</td>
<td>serious'</td>
</tr>
<tr>
<td></td>
<td></td>
<td>no serious inconsistency</td>
</tr>
<tr>
<td>HF Hospitalisation (no. of patients) (follow-up 23-41 months)</td>
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<tr>
<td>3</td>
<td>randomised trial</td>
<td>serious'</td>
</tr>
<tr>
<td>Combined outcome: CV death or hospital admission for CHF (follow-up median 41 months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>randomised trial</td>
<td>no serious limitations</td>
</tr>
<tr>
<td>Hypotension (follow-up 2-41 months)</td>
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</tr>
<tr>
<td>4</td>
<td>randomised trial</td>
<td>serious'</td>
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<tr>
<td>Hyperkalaemia (follow-up 12 wks to 24.7 months)</td>
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</tr>
<tr>
<td>2</td>
<td>randomised trial</td>
<td>no serious limitations</td>
</tr>
<tr>
<td>Increased serum creatinine (number of patients) (follow-up median 41 months)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>randomised trial</td>
<td>no serious limitations</td>
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</tr>
<tr>
<td><strong>Improved NYHA class (follow-up 6wks and 23 months)</strong></td>
<td>2 Cocco 2002 Val-Heft</td>
<td>serious²</td>
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<td></td>
<td></td>
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<tr>
<td><strong>Unchanged NYHA class (follow-up 8 weeks)</strong></td>
<td>1 Cocco 2002</td>
<td>serious⁵</td>
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<tr>
<td><strong>Worsened NYHA class (follow-up 6 wks and 23 months)</strong></td>
<td>2 Cocco 2002 Val-Heft</td>
<td>serious⁵</td>
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</tbody>
</table>

¹ All studies double blind, ITT analysis and <20% dropouts, 2/3 unclear allocation concealment, 1/3 allocation concealment; 1 study unclear if ITT analysis performed

² All trials double blind and powered; 2/4 allocation concealment, all <20% drop-outs, 2/4 ITT analysis

³ <300 events

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)
ARB + ACEI vs placebo + ACEI

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 had no difference on:
- Mortality [moderate quality]
- Hyperkalaemia [high quality]
- Increased serum creatinine (µmol/L) [low quality]

The evidence profile below summarises the quality of the evidence and outcome data from 2 studies. 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)

**Date:** 2009-05-18  
**Question:** Should ARB + ACEI (no BB) vs Placebo + ACEI (no BB) be used for CHF?  
**Settings:** CHF  

<table>
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<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
<th>Quality</th>
<th>Importance</th>
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<tr>
<td>Mortality (follow-up mean 23 months)</td>
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<tr>
<td>1 (Val-HeFT subgroup – Krum et al)</td>
<td>randomised trial</td>
<td>serious¹</td>
<td>no serious inconsistency</td>
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<tr>
<td>First hospitalisation (follow-up mean 23 months)</td>
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<tr>
<td>1 (Val-HeFT subgroup – Krum et al)</td>
<td>randomised trial</td>
<td>serious¹</td>
<td>no serious inconsistency</td>
</tr>
<tr>
<td>Hyperkalaemia (follow-up 41 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Houghton et al)</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
</tr>
<tr>
<td>Increased serum creatinine (umol/L) (follow-up 12 weeks; range of scores: -; Better indicated by less)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Houghton et al)</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
</tr>
<tr>
<td>Quality of Life (MLHQ) (follow-up mean 23 months; measured with: umol/L; range of scores: -; Better indicated by less)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Val-HeFT subgroup – Krum et al)</td>
<td>randomised trial</td>
<td>serious¹</td>
<td>no serious inconsistency</td>
</tr>
</tbody>
</table>

1 Subgroup analysis of the Val-HeFT RCT  
2 No explanation was provided  
3 No details of SD, SE or effect size CIs given
5.2.6.4 Health Economic Methodological introduction

McMurray et al. (2006)\textsuperscript{77} developed an economic analysis based on the CHARM programme. This analysis was presented in Section 5.2.1.5. In addition, a health economic assessment comparing adding an ARB or adding an aldosterone antagonist to optimal medical treatment, based on EPHESUS and VALIANT, was presented and discussed in Section 5.2.3.5.

5.2.6.5 Summary of evidence statements

Four studies that recruited patients with heart failure and left ventricular systolic dysfunction combined ACEI and beta-blockers with ARB. The CHARM-Added study\textsuperscript{74} where all the patients were on ACEI and 55% of the patients were on beta-blockers; the Val-HeFT trial\textsuperscript{75} where 92% of the patients were on ACEI and 35% were on beta-blockers; Cocco \textit{et al} where all the patients were on both the ACEI and the beta-blockers\textsuperscript{98}, and the VALIANT trial\textsuperscript{76}. The latter had 77% of the patients on beta-blockers. The patients in VALIANT trial were randomised into ARB and ACEI vs ACEI vs ARB. The latter design and the fact the heart failure in the VALIANT trial was due to a recent myocardial infarction, differentiate this from the other three trials. Candesartan was the ARB used in the first trial, and Valsartan was the ARB used in the remaining three trials.

The addition of ARB to the combined ACEI and beta-blockers significantly reduced heart failure hospitalisation, and the combined end-point of heart failure hospitalisation and mortality. There was significantly less chance of worsening NYHA functional class with the addition of ARB. The incidence of hyperkalaemia, hypotension and raised serum creatinine were significantly increased. The addition of ARB to the combined ACEI and beta-blockers in patients with heart failure and left ventricular systolic dysfunction did not affect all cause mortality.

Two studies were reviewed on the addition of ARB to ACEI in the absence of beta-blockade for patients with heart failure and left ventricular systolic dysfunction. A sub-study of the Val-HeFT trial\textsuperscript{99} using Valsartan, and Houghton \textit{et al}\textsuperscript{100} using Losartan. Compared to placebo, the addition of ARB to ACEI in these two trials resulted in significant reduction of the rate of first hospitalisation and improved the quality of life. It did not, however, affect the mortality rate, the frequency of hyperkalaemia and raised serum creatinine.

From the health economic review, a cost-effectiveness analysis assessed the use of candesartan in addition to ACEI and beta-blockers in patients with heart failure due to LVSD (based on CHARM-Added)\textsuperscript{77}, and concluded that this is cost-effective in a UK context.

5.2.6.6 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 β blockers and combining ARB with ACEI.

For the first part, there were four appraised studies. Three of the studies were of similar design adding the candesartan \textsuperscript{74}(CHARM-Added study), or Valsartan \textsuperscript{75,98}(Val-HeFT, Cocco \textit{et al}) to treatment with an ACEI that was given to 92% of the patients in Cocco \textit{et al} or 100% of the patients in the other two studies. In addition, β blockers were given to 100% of the patients in the Cocco \textit{et al} study, 55% of the patients in CHARM-Added or 35% of the patients in the Val-HeFT study. The fourth study \textsuperscript{76}(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 and Valsartan. In the VALIANT study 77% of the patients were on β blockers.
The addition of ARB to the combined ACEI and BB in patients with heart failure and LVSD did not affect all cause mortality. It did, however, 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. However, 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 about the safety of combining ARB with β blockers in patients with heart failure. This had led to the safety warning in the existing NICE guidelines on heart failure from 2003. However, given the results of the other studies that used both Candesartan (CHARM-Added) and Valsartan (VALIANT), the GDG concluded this combination could be used.

The second part of the question was combining ARB with ACEI. Two studies were appraised: Krum et al (sub-study of Val-HeFT trial) and Houghton et al. These used Valsartan and Losartan, respectively.

Compared to placebo, the addition of Valsartan to ACEI in the Krum et al trial 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, however, of adding Losartan in the Houghton et al study 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 β blockers results in significantly reduced combined score of cardiovascular mortality and heart failure hospitalisation; and for the increased risk of hyperkalaemia.

The evidence is of moderate quality 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 supporting the remainder of the statements was of low quality.

The evidence behind the statements derived from the Houghton et al study of the addition of ARB to ACEI was of moderate quality. Whereas the main statements derived from the results of the Krum study, were based on evidence of low quality. 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 therapeutics for heart failure with LVSD does not reduce all cause mortality. It reduces morbidity as evident from the reduction in 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. In addition, the GDG expressed concern that some patients with heart failure and LVSD could be prescribed ACEI, β blockers, ARB and an aldosterone antagonist. Although some patients in the randomised controlled trials were on quadruple therapy, these were the minority. The GDG does not believe there is sufficient evidence to support the widespread use of this quadruple therapy.

**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.
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.

5.2.6.7 Recommendation

R42 Consider adding an ARB to an ACE inhibitor and a beta-blocker in patients with heart
failure due to left ventricular systolic dysfunction who remain symptomatic and are
intolerant of aldosterone antagonists. This decision should be made by a specialist.

[New 2010]

Drugs not within scope of partial update

There were agents that were outside the scope of the partial update. These included:
Aspirin, HMG-CoA reductase inhibitors (statins). For more information refer to Appendix M,
the 2003 Guideline:
• 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
• Statins for the prevention of cardiovascular events (NICE Technology Appraisal

5.2.7 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/GG76

R28 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, R44]

Angiotensin converting enzyme inhibitors (ACE)

R29 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]

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 and electrolytes after initiation of an ACE inhibitor
and at each dose increment. [2010]
### Beta blockers

R32 Offer beta-blockers licensed for heart failure to all patients with heart failure due to left ventricular systolic dysfunction, including those with:
- peripheral vascular disease
- erectile dysfunction
- diabetes mellitus
- interstitial pulmonary disease and
- chronic obstructive pulmonary disease (COPD) without reversibility.

There is no upper age limit. [new 2010]

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

R35 Offer an aldosterone antagonist to patients with heart failure due to left ventricular systolic dysfunction if moderate to severe symptoms persist despite optimal therapy with an ACE inhibitor and beta-blocker. [new 2010]

R36 Seek specialist advice before offering aldosterone antagonists to patients with heart failure due to left systolic dysfunction. [new 2010]

R37 In patients with heart failure due to left ventricular systolic dysfunction who are taking aldosterone antagonists, monitor potassium and creatinine levels for signs of hyperkalaemia and/or deteriorating renal function. Halve the dose of aldosterone antagonist and recheck the potassium and creatinine levels if the patient develops hyperkalaemia or renal impairment. [new 2010]

R38 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]).

R39 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 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]).

### Isosorbide/hydralazine combination

R40 Offer isosorbide in combination with hydralazine to black patients who remain symptomatic with ACE inhibitors and beta-blockers. [new 2010]

### Angiotensin II receptor antagonists

R41 Do not substitute angiotensin II receptor antagonists (ARBs) for ACE inhibitors in patients with heart failure due to left ventricular systolic dysfunction unless there are intolerable side effects with ACE inhibitors. [new 2010]

---

8 Black patients are those of African or Caribbean descent, and not mixed-race, Asian or Chinese patients.
R42 Consider adding an ARB to an ACE inhibitor and a beta-blocker in patients with heart failure due to left ventricular systolic dysfunction who remain symptomatic and are intolerant of aldosterone antagonists. This decision should be made by a specialist. [new 2010]

R43 Monitor renal function and serum electrolytes for signs of renal impairment or hyperkalaemia in patients with heart failure who are taking an ARB. [new 2010]

Diuretics

R44 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, R21]

R45 The diagnosis and treatment of diastolic dysfunction 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, R51]

Digoxin

R46 Digoxin is recommended for:

- worsening or severe heart failure due to left ventricular systolic dysfunction despite ACE inhibitor, beta-blocker and diuretic therapy
- patients with atrial fibrillation and any degree of heart failure. [2003, R31]

Calcium channel blockers

R47 Amlodipine should be considered for the treatment of co-morbid hypertension and/or angina in patients with heart failure, but verapamil, diltiazem or short-acting dihydropyridine agents should be avoided. [2003, R43]

Amiodarone

R48 The decision to prescribe amiodarone should be made in consultation with a specialist. [2003, R34]

R49 The need to continue the amiodarone prescription should be reviewed regularly. [2003, R35]

R50 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, R36]

Anticoagulants

R51 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, R38]

Aspirin

R52 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, R39]

Statins

R53 Patients with the combination of heart failure and known atherosclerotic vascular disease should receive statins only in accordance with current indications. Specific trials in this area are ongoing. [2003, R40]
Inotropic agents

R54 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, R42]

Patients with valve disease

R55 Patients with heart failure due to valve disease should be referred for specialist assessment and advice regarding follow-up. [2003, R49]
R56 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, R50]

Patients with valve disease (but no heart failure) should also be assessed by a specialist, as the onset of heart failure increases the risk of surgery and reduces the likelihood of full recovery.

General

Age

R57 The management of heart failure should be determined by clinical criteria, irrespective of the age of the patient. [2003, R54]
R58 Tolerance of drugs may be lower and side effects require closer and more frequent monitoring in older patients. [2003, R55]

Gender

R59 The principles of pharmacological management of heart failure should be the same for men and women. [2003, R56]
R60 The potential teratogenic effects of drugs should be considered. [2003, R57]
R61 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, R58]

Ethnicity

R62 ACE inhibitors are less effective in black patients than other patients. Otherwise the principles of pharmacological management should be the same for all patients with heart failure, irrespective of ethnicity. [new 2010]

Comorbidities

R63 Comorbidities should be managed according to relevant NICE guidelines. This is particularly important in heart failure with preserved ejection fraction. [new 2010]

5.2.8 Recommendations for pharmacological treatment of heart failure to be deleted

R22 All patients with heart failure due to left ventricular systolic dysfunction should be considered for treatment with an ACE inhibitor. [2003, R22]
R23 ACE inhibitor therapy should be instituted in patients with heart failure due to left ventricular

9 Black patients are those of African or Caribbean descent, and not mixed-race, Asian or Chinese patients.
systolic dysfunction before beta-blockade is introduced. [2003, R23]

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). [2003, R26]

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). [2003, R32]

The triple combination of ACE inhibitor, beta-blocker and angiotensin-II receptor antagonist should be avoided, pending the results of further trials. [2003, R33]

Anticoagulation is indicated for patients with the combination of heart failure and atrial fibrillation. [2003, R37]

An isosorbide/hydralazine combination may be used in patients with heart failure who are intolerant of ACE inhibitors or angiotensin-II receptor antagonists. [2003, R41]

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). [2003, R52]

5.3 Other causes of heart failure

Valve disease, atrial fibrillation and other causes of heart failure were not reviewed in the 2010 partial update

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.

5.4 Invasive procedures

5.4.1 Introduction

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. For more information refer to:


NICE will consult on review plans for this guidance in 2010. Please refer to the NICE website for updates on the review status of this appraisal.
5.4.3 **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:


NICE will consult on review plans for this guidance in 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:

- Coronary revascularisation (7.4.1)
- Cardiac transplantation (7.4.2)
- Ventricular assist devices (7.4.3)
- Mitral valve surgery and cardiomyoplasty (7.4.6)

5.4.4 **Recommendations for invasive procedures**

**Coronary revascularisation**

R64 Coronary revascularisation should not be routinely considered in patients with heart failure due to systolic left ventricular impairment, unless they have refractory angina. [2003, R45]

**Cardiac transplantation**

R65 Specialist referral for transplantation should be considered in patients with severe refractory symptoms or refractory cardiogenic shock. [2003, R46]

**Implantable cardioverter-defibrillators (ICDs)**

Refer to the following technology appraisals and their updates:

- Implantable cardioverter defibrillators (ICDs) for the treatment of arrhythmias (review of TA11) (NICE Technology appraisal 95 [2006])
- Cardiac resynchronisation therapy for the treatment of heart failure (NICE Technology appraisal 120 [2007])

5.4.5 **Recommendations for invasive procedures to be deleted**

**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]

**Implantable cardioverter-defibrillators (ICDs)**

The use of implantable cardioverter defibrillators (ICDs) should be routinely considered for patients in the following categories:

“Secondary prevention” is 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:
  1. non sustained VT on Holter (24 hour ECG) monitoring;
  2. inducible VT on electrophysiological testing;
  3. 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]
5.5 Treatment algorithm

For practical recommendations on the use of ACEI, beta blockers and Aldosterone antagonists refer to Appendix J.
6 Rehabilitation in chronic heart failure

6.1 Clinical introduction

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

Heart failure adversely affects the patient physically and psychologically. Fatigue and dyspnoea are major obstacles to patient’s ability to exercise. In addition the depression caused by heart failure and the patient’s anxieties about potential complications all result in a complex situation characterised by both an inability to exercise and fear from performing exercise. Other interventions to deliver education and improve the patient’s exercise tolerance and life-style are the aims of rehabilitation. Since the publication of the 2003 guidance on heart failure, several studies into the impact of rehabilitation programmes on heart failure patients were 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 findings 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

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 hospitalization, quality of life (Minnesota Living with Heart Failure Questionnaire), 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 assessment 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.\textsuperscript{101-112} Table 6.1 below summarises the population, intervention and outcomes for each of the studies.

Specialist nurse care plus exercise based cardiac rehabilitation with specialist nurse care only

One study was identified comparing care from a specialist nurse plus exercise based cardiac rehabilitation with specialist nurse care only.\textsuperscript{113}

Data was reported on the following outcomes:

- All cause hospitalisation (12 month follow-up)
- Hospitalisation (cardiac) (12 month follow-up)
- ISWT/m (6 month follow-up)
- MLHF (12 month follow-up)
SUMMARY OF INCLUDED STUDIES exercise based cardiac rehab vs standard care

Table 6.1: Summary of studies

<table>
<thead>
<tr>
<th>STUDY</th>
<th>POPULATION</th>
<th>INTERVENTION</th>
<th>COMPARISON</th>
<th>OUTCOMES</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’CONNOR 2009</td>
<td>LVEF ≤35%</td>
<td>Structured supervised group exercise phase: 3 sessions/week of walking, treadmill or stationary cycling</td>
<td>usual care: no formal exercise programme, given educational leaflet which included information about exercise.</td>
<td>all cause death - CV death - all cause hospitalisation - median 6MWT (12 months follow-up) - change in NYHA class - Median 30 months</td>
</tr>
<tr>
<td></td>
<td>(HF-ACTION trial)</td>
<td>- Home exercise phase after 36 sessions (3 months): cycling or treadmill 5 times/week</td>
<td>- telephone calls to give comparable level of attention as per the exercise group</td>
<td>- 8% of patients were doing their own continuous exercise</td>
</tr>
<tr>
<td></td>
<td>- median age 59 years - N=2331</td>
<td>- telephone follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COVERA 2004</td>
<td>LVEF ≤40%</td>
<td>Home walking exercise 1/day for 5 days/week</td>
<td>control group: maintained normal exercise and measured with pedometer</td>
<td>all cause death - all cause hospitalisation - mean 6MWT (12 week follow up)</td>
</tr>
<tr>
<td></td>
<td>(mean age 61.3-63.8 years - N=79)</td>
<td>- pedometer use - nurse home visits and reviews</td>
<td>- nurse home visits and reviews</td>
<td></td>
</tr>
<tr>
<td>NILSSON 2008</td>
<td>LVEF &lt;40% or ≥40% with clinical symptoms of HF</td>
<td>standard care plus group based high intensity 16 week aerobic interval training</td>
<td>- Standard care: outpatient monitoring by nurse specialist with cardiologist supervision. Follow up in primary care.</td>
<td>mean Qol score - mean 6MWT (4 month follow up)</td>
</tr>
<tr>
<td></td>
<td>(NYHA class II-IIIB)</td>
<td>(2days/week) each 50 mins; followed by 15-30 mins counselling by physical therapist</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- mean age 69-72 - N=80</td>
<td>- 4 individual counselling sessions with CHF nurse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NILSSON 2008 (follow up)</td>
<td>AS ABOVE</td>
<td>AS ABOVE</td>
<td>AS ABOVE</td>
<td>mean Qol score - mean 6MWT (12 month follow up)</td>
</tr>
<tr>
<td>AUSTIN 2005</td>
<td>LVEF ≤40%</td>
<td>standard care plus 8 week cardiac rehabilitation programme by a nurse specialist 2/week for 2.5 hrs</td>
<td>- standard care: 8 weekly outpatient monitoring of clinical status by nurse specialist. - advice and treatment self monitoring information</td>
<td>all cause death - all cause hospitalization - mean Qol score - mean 6MWT (NYHA class follow up: 24 weeks)</td>
</tr>
<tr>
<td></td>
<td>(NYHA class II-III)</td>
<td>- followed by 16 weeks of community based weekly 1hr sessions of aerobic endurance training</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- mean age 72 - N=200</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STUDY</td>
<td>POPULATION</td>
<td>INTERVENTION</td>
<td>COMPARISON</td>
<td>OUTCOMES</td>
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<td>---------------</td>
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<td>-------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>AUSTIN 2008</td>
<td>AS ABOVE</td>
<td>5-year follow-up of previous 24-week trial (see above)</td>
<td>5-year follow-up of previous 24-week trial (see above)</td>
<td>- all cause death</td>
</tr>
<tr>
<td></td>
<td>(follow up)</td>
<td></td>
<td></td>
<td>- all cause hospitalization</td>
</tr>
<tr>
<td></td>
<td>N=112</td>
<td></td>
<td></td>
<td>- mean Qol score</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>- mean 6MWT</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(follow up: 5 years)</td>
</tr>
<tr>
<td>CIDER 2003</td>
<td>LVEF &lt;45%</td>
<td>Hydrotherapy: 45 min sessions in pool, 3/week over 8 weeks.</td>
<td>control group: instructed to live life as normal and not to increase physical activity during the 8 weeks</td>
<td>- mean Qol score</td>
</tr>
<tr>
<td></td>
<td>NYHA class II-III</td>
<td></td>
<td></td>
<td>- mean 6MWT</td>
</tr>
<tr>
<td></td>
<td>mean age 70-75 years</td>
<td></td>
<td></td>
<td>(follow up: 8 weeks)</td>
</tr>
<tr>
<td></td>
<td>N=25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COLLINS 2004</td>
<td>LVEF &lt;40%</td>
<td>Rehabilitation programme: supervised moderate aerobic exercise programme</td>
<td>control group: seen bi-weekly by nurse, and asked not to change their level of exercise.</td>
<td>- mean change in Qol score</td>
</tr>
<tr>
<td></td>
<td>NYHA class II-III</td>
<td>- Included polestriding and treadmill walking: 3/week with duration increasing to 45-50 mins by week 12.</td>
<td></td>
<td>(follow up: 12 weeks)</td>
</tr>
<tr>
<td></td>
<td>mean age 62-66 years</td>
<td>- Exercise physiotherapist or specialist nurse supervised sessions.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N=31</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SARULLO 2006</td>
<td>LVEF &lt;40%</td>
<td>Supervised physical training programme: bicycle ergometer 30 mins 3/week</td>
<td>control group: no change to physical activity</td>
<td>- mean Qol score</td>
</tr>
<tr>
<td></td>
<td>NYHA class II-III</td>
<td></td>
<td></td>
<td>- NYHA class</td>
</tr>
<tr>
<td></td>
<td>mean age 53 years</td>
<td></td>
<td></td>
<td>(follow up: 3 months)</td>
</tr>
<tr>
<td>STUDY</td>
<td>POPULATION</td>
<td>INTERVENTION</td>
<td>COMPARISON</td>
<td>OUTCOMES</td>
</tr>
<tr>
<td>-----------</td>
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<td>-------------------------------------------------------------------------------</td>
<td>------------------------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>DRACUP 2007</td>
<td>- LVEF ≤ 40%</td>
<td>- Low level aerobic and resistive/strength training programme.</td>
<td>- control group: no change to physical activity</td>
<td>- all cause death</td>
</tr>
<tr>
<td></td>
<td>- NYHA class II-IV</td>
<td>- walking 4/week, increasing to 45 mins at 12 weeks</td>
<td></td>
<td>- all cause hospitalization</td>
</tr>
<tr>
<td></td>
<td>- mean age 53-54 years</td>
<td>- Resistance programme 3/week on days they did not walk</td>
<td></td>
<td>(follow up: 1 year)</td>
</tr>
<tr>
<td></td>
<td>- N=173</td>
<td></td>
<td></td>
<td>- mean Qol score</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- mean 6MWT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(follow up: 6 months)</td>
</tr>
<tr>
<td>WITHAM 2005</td>
<td>- LVEF: not reported (just those with LVSD)</td>
<td>- 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</td>
<td>- control group: usual care, no restriction of their exercise activities</td>
<td>- mean 6MWT (follow up: 6 months)</td>
</tr>
<tr>
<td>BELARDINELLI 1999 (from OLD GUIDELINE)</td>
<td>- LVEF ≤ 40%</td>
<td>- 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</td>
<td>- Control group: no exercise.</td>
<td>- CV death - HF hospitalization - Mean Qol score (follow-up: 14 months)</td>
</tr>
</tbody>
</table>
### 6.3 Clinical evidence statements

#### a) Exercise based cardiac rehabilitation vs. standard care.

Compared with standard care, exercise rehabilitation significantly reduced:

- HF hospitalization (up to 4.4 years) [moderate quality]

Compared with standard care, exercise rehabilitation significantly improved:

- Quality of Life (QoL) (up to 5 year follow-up) [moderate quality]*
- Mean 6MWD (up to 6 months) [moderate quality]* and 12 months [high quality]

There was no significant difference between exercise rehabilitation and standard care for:

- All cause mortality (up to 30 months) and at 5 year follow-up [moderate quality]
- All cause hospitalisation (up to 30 months) [very low quality]*
- CV death (up to 4.4 years) [very low quality]*
- Quality of life (up to 6 months) [high quality]
- Mean change in QoL (up to 3 months) [low quality]
- Mean 6MWT (at 5 year follow-up) [moderate quality]

#### Change in NYHA class

**O'Connor 2009** (follow-up median 30 months):

- Improvement by 1 class: standard group 25%; experimental group 30%

**Austin 2005** (follow up: 24 weeks):

- Deterioration (by 1 class): standard group: 8/94; experimental group: 3/85
- No change: standard group: 76/94; experimental group: 44/85
- Improvement (by 1 class): standard group: 9/94; experimental group: 35/85
- Improvement (by 2 classes): standard group: 1/94; experimental group: 3/85

**Austin 2008** (follow up: 5 years):

- Deterioration by 1 class: standard group: 31%; experimental group: 33%
- No change: standard group: 51%; experimental group: 37%
- Improvement by 1 class: standard group: 9%; experimental group: 25%
Sarullo 2006 (3 months):

- Exercise: decreased from 2.6 (0.1) to 1.06 (0.1); Control: decreased from 2.5 (0.1) to 2.4 (0.2); MD between groups at 3 months: -1.34, p=0.0001

*NOTE:* for these outcome measures, there was significant heterogeneity between the trials when pooled into meta-analyses. Possible sources of heterogeneity are likely to be due to the huge variation between interventions between the trials (for example, hospital-based rehabilitation, home-based rehabilitation, different exercise modalities) and also 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) \(^{101-112}\) 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

**Settings:**
- **Date:** 2009-06-15
- **Authors:**

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>Exercise based cardiac rehabilitation</td>
</tr>
<tr>
<td>All cause mortality (follow-up 3-30 months)</td>
<td></td>
</tr>
<tr>
<td>4 AUSTIN 2005 CORVERA 2004 DRACUP 2007 O'CONNOR 2009</td>
<td>randomised trial</td>
</tr>
<tr>
<td>All cause mortality (follow-up 5 years)</td>
<td></td>
</tr>
<tr>
<td>1 AUSTIN 2005</td>
<td>randomised trial</td>
</tr>
<tr>
<td>CV mortality up (follow-up mean 30 months-4.4 years)</td>
<td></td>
</tr>
<tr>
<td>2 BELARDINELLI 1999 O'CONNOR 2009</td>
<td>randomised trial</td>
</tr>
<tr>
<td>All cause hospitalization (follow-up 3-30 months)</td>
<td></td>
</tr>
<tr>
<td>4 AUSTIN 2005 CORVERA 2004 DRACUP 2007 O'CONNOR 2009</td>
<td>randomised trial</td>
</tr>
</tbody>
</table>

**Quality assessment**
- **No of studies:**
  - 4
- **Design:**
  - randomised trial
- **Limitations:**
  - serious
- **Inconsistency:**
  - no serious
- **Indirectness:**
  - no serious
- **Imprecision:**
  - no serious
- **Other considerations:**
  - none
- **Quality:**
  - @@@@
- **Importance:**
  - MODERATE

**Summary of findings**
- **No of patients:**
  - 205/1373 (14.9%)
  - 211/1389 (15.2%)
  - 31/100 (31%)
  - 38/100 (38%)
  - 140/1209 (11.6%)
  - 163/1221 (13.3%)
  - 778/1373 (56.7%)
  - 834/1389 (60%)
- **Effect:**
  - RR 0.98 (0.82 to 1.17)
  - RR 0.82 (0.56 to 1.2)
  - RR 0.69 (0.34 to 1.4)
  - RR 0.77 (0.53 to 1.12)
- **Absolute:**
  - 3 fewer per 1000 (from 27 fewer to 26 more)
  - 68 fewer per 1000 (from 167 fewer to 76 more)
  - 41 fewer per 1000 (from 88 fewer to 53 more)
  - 138 fewer per 1000 (from 282 fewer to 72 more)
### HF hospitalization (follow-up mean 4.4 years)

| 2009 | 65% | 149 fewer per 1,000 |

| 1 BLEARDINELLI 1999 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious | none | 5/50 (10%) | 14/49 (28.6%) | RR 0.35 (0.14 to 0.9) | 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 | randomised trial | no serious limitations | no serious inconsistency | no serious indirectness | serious | none | 141 | 147 | - | MD -0.96 (-7.36 to 5.44) | ⚫⚫⚫⚫MODERATE |

| 3 AUSTIN 2008 | randomised trial | no serious limitations | serious | no serious indirectness | serious | none | 147 | 144 | - | MD -6.78 (-11.4 to -2.16) | ⚫⚫⚫⚫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 | no serious inconsistency | no serious indirectness | serious | 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 | randomised trial | no serious limitations | serious | no serious indirectness | no serious imprecision | none | 224 | 215 | - | MD 32.57 (14.42 to 50.71) | ⚫⚫⚫⚫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 | no serious inconsistency | no serious indirectness | serious | 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)
1. 1/3 unclear allocation concealment; 3/3 unclear blinding; 1/3 43% drop out but 5 yr follow up; 1/3 unclear ITT
2. serious heterogeneity I²=50%
3. unclear allocation concealment; unclear blinding; unclear ITT
4. 3/5 unclear allocation concealment; 4/5 unclear blinding
5. serious heterogeneity I²=64%
6. unclear blinding; 45% drop-out but 5 yr follow up
7. 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. 
**Evidence profile: specialist nurse care plus exercise based cardiac rehabilitation vs. specialist nurse care**

**Author(s):**

Jolly K, Taylor RS, Lip GY et al.

**Date:** 2009-07-16

**Question:** Should specialist plus exercise vs specialist be used for chronic heart failure?


<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>All cause hospitalisation (follow-up 12 months)</th>
<th>Hospitalisation (cardiac) (follow-up 12 months)</th>
<th>ISWT/m (follow-up 6 months; range of scores: -; Better indicated by less)</th>
<th>Minnesota Living with Heart Failure (follow-up 12 months; range of scores: -; Better indicated by less)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No of studies</strong></td>
<td><strong>Design</strong></td>
<td><strong>Limitations</strong></td>
<td><strong>Inconsistency</strong></td>
<td><strong>Indirectness</strong></td>
</tr>
<tr>
<td>1 Jolly 2009</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
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<td></td>
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<tr>
<td>1 Jolly 2009</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
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<tr>
<td>1 Jolly 2009</td>
<td>randomised trial</td>
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<td>no serious indirectness</td>
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</tbody>
</table>

* 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
* 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, no conclusion was made in light of the included cost-effectiveness analysis assessing a rehabilitation programme for patients with heart failure (Georgiou 2001). In addition, the 2003 Guideline 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 assessing exercise-based cardiac rehabilitation in patients with chronic heart failure, and this has been presented to the GDG.

Georgiou et al. (2001) 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 and it reported cost per life-year gained.

The Belardinelli 1999 study was conducted in a population of NYHA class II-III heart failure patients aged from 55 to 64 years. The Georgiou 2001 economic analysis 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. 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), which was adjusted with sex-specific rates, and increased by 23% to account for ACEi intake introduced after the National Survey (Pfeffer 1992; Garg 1995). 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Study quality*</th>
<th>Study applicability**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Georgiou 2001</td>
<td>Potentially serious limitations (a)</td>
<td>Partially applicable (b)</td>
</tr>
</tbody>
</table>

*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 are presented in Table 6.3. The study showed that an exercise training programme like the one used in the Belardinelli 1999 study 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 £239 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\textsuperscript{112} 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>
<thead>
<tr>
<th>Incremental cost (£)</th>
<th>Incremental effects</th>
<th>ICER</th>
<th>Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>£2015 Life expectancy (years): 1.82</td>
<td>Base-case analysis: £1,107 per LYG (Life-Year Gained)</td>
<td>Sensitivity analyses: \begin{itemize} \item (1) Patient-level cost removed: £239 per LYG; \item (2) Within-trial survival rates varied: £5,448 to £632 per LYG; \item (3) Post-trial survival rates varied: £1,060 to £1,159 per LYG; \item (4) Hospitalisation rates varied: £1,481 to £748 per LYG \end{itemize}</td>
<td></td>
</tr>
</tbody>
</table>

The Georgiou 2001 economic analysis\textsuperscript{114} was included in a 2006 review by Hagberg et al.\textsuperscript{118} of cost-effectiveness studies of healthcare-based interventions aimed at improving physical activity in different populations and perspectives. The Georgiou 2001 study\textsuperscript{114} was the only included study developed on patients with chronic heart failure. The Hagberg 2006 review\textsuperscript{118} suggested 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).

### 6.6 Summary of evidence statements

The role of exercise based rehabilitation in the management of patients with heart failure was considered through the appraisal of 12 randomised controlled trials (RCTs) that compared exercise based rehabilitation programmes versus standard therapy and one RCT comparing specialist nurse care plus exercise based rehabilitation versus specialist nurse care.\textsuperscript{101-112} In these RCTs the outcome measures that were compared were all cause mortality, all cause hospitalisation, quality of life (as measured by the Minnesota Living with Heart Failure Questionnaire), the improvement in exercise tolerance (using the six-minute walk test) and the improvement in the New York Heart Association Functional Class (NYHA).

The studies demonstrated that the exercise-based rehabilitation programme significantly reduced the rate of heart failure hospitalisation at 4.4 years of follow-up, and significantly improved the quality of life (at 5 years of follow up) and the exercise tolerance (at 6 and 12 months) of the patients randomised to receive rehabilitation. On the other hand, the rehabilitation programme did not affect the all cause mortality (at 30 months and at 5 years), cardiovascular mortality (at 4.4 years), all cause hospitalisation (at 30 months), the quality of life (at 6 months), the mean change in the quality of life (at 3 months) and the 6 minute walk test distance at 5 years. The work by Nilsson confirmed reduction of hospitalisation in heart failure patients who are elderly and women.

From the results of the meta-analysis, there was significant heterogeneity for the outcomes of cv mortality (follow-up mean 30 months to 4.4 years), all cause hospitalisation (follow up 3 to 30 months), mean QoL score (follow up 1 to 5 years), mean 6MWT (follow up 2 to 6 months). The heterogeneity was thought to be due to widely differing types of exercise-based rehabilitation programmes, including their frequency and duration, used in the studies.
The health economic review was based on one cost-effectiveness analysis of exercise based rehabilitation programme in heart failure based on the Belardinelli trial. This analysis, developed from a US perspective, showed that the exercise based rehabilitation programme in heart failure was cost-effective.

6.7 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 patients' representative about the availability of rehabilitation programmes and the patchy adherence to the previous NICE guidance on the subject. 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 important components of standard care. Therefore, the GDG elected to review the role of exercise-based rehabilitation programmes in the management of patients with heart failure. In addition, the objective physical assessment expected of the trials reviewed was based on the 6 minute walking test. This was preferred to the rigorous formal cardio-pulmonary exercise testing given the easy access to the former, and its applicability to much wider population of heart failure patients particularly the elderly. Besides, the 6 minute walking test is well validated.

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 exercise programmes used were inhomogeneous, but always included structured exercises that ranged from walking, to intensive gym based exercises 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. There was a welcome tendency to include older people which is most appropriate. All the trials included patients with symptomatic heart failure. The majority were patients with NYHA class II-III. However, three trials included patients with NYHA class IV. Although these were in small numbers and the GDG did not feel it was appropriate to recommend exercise rehabilitation in that subgroup because these are unstable. One trial included patients with heart failure with preserved left ventricular ejection fraction. However, the latter trial's total population, with both LVSD and HFPEF, was 80 patients only. Therefore, there was almost a lack of sufficient evidence to review on the role of rehabilitation in patients with HFPEF. Having carefully considered the subject of rehabilitation programmes based on exercise in patients with heart failure and preserved left ventricular ejection fraction, the GDG feels that such a programme should be offered to all heart failure patients who do not have a contra-indication for the enrolment in such a programme, irrespective of whether the heart failure is caused by LVSD or HFPEF.

The rationale for the GDG's decision to make this recommendation is based on several factors. First, there is a small evidence alluded to above for the use of these programmes in patients with HFPEF. Secondly, the symptoms and the prognosis of patients with HFPEF do not differ significantly from those with heart failure due to LVSD. Thirdly, the GDG recognises the differentiation of patients with HFPEF from those with LVSD remains controversial, and some believe that in patients with HFPEF there is dysfunction of the longitudinal axis of the left ventricle which is frequently not detected by most measurements of the left ventricular ejection fraction, thus the GDG felt that denying access to rehabilitation programmes to the patients with HFPEF is not justified and could lead to inequality.

Although at 5 years, there was a significant rise in the rate of heart failure hospitalisation in those randomised to receive exercise based rehabilitation, the GDG felt that not all hospitalisation in this group constitute set-backs. In addition, it was not clear whether the patients were at that stage continuing to exercise. The GDG did not have access to accurate information as to the number of patients remaining available for follow up at 5 years to make that observation.
The GDG noted that the majority of the programmes included group exercises which provide the patients with support and become an educational opportunity to the patients involved through formal counselling as well as iterative learning about their condition and how to cope with it. An assessment of the patient suitability for the programme ought to be made at the outset. However, the GDG believes that most patients should be included following the assessment and the determination of the most suitable training programme for their needs.

Some healthcare institutions would set up rehabilitation programmes designed specifically to meet the needs of patients with chronic heart failure. Other healthcare institutions may decide to incorporate this service within their existing cardiac rehabilitation programmes, that serve patients after myocardial infarction or 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. 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\textsuperscript{101}. While there was no impact on reducing the all cause mortality, there was also no evidence of increased mortality in the patients with significant heart failure recruited to the exercise based rehabilitation programme, thus 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\textsuperscript{114} from 2001. This showed that the exercise based rehabilitation programme in heart failure was cost effective; the incremental cost-effectiveness ratio (ICER) was £239 per life year gained when considering direct medical costs only. The GDG believed that the analysis has 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\textsuperscript{114} economic analysis was the only one assessing patients with heart failure included in the 2006 review by Hagberg\textsuperscript{118} of cost-effectiveness studies of healthcare-based interventions aimed at improving physical activity. With regard to the limitations of the Georgiou cost effectiveness analysis\textsuperscript{114} and to the limited applicability of the results to the UK NHS, the conclusions of the Hagberg 2006 review was 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).
6.8 Recommendations for rehabilitation

R66 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.
- The programme may be incorporated within an existing cardiac rehabilitation programme. [new 2010]

* 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.

6.9 Recommendations to be deleted

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 [2003, R12].
7 Monitoring

Heart failure is a progressive disease, characterised by high re-hospitalisation rates and a tendency to develop complications that could result in a decline in the renal, hepatic and neurological functions. 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. Early intervention may reduce re-hospitalisation, and enables adjustment of therapy to accommodate the changes in the patient’s clinical and haemodynamic condition, renal and neurological functions. Early detection of psychological disturbances such as anxiety and depression are also important outcomes of monitoring.

This update concentrated on the use of natriuretic peptides and tele-monitoring in monitoring heart failure patients.

The topics within monitoring that were outside of the scope of the partial update are:

1. Clinical review, For more information please refer to Section 8.1 of the 2003 Guideline.
2. Review of management plan – including medication, For more information please refer to Section 8.2 of the 2003 Guideline.
3. Serial cardiac imaging, For more information please refer to Section 8.3 of the 2003 Guideline.
4. Therapeutic drug monitoring of serum digoxin concentrations, For more information please refer to Section 8.4 of the 2003 Guideline.

7.1 Serial measurement of circulating natriuretic peptide concentration

BNP 3: 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. However, this was insufficient to produce a statement in the guidance of 2003, on the use of natriuretic peptides in the monitoring of heart failure patients.

Reason for review

Given the emergence of new studies on the use of natriuretic peptides in monitoring patients with heart failure, this update became justified.

7.1.2 Clinical methodological introduction

BNP 3: Does serial BNP monitoring improve outcome compared to standard care in adults with chronic heart failure?

Population: All chronic heart failure

Intervention: serial measurement of circulating natriuretic peptide concentration (BNP-guided therapy)

Comparison: clinically guided monitoring or usual care
Outcomes: All cause death up to 5 yrs, all cause hospitalization, HF hospitalization, and Quality of life (Minnesota Living with Heart Failure questionnaire)

Five randomised-controlled trials (RCT) were on patients with chronic heart failure. Four of the trials compared BNP-guided therapy with clinically-guided therapy. For details see Table 7.1 below. One trial used the BNP level to up-titrate beta-blocker dosage only. One trial compared BNP-guided therapy with either clinically-guided therapy or usual care provided by a primary care physician. The latter comparison is presented separately below.

Table 7.1: Trials comparing BNP-guided therapy with clinically guided therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lainchbury 2010</td>
<td>Included patients with persevered LVEF mean 40%</td>
<td>Treatment was altered according to a drug algorithm if NT proBNP level &gt; 150 pmol/L and/or heart failure score ≥ 2 (derived from Framlingham method of diagnosis)</td>
<td>Treatment was altered if the heart failure score was ≥ 2 (derived from Framlingham method of diagnosis)</td>
</tr>
<tr>
<td>BATTLESCARRED</td>
<td>Symptomatic HF. 75% NYHA II or III Inclusion criteria included NT proBNP &gt; 50 pmol/L Age (median) 76 yrs</td>
<td>-Treatment was altered if the heart failure score was ≥ 2 (derived from Framlingham method of diagnosis)</td>
<td>-Treatment was altered if the heart failure score was ≥ 2 (derived from Framlingham method of diagnosis)</td>
</tr>
<tr>
<td>Beck-da-Silva, 2005</td>
<td>(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 &lt; 50% males</td>
<td>-β blocker dosage up-titrated according to plasma BNP levels plus standard care</td>
<td>-β blocker dosage up-titrated according to plasma BNP levels plus standard care</td>
</tr>
<tr>
<td>Troughton, 2000</td>
<td>LVSD (LVEF &lt;40% on echo) Established symptomatic HF (NYHA class II-IV) Age (range): 35- 85 yrs &lt;50% females</td>
<td>-N-BNP guided treatment -The treatment target was N-BNP below 200pmol/l -If the targets were not achieved drug treatment was intensified according to a strict and predetermined stepwise protocol</td>
<td>-Treatment guided by standardised clinical assessment -The treatment target was clinically compensated heart failure according to an objective score</td>
</tr>
<tr>
<td>Jourdain, 2007</td>
<td>Symptomatic (New York Heart Association functional class II to III) systolic heart failure defined by left ventricular ejection</td>
<td>-Medical therapy was increased with the aim of lowering plasma BNP levels (target &lt;100 pg/ml) - Each class of therapy</td>
<td>-Medical therapy was increased with the aim of lowering plasma BNP levels (target &lt;100 pg/ml) - Each class of therapy</td>
</tr>
<tr>
<td>Condition</td>
<td>Criteria</td>
<td>Intervention</td>
<td>Notes</td>
</tr>
<tr>
<td>-----------</td>
<td>----------</td>
<td>--------------</td>
<td>-------</td>
</tr>
</tbody>
</table>
| Fraction (LVEF) <45% | - Age (mean): 65 yrs  
- <50% females | modified according to the judgement of the investigator. |       |
| Pfisterer, 2009 TIME-CHF | - Dyspnea (New York Heart Association class ≥ II with current therapy), a history of hospitalisation for heart failure within the last year  
- Age (mean): 76 yrs  
- <50% females | - BNP guided plus symptom guided medical therapy.  
- 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 symptoms to NYHA class of II or less. | - Symptom guided medical therapy.  
- Medical therapy to reduce symptoms to NYHA class of II or less. |

1 The Beck-da-Silva trial of 2005 concentrated on uptitrating the 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 and BATTLESCARRED trial, 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) and Pfisterer (2009), the investigators in the natriuretic peptide guided therapy had to work towards a target level for the natriuretic peptide.

Data were reported for the following outcomes:
- Mortality (all cause) – 9.5 to 18 months
- Mortality (all cause) – 3 yrs
- Mortality (heart failure (HF)) – 3 to 15 months
- Hospitalisation (all cause) (no. of patients) – 3 to 15 months
- Hospitalisation (heart failure) (no. of patients) – 9.5 to 15 months
- Hospitalisation (heart failure) (no. of patients) – 3 yrs
- Quality of life (Minnesota Living with Heart Failure) – 12 to 18 months

18 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 (≤ 75 yrs vs > 76s) and (< 75 yrs vs ≥ 76 yrs).

Data were reported for the following outcomes:
- 76 yrs or more - Mortality (all cause) - 18 mths to 3 yrs
- 75 yrs or less - Mortality (all cause) - 18 mths to 3 yrs
- 76 yrs or more - Hospitalisation (heart failure) (no. of patients) – 18 mths to 3 yrs
- 75 yrs or less - Hospitalisation (heart failure) (no. of patients) – 18 mths to 3 yrs

18 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.
Table 7.2: BNP guided therapy vs usual care

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lainchbury 2010</td>
<td>Included patients with persevered LVEF mean 40% Symptomatic HF. 75% NYHA II or III Inclusion criteria included NT proBNP &gt; 50 pmol/L Age (median) 76 yrs</td>
<td>Treatment was altered according to a drug algorithm if NT proBNP level &gt; 150 pmol/L and/or heart failure score was ≥ 2 (derived from Framingham method of diagnosis)</td>
<td>Usual care Managed in primary care with or without additional visits to a hospital cardiologist or specialised heart failure clinic</td>
</tr>
</tbody>
</table>

Data were reported for the following outcomes:

- Mortality (all cause) – one year
- Mortality (all cause) - three years
- Hospitalisation (heart failure) – one year
- Hospitalisation (heart failure) – three years

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)

Data were reported for the following outcomes:

- 76 yrs or more – Mortality (all cause) – three years
- 75 yrs or less – Mortality (all cause) – three years
- 76 yrs or more – Hospitalisation (heart failure) – one year
- 75 yrs or less – Hospitalisation (heart failure) - one year
- 76 yrs or more – Hospitalisation (heart failure) – three years
- 75 yrs or less – Hospitalisation (heart failure) – three years
7.1.3 Clinical evidence statements

Compared to clinically-guided therapy, BNP-guided therapy resulted in a significant reduction for:

- 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?

<table>
<thead>
<tr>
<th>No of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Quality assessment</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality (all causes) (follow-up 9.5-18 months)</strong></td>
<td>3</td>
<td>BATTLESCARRED 2009</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious</td>
<td>None</td>
</tr>
<tr>
<td><strong>Mortality (all cause) (follow-up 3 years)</strong></td>
<td>1</td>
<td>BATTLESCARRED 2009</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious</td>
<td>None</td>
</tr>
<tr>
<td><strong>Mortality (HF) (follow-up 3 to 15 months)</strong></td>
<td>2</td>
<td>Beck-de-Silva 2005</td>
<td>randomised trial</td>
<td>serious</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious</td>
<td>None</td>
</tr>
<tr>
<td><strong>Hospitalisation (all cause) (no. of patients) (follow-up 3 to 15 months)</strong></td>
<td>2</td>
<td>STARS-BNP 2007 Beck-de-Silva 2005</td>
<td>randomised trial</td>
<td>serious</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious</td>
<td>None</td>
</tr>
</tbody>
</table>
### Hospitalisation (heart failure) (no. of patients) (follow-up 9.5-15 months)

<table>
<thead>
<tr>
<th>Study/Condition</th>
<th>Method</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Type</th>
<th>Events</th>
<th>RR</th>
<th>95% CI</th>
<th>Events</th>
<th>RR</th>
<th>95% CI</th>
<th>p-value</th>
<th>Methodological Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>BATTLESCARRED 2009</td>
<td>Randomised trial</td>
<td>No serious limitations</td>
<td>No serious inconsistency</td>
<td>Serious</td>
<td>None</td>
<td>86/515 (16.7%)</td>
<td>RR 0.66</td>
<td>(0.52 to 0.84)</td>
<td>131/515 (12%)</td>
<td>40 fewer per 1,000</td>
<td>81 fewer per 1,000</td>
<td>⬤抵抗力</td>
<td>No serious limitations, no serious inconsistency, no serious indirectness, serious type of patients</td>
</tr>
</tbody>
</table>

### Hospitalisation (heart failure) (no. of patients) (follow-up 3 years)

<table>
<thead>
<tr>
<th>Study/Condition</th>
<th>Method</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Type</th>
<th>Events</th>
<th>RR</th>
<th>95% CI</th>
<th>Events</th>
<th>RR</th>
<th>95% CI</th>
<th>p-value</th>
<th>Methodological Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>BATTLESCARRED 2009</td>
<td>Randomised trial</td>
<td>No serious limitations</td>
<td>No serious inconsistency</td>
<td>Serious</td>
<td>None</td>
<td>44/121 (36.4%)</td>
<td>RR 0.90</td>
<td>(0.65 to 1.24)</td>
<td>49/121 (40.5%)</td>
<td>41 fewer per 1000 (from 142 fewer to 97 more)</td>
<td>⬤抵抗力</td>
<td>No serious limitations, no serious inconsistency, no serious indirectness, serious type of patients</td>
<td></td>
</tr>
</tbody>
</table>

### Quality of Life (MLHF) (follow-up 12-18 months; range of scores: 0-105; Better indicated by less)

<table>
<thead>
<tr>
<th>Study/Condition</th>
<th>Method</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Type</th>
<th>Events</th>
<th>MD</th>
<th>95% CI</th>
<th>p-value</th>
<th>Methodological Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>BATTLESCARED 2009</td>
<td>Randomised trial</td>
<td>No serious limitations</td>
<td>No serious inconsistency</td>
<td>Serious</td>
<td>None</td>
<td>372</td>
<td>MD 1.30</td>
<td>(-1.63 to 4.22)</td>
<td>369</td>
<td>⬤抵抗力</td>
</tr>
</tbody>
</table>

---

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?

**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

<table>
<thead>
<tr>
<th>No of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>BNP-guided</th>
<th>clinically-guided</th>
<th>Relative (95% CI)</th>
<th>Absolute</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>76 yrs or more - Mortality (all cause) - 18 mths to 3 yrs (follow-up 1.5-3 years)</td>
<td>2 BATTLESCARED 2009 TIME-CHF 2009</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious¹</td>
<td>None</td>
<td>64/206 (31.1%)</td>
<td>60/212 (25%)</td>
<td>RR 1.10 (0.82 to 1.47)</td>
<td>25 more per 1,000</td>
<td>35 more per 1,000</td>
</tr>
<tr>
<td>75 yrs or less - Mortality (all cause) - 18 mths to 3 yrs (follow-up 1.5-3 years)</td>
<td>2 BATTLESCARED 2009 TIME-CHF 2009</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious¹</td>
<td>None</td>
<td>11/108 (10.2%)</td>
<td>11/102 (20%)</td>
<td>RR 0.49 (0.30 to 0.79)</td>
<td>50 fewer per 1,000</td>
<td>158 fewer per 1,000</td>
</tr>
<tr>
<td>76 yrs or more - Hospitalisation (HF) - 18 mths to 3 yrs (follow-up 1.5-3 years)</td>
<td>2 BATTLESCARED 2009 TIME-CHF 2009</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious¹</td>
<td>None</td>
<td>53/206 (25.7%)</td>
<td>56/212 (20%)</td>
<td>RR 0.98 (0.72 to 1.34)</td>
<td>3 fewer per 1,000</td>
<td>8 fewer per 1,000</td>
</tr>
<tr>
<td>75 yrs or less - Hospitalisation (HF) - 18 mths to 3 yrs (follow-up 1.5-3 years)</td>
<td>2 BATTLESCARED 2009 TIME-CHF 2009</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious¹</td>
<td>None</td>
<td>26/166 (15.7%)</td>
<td>38/157 (16%)</td>
<td>RR 0.65 (0.42 to 1)</td>
<td>56 fewer per 1,000</td>
<td>140 fewer per 1,000</td>
</tr>
</tbody>
</table>

¹ < 300 events
BNP-guided compared with usual care

Compared to usual care, BNP-guided therapy resulted in a significant reduction for:

- 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 trials 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?

**Author(s):**

**Date:** 2009-09-23

**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.

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>BNP-guided monitoring</td>
<td>Usual care</td>
</tr>
<tr>
<td>76 yrs or more - Mortality (all cause) - three yrs (follow-up 3 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 BATTLESCARRED 2010</td>
<td>randomised trial</td>
<td>no serious limitations</td>
</tr>
<tr>
<td>75 yrs or less - Mortality (all cause) - three yrs (follow-up 3 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 BATTLESCARRED 2010</td>
<td>randomised trial</td>
<td>no serious limitations</td>
</tr>
<tr>
<td>76 yrs or more - Hospitalisation (HF) - one year (follow-up 1 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 BATTLESCARRED 2010</td>
<td>randomised trial</td>
<td>no serious limitations</td>
</tr>
<tr>
<td>75 yrs or less - Hospitalisation (HF) - one year (follow-up 1 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 BATTLESCARRED 2010</td>
<td>randomised trial</td>
<td>no serious limitations</td>
</tr>
<tr>
<td>76 yrs or more - Hospitalisation (HF) - three yrs (follow-up 3 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 BATTLESCARRED 2010</td>
<td>randomised trial</td>
<td>no serious limitations</td>
</tr>
<tr>
<td>75 yrs or less - Hospitalisation (HF) - three yrs (follow-up 3 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 BATTLESCARRED 2010</td>
<td>randomised trial</td>
<td>no serious limitations</td>
</tr>
</tbody>
</table>

<sup>1</sup> < 300 events
BNP-monitoring vs usual care - Sub-group analysis by age

Compared to standard care, BNP monitoring resulted in a significant reduction for:

- 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

Author(s): Lainchbury JG, Troughton RW, Strangman KM et al.

Date: 2009-09-23

Question: Should BNP-guided monitoring vs Usual care be used for chronic heart failure?


<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of studies</td>
<td>Design</td>
</tr>
<tr>
<td>76 yrs or more - Mortality (all cause) - three yrs (follow-up 3 years)</td>
<td></td>
</tr>
<tr>
<td>1 BATTLESCARRED 2010</td>
<td>randomised trial</td>
</tr>
<tr>
<td>75 yrs or less - Mortality (all cause) - three yrs (follow-up 3 years)</td>
<td></td>
</tr>
<tr>
<td>1 BATTLESCARRED 2010</td>
<td>randomised trial</td>
</tr>
<tr>
<td>76 yrs or more - Hospitalisation (HF) - one year (follow-up 1 years)</td>
<td></td>
</tr>
<tr>
<td>1 BATTLESCARRED 2010</td>
<td>randomised trial</td>
</tr>
<tr>
<td>75 yrs or less - Hospitalisation (HF) - one year (follow-up 1 years)</td>
<td></td>
</tr>
<tr>
<td>1 BATTLESCARRED 2010</td>
<td>randomised trial</td>
</tr>
<tr>
<td>76 yrs or more - Hospitalisation (HF) - three yrs (follow-up 3 years)</td>
<td></td>
</tr>
<tr>
<td>1 BATTLESCARRED 2010</td>
<td>randomised trial</td>
</tr>
<tr>
<td>75 yrs or less - Hospitalisation (HF) - three yrs (follow-up 3 years)</td>
<td></td>
</tr>
<tr>
<td>1 BATTLESCARRED 2010</td>
<td>randomised trial</td>
</tr>
</tbody>
</table>

¹ < 300 events
7.1.4 Health Economic Methodological introduction

From the 2003 Guideline\textsuperscript{19}, 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.

\textbf{US published evidence}

Morimoto et al. (2004)\textsuperscript{126} developed a cost-utility analysis reporting cost per QALY gained. The assessment was based on the Troughton 2000 clinical study\textsuperscript{121} and on an economic model for patients with heart failure developed by Delea in 1999\textsuperscript{127}. 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\textsuperscript{128} for outpatient follow-up after hospitalisation for CHF. The utility values used to calculate QALYs were obtained from data by Havranek 1999\textsuperscript{129} (symptomatic CHF patients with reduced LVEF). The probabilities considered in the analysis, from Troughton 2000\textsuperscript{121} and Delea 1999\textsuperscript{127}, 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 \textpm 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.

\textbf{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\textsuperscript{126} was based on one RCT\textsuperscript{121} 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).

Table 7.3: Economic study assessment

<table>
<thead>
<tr>
<th>Study</th>
<th>Study quality*</th>
<th>Study applicability**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morimoto 2004\textsuperscript{126}</td>
<td>Potentially serious limitations (a)</td>
<td>Partially applicable (b)</td>
</tr>
<tr>
<td>NCGC analysis (developed for this Guideline update)</td>
<td>Minor limitations</td>
<td>Directly applicable</td>
</tr>
</tbody>
</table>

*aVery 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
7.1.5 Health economic evidence statements

US published evidence

In the base-case analysis, Morimoto et al. (2004)\textsuperscript{126} (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 inpatients 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\textsuperscript{126}

<table>
<thead>
<tr>
<th></th>
<th>6 months</th>
<th>9 months (base-case analysis)</th>
<th>12 months</th>
<th>15 months</th>
<th>18 months</th>
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<tr>
<td><strong>BNP Group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QALY</td>
<td>0.38</td>
<td>0.57</td>
<td>0.74</td>
<td>0.91</td>
<td>1.07</td>
</tr>
<tr>
<td>Cost</td>
<td>£3498</td>
<td>£6007</td>
<td>£8429</td>
<td>£10,762</td>
<td>£13,008</td>
</tr>
<tr>
<td><strong>Clinical Group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QALY</td>
<td>0.38</td>
<td>0.55</td>
<td>0.70</td>
<td>0.83</td>
<td>0.94</td>
</tr>
<tr>
<td>Cost</td>
<td>£3907</td>
<td>£6,355</td>
<td>£8576</td>
<td>£10,578</td>
<td>£12,372</td>
</tr>
<tr>
<td><strong>Result</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICER</td>
<td>Dominant*</td>
<td>Dominant*</td>
<td>Dominant*</td>
<td>£2,190 per QALY</td>
<td>£4,884 per QALY</td>
</tr>
</tbody>
</table>

*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\textsuperscript{[Section 7.1.2]}, which assessed serial measurement of natriuretic peptide concentration for optimizing the medical therapy in CHF (Troughton 2000\textsuperscript{121}, Jourdain 2007\textsuperscript{123}, Pfisterer 2009\textsuperscript{124}, Battlescarred 2010\textsuperscript{125}). Troughton 2000\textsuperscript{121}, Jourdain 2007\textsuperscript{123}, and Pfisterer 2009\textsuperscript{124} compared serial
measurement in secondary care of natriuretic peptide concentration and clinical
assessment in secondary care. Battlescarred 2010\textsuperscript{125} compared natriuretic peptide
measurement in secondary care, clinical assessment in secondary care, and usual
care in the community.

The Trougton 2000\textsuperscript{121}, Jourdain 2007\textsuperscript{123}, and Pfisterer 2009\textsuperscript{124} clinical trials were
conducted in patients with CHF and LVSD. Battlescarred 2010 clinical trial\textsuperscript{125} was
conducted on patients with CHF of any causes. Hence, outcomes of the three clinical
trials on patients with LVSD \textsuperscript{121, 123, 124} were meta-analysed for use in this economic
analysis, and outcomes from the Battlescarred clinical trial\textsuperscript{125} were utilized
independently. Furthermore, age subgroups (<75 years / \geq 75 years) were assessed
in Pfisterer\textsuperscript{124} and Battlescarred\textsuperscript{125}, 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
Battlescarred main analysis, and between the clinical assessment and the usual care
cohorts in Battlescarred age-subgroup analyses (<75 years / \geq 75 years)\textsuperscript{125}.
Therefore, cost-effectiveness assessments were conducted on these analyses on a
three-year time horizon. In addition, for Battlescarred\textsuperscript{125} 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 (Battlescarred\textsuperscript{125} and
Pfisterer\textsuperscript{124}), 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\textsuperscript{121, 124, 123, 125} did not report utility scores. We used mean utility
scores stratified by NYHA class for patients with CHF reported by Gohler 2009\textsuperscript{130} to
calculate a mean utility score from patients’ baseline characteristics, as observed in
the trials. We assumed that mean utility scores stayed 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\textsuperscript{124}
drug usage was used for the base case; drug usage from Jourdain\textsuperscript{123} and
Troughton\textsuperscript{121} were applied in sensitivity analyses. Secondly, Jourdain\textsuperscript{123} and Pfisterer\textsuperscript{124} clinical trials were modelled independently in addition to the assessment combining outcomes from Pfisterer\textsuperscript{124}, Jourdain\textsuperscript{123}, and Troughton\textsuperscript{121}, because of some inconsistencies in outcomes. Troughton\textsuperscript{121} was not modelled independently since it was small and did not report all-cause mortality. Furthermore, as discussed above, the cost-effectiveness assessment from Battlescarred\textsuperscript{125} main analysis was conducted on a three-year time horizon, and cost-effectiveness assessments from Battlescarred\textsuperscript{125} 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\textsuperscript{124} and 15 months\textsuperscript{123}). Considering that mortality ratios in natriuretic peptide and clinical assessment cohorts for all-age analyses might be the same at three years as in Battlescarred\textsuperscript{125} main analysis, we conducted additional analyses on patients with CHF and LVSD on a three-year time horizon. Finally, we used in the sensitivity analysis 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\textsuperscript{124}, Jourdain\textsuperscript{123}, and Troughton\textsuperscript{121} 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\textsuperscript{123} with a three-year time horizon, the natriuretic peptide option was actually cost-saving compared to clinical assessment.

### Table 7.5: Cost and QALY results

<table>
<thead>
<tr>
<th>Resource use</th>
<th>Natriuretic peptide</th>
<th>Clinical assessment</th>
<th>Difference NP-Clinic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natriuretic peptide test</td>
<td>£136</td>
<td>£0</td>
<td>£136</td>
</tr>
<tr>
<td>Drugs</td>
<td>£404</td>
<td>£377</td>
<td>£27</td>
</tr>
<tr>
<td>Biochemistry test</td>
<td>£1.66</td>
<td>£1.04</td>
<td>£0.62</td>
</tr>
<tr>
<td>Outpatient visit</td>
<td>£482</td>
<td>£422</td>
<td>£60</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>£161</td>
<td>£279</td>
<td>-£118</td>
</tr>
<tr>
<td>Post-trial cost</td>
<td>£8,337</td>
<td>£7,698</td>
<td>£639</td>
</tr>
<tr>
<td><strong>Total cost</strong></td>
<td><strong>£9,521</strong></td>
<td><strong>£8,777</strong></td>
<td><strong>£744</strong></td>
</tr>
<tr>
<td>Life years</td>
<td>7.23</td>
<td>6.74</td>
<td>0.49</td>
</tr>
<tr>
<td>QALYs</td>
<td>5.18</td>
<td>4.82</td>
<td>0.36</td>
</tr>
</tbody>
</table>

NP = Natriuretic Peptide; Clinic = Clinical assessment

* Discounting at 3.5% applied after one year
Table 7.6: Cost effectiveness results (LVSD)

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Time horizon</th>
<th>Cost difference (NP-Clinic)</th>
<th>QALY difference (NP-Clinic)</th>
<th>INMB (20k/QALY)</th>
<th>Probability NP being cost-effective</th>
<th>ICER</th>
<th>ICER (Sensitivity analysis - NP measurement £20)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Base-case analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF and LVSD (Pfisterer drug usage)</td>
<td>Lifetime</td>
<td>£744</td>
<td>0.36</td>
<td>£6,373</td>
<td>98.3%</td>
<td>£2,091</td>
<td>£1,985</td>
</tr>
<tr>
<td><strong>Age subgroups</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pfisterer &lt;75 years</td>
<td>Lifetime</td>
<td>£1,187</td>
<td>0.72</td>
<td>£13,248</td>
<td>99.0%</td>
<td>£1,644</td>
<td>£1,592</td>
</tr>
<tr>
<td>Pfisterer &gt;75 years</td>
<td>Lifetime</td>
<td>£321</td>
<td>0.09</td>
<td>£1,383</td>
<td>67.6%</td>
<td>£3,766</td>
<td>£3,323</td>
</tr>
<tr>
<td><strong>Sensitivity analysis - Independent clinical trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pfisterer all ages</td>
<td>Lifetime</td>
<td>£646</td>
<td>0.35</td>
<td>£6,264</td>
<td>98.4%</td>
<td>£1,870</td>
<td>£1,761</td>
</tr>
<tr>
<td>Jourdain</td>
<td>Lifetime</td>
<td>£157</td>
<td>0.21</td>
<td>£3,970</td>
<td>89.8%</td>
<td>£762</td>
<td>£579</td>
</tr>
<tr>
<td><strong>Sensitivity analysis - Drug usage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF and LVSD (Jourdain drug usage)</td>
<td>Lifetime</td>
<td>£735</td>
<td>0.36</td>
<td>£6,382</td>
<td>98.3%</td>
<td>£2,065</td>
<td>£1,959</td>
</tr>
<tr>
<td>CHF and LVSD (Troughton drug usage)</td>
<td>Lifetime</td>
<td>£767</td>
<td>0.36</td>
<td>£6,350</td>
<td>98.2%</td>
<td>£2,155</td>
<td>£2,048</td>
</tr>
<tr>
<td><strong>Sensitivity analysis - Time horizon</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pfisterer all ages</td>
<td>3 years</td>
<td>£359</td>
<td>0.17</td>
<td>£3,124</td>
<td>99.4%</td>
<td>£2,060</td>
<td>£1,843</td>
</tr>
<tr>
<td>Jourdain</td>
<td>3 years</td>
<td>-£83</td>
<td>0.05</td>
<td>£1,148</td>
<td>92.1%</td>
<td>NP dominates*</td>
<td>NP dominates*</td>
</tr>
<tr>
<td>CHF and LVSD (Pfisterer drug usage)</td>
<td>3 years</td>
<td>£327</td>
<td>0.10</td>
<td>£1,690</td>
<td>97.9%</td>
<td>£3,240</td>
<td>£2,865</td>
</tr>
<tr>
<td>CHF and LVSD (Jourdain drug usage)</td>
<td>3 years</td>
<td>£313</td>
<td>0.10</td>
<td>£1,698</td>
<td>97.78%</td>
<td>£3,150</td>
<td>£2,775</td>
</tr>
<tr>
<td>CHF and LVSD (Troughton drug usage)</td>
<td>3 years</td>
<td>£349</td>
<td>0.10</td>
<td>£1,667</td>
<td>97.7%</td>
<td>£3,465</td>
<td>£3,090</td>
</tr>
</tbody>
</table>

2 NP = Natriuretic Peptide; Clinic = Clinical assessment; INMB = Incremental Net Monetary Benefit; ICER = Incremental Cost-Effectiveness Ratio
3 * Natriuretic peptide is more effective and less costly than clinical assessment
4 5
5 6
6 Table 7.7 presents a breakdown of cost components, life years, and QALYs for the base-case cost-effectiveness analysis developed from Battlescarred. 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.
7 8 For the age-subgroup cost-effectiveness assessment conducted on patients younger than 75 years 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-
9 10...
effective compared to usual care in the community for patients with CHF younger than 75 years (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)

<table>
<thead>
<tr>
<th>Resource use</th>
<th>Natriuretic peptide</th>
<th>Clinical assessment</th>
<th>Usual care</th>
<th>Difference NP-Clinic</th>
<th>Difference Clinic-UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natriuretic peptide test</td>
<td>270</td>
<td>0</td>
<td>0</td>
<td>270</td>
<td>0</td>
</tr>
<tr>
<td>Drugs</td>
<td>415</td>
<td>433</td>
<td>349</td>
<td>-18</td>
<td>84</td>
</tr>
<tr>
<td>Biochemistry test</td>
<td>1.65</td>
<td>1.03</td>
<td>0</td>
<td>0.62</td>
<td>1.03</td>
</tr>
<tr>
<td>Outpatient visit</td>
<td>951</td>
<td>894</td>
<td>461</td>
<td>57</td>
<td>433</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>638</td>
<td>699</td>
<td>588</td>
<td>-61</td>
<td>111</td>
</tr>
<tr>
<td>Total cost</td>
<td>2,276</td>
<td>2,027</td>
<td>1,399</td>
<td>249</td>
<td>628</td>
</tr>
<tr>
<td>Life years</td>
<td>2.44</td>
<td>2.41</td>
<td>2.30</td>
<td>0.03</td>
<td>0.11</td>
</tr>
<tr>
<td>QALYs</td>
<td>1.84</td>
<td>1.82</td>
<td>1.73</td>
<td>0.02</td>
<td>0.09</td>
</tr>
</tbody>
</table>

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)
1. **Table 7.8: Cost effectiveness results (CHF any cause)**

<table>
<thead>
<tr>
<th>Time horizon</th>
<th>Compared interventions</th>
<th>Cost difference (Clinic-UC) (NP-Clinic) (NP-UC)</th>
<th>QALY difference (Clinic-UC) (NP-Clinic) (NP-UC)</th>
<th>INMB (20k/QALY)</th>
<th>Probability NP/Clinic* being cost-effective</th>
<th>ICER</th>
<th>Sensitivity analysis - NP measurement £20 (ICER)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Battlescarred all ages</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 years</td>
<td>Clinic vs Usual care</td>
<td>£628</td>
<td>0.09</td>
<td>£1,120</td>
<td>99.9%</td>
<td>£6,891</td>
<td>£7,188</td>
</tr>
<tr>
<td>3 years</td>
<td>NP vs Clinic</td>
<td>£249</td>
<td>0.02</td>
<td>£171</td>
<td>90.9%</td>
<td>£11,860</td>
<td>£8,278</td>
</tr>
<tr>
<td><strong>Battlescarred &lt;75 years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifetime</td>
<td>NP vs Usual care</td>
<td>£1,905</td>
<td>1.08</td>
<td>£19,734</td>
<td>97.9%</td>
<td>£1,761</td>
<td>£1,692</td>
</tr>
<tr>
<td>3 years</td>
<td>NP vs Usual care</td>
<td>£720</td>
<td>0.32</td>
<td>£5,671</td>
<td>100.0%</td>
<td>£2,253</td>
<td>£2,018</td>
</tr>
<tr>
<td><strong>Battlescarred &gt;75 years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifetime</td>
<td>Clinic vs Usual care</td>
<td>£697</td>
<td>0.07</td>
<td>£670</td>
<td>50.1%</td>
<td>£10,191</td>
<td>N/A</td>
</tr>
<tr>
<td>3 years</td>
<td>Clinic vs Usual care</td>
<td>£688</td>
<td>0.05</td>
<td>£333</td>
<td>86.8%</td>
<td>£13,354</td>
<td>N/A</td>
</tr>
</tbody>
</table>

2. NP = Natriuretic Peptide; Clinic = Clinical assessment; UC = Usual Care; INMB = Incremental Net Monetary Benefit; ICER = Incremental Cost-Effectiveness Ratio
3. * Clinic for Clinic vs Usual care; NP for NP vs Clinic; NP for NP vs Usual care
4. **Figure 7.2 Cost effectiveness results (CHF any cause; age subgroups)**

---

**Battlescarred <75 (Lifetime horizon)**

- Additional cost per patient vs QALYs gained per patient
- £1,761 per QALY

**Battlescarred >75 (Lifetime horizon)**

- Additional cost per patient vs QALYs gained per patient
- £10,191 per QALY

**Battlescarred <75 (3 yrs time horizon)**

- Additional cost per patient vs QALYs gained per patient
- £2,253 per QALY

**Battlescarred >75 (3 yrs time horizon)**

- Additional cost per patient vs QALYs gained per patient
- £13,354 per QALY

---
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 usual care in the community:

- Clinical assessment was more costly than usual care
- Clinical assessment was more effective and more cost-effective than usual care
- Natriuretic peptide monitoring was more costly than clinical assessment (with the exception of the analysis based on Jourdain\textsuperscript{123} and the one based on Battlescarred\textsuperscript{125} ≥75)
- Natriuretic peptide monitoring was more effective and more cost-effective than clinical assessment (with the exception of the analysis based on Battlescarred\textsuperscript{125} ≥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 Battlescarred trial\textsuperscript{125}, the same number of patient was alive in the three compared cohorts. In the base-case cost-effectiveness analysis based on Battlescarred\textsuperscript{125} (patient with CHF due to any cause), 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\textsuperscript{121} only and were applied to all cost-effectiveness analyses for natriuretic peptide and clinical assessment cohorts. Troughton\textsuperscript{121} 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 Battlescarred’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 Battlescarred trial\textsuperscript{125} (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 differenced using outcomes from Battlescarred\textsuperscript{125} or from Pfisterer\textsuperscript{124}. The natriuretic peptide intervention improved survival in Pfisterer\textsuperscript{124} and decreased it in Battlescarred\textsuperscript{125} (compared to clinical assessment). It might be because patients with heart failure and preserved ejection fraction (HFPEF) were included in Battlescarred\textsuperscript{126} and excluded in Pfisterer\textsuperscript{124}. 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 primary care could be drawn. Considering the influence of the outpatient visit cost in the Battlescared 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 Summary of evidence statements

The medical therapy of heart failure due to left ventricular systolic dysfunction (left ventricular ejection fraction of <40-45%) driven by the usual clinical assessment was compared in four randomised controlled trials (RCT's) to that directed by the serial monitoring of serum natriuretic peptides. The fifth randomised controlled trial (Lainchbury 2009; BATTLESCARRED) differed in that it included mainly patients with heart failure due to left ventricular systolic dysfunction, in addition to some patients with heart failure and preserved left ventricular ejection fraction.

The trials recruited patients with symptomatic heart failure with New York Heart Association (NYHA) class II-III in the study by Jourdain et al., or class II-IV in the remaining studies. However, in the Battlescared trial 75% of the patients were in NYHA functional class II-III.

The five trials reported variably on several outcomes. From the meta-analysis, the natriuretic peptide guided medical therapy, compared to standard medical therapy, resulted in significant reduction of heart failure hospitalisation at 9.5-15 months. There was no significant difference between the natriuretic peptide driven medical therapy and standard care in: all cause mortality (with follow-up at 18 months, and 3 years), heart failure mortality (follow-up 3 to 15 months), all cause hospitalisation (at 3-15 months), heart failure hospitalisation (at 3 years) and in quality of life (12 to 18 months of follow-up).

Two of the trials had pre-specified sub-group analyses of the implication of this strategy in different age groups. These were the TIME-CHF trial and the BATTLESCARRED trial. They reported on all cause mortality (18 months to 3 years), and on heart failure hospitalisation (18 months to 3 years) in the patients 75 years or less and in patients > 76 years. The meta-analysis reported a significant reduction in all cause mortality for NP guided therapy compared to standard medical therapy in patients 75 years or less. No other statistically significant differences were noted.

The TIME-CHF and BATTLESCARRED had looked at two different age groups (<75 years and >75 years). In both trials the beneficial effect of biomarker-guided therapy appear to be in those aged <75 years.

The health economic review identified one study by Morimoto et al. (2004) which was developed from the US perspective. This study looked at the use of natriuretic peptide monitoring to guide the medical therapy of patients with heart failure due to left ventricular systolic dysfunction as based on the randomised clinical trial by Troughton et al. (2000). The analysis concluded the cost effectiveness of this therapy in a US context.

The economic analysis developed from a UK perspective for this Guideline concluded 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. 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. Furthermore, 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.

7.1.7 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 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 the 3 year
mortality, the 1 year and 3 years of heart failure hospitalisation.

The GDG were not convinced by the evidence of 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. To date, patients with this type of heart
failure have not benefited from most of the therapeutic interventions used in the trials.
This may be diluting any potential impact of the NP-guided therapy.

Amongst the trials, the BATTLESCARRED offered the unique comparison with the
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 the 1 year mortality for the whole cohort of the trial, and with a
significant reduction in the 3 year mortality in the patients 75 years or less. This is
taken as evidence that usual care in general practice is sub-optimal and is thus
unacceptable, not simply a justification for using natriuretic peptide monitoring.

Quality of evidence

The evidence of the comparison between strategies from the five RCT’s was not of
high quality, with the evidence of moderate quality for the majority of outcomes.

The effects on mortality were only seen when the NP-guided therapy was compared
to a restricted form of what was called usual care. The latter implied that no form of
monitoring was being made unless the patient had actually deteriorated, which is less
than optimal care. While this is important to demonstrate, it does not justify the use of
natriuretic peptide for monitoring, as the same trial (Battlescarred) showed equality
between the NP-guided medical therapy and clinically-guided medical therapy in
terms of mortality rate at 1 year and 3 years.

The GDG noted, however, that unlike the other trials, the Battlescarred trial included
a small percentage of its cohort who were asymptomatic heart failure patients. In
addition, this trial included elderly patients who had heart failure with preserved left
ventricular ejection fraction. The latter point derives its importance from the current
lack of convincing evidence of effectiveness of medical therapy beyond diuretics and
correction of the co-morbidity in the management of heart failure with preserved left
ventricular ejection fraction. This and the potential harm from increasing diuretics in
these elderly patients whose NP level is elevated, may explain the lack of positive impact of NP-guided therapy in those over the age of 75 years.

**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.

The adjustments of medication occurred on the whole more frequently in the patients monitored by natriuretic peptide in addition to the standard clinical strategies.

The strategy of NP-guided medical therapy was sometimes associated with 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 the 3 year mortality in those 75 years or less in the Battlescarred trial, compared to usual care.

When the age subgroups (75 years or less and 76 years and over) were looked at with regards to all cause mortality and heart failure hospitalisation; no difference was found in two relatively large trials (TIME-CHF and Battlescarred) between NP-guided and the clinically guided medical therapy. Thus, confirming that there is no justification to use natriuretic peptide for the routine monitoring of patients with heart failure, irrespective of the patient age group.

The GDG recognised that raised natriuretic peptide levels are associated with poor prognosis, and suggest that the heart failure is not controlled. The GDG accepts that lowering the natriuretic peptide levels is associated with improved prognosis and better control in the heart failure clinical status.

The GDG noted that any impact of the strategy 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 heralded by the rising level of natriuretic peptides.

Thus, the natriuretic peptide monitoring strategy cannot be justified routinely in the patients whose medical therapy had been optimised.

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 believe that the use of the measurement of natriuretic peptide levels as an early warning system ought to be considered as a research topic, particularly given the prognostic implication of those levels.

The level to which the natriuretic peptides are lowered needs to be agreed within the local networks, but a drop of 50-80% in the level of the natriuretic peptide is an indicator that the patient is responding positively to the therapeutic intervention.

In addition, the GDG notes that the levels found during monitoring are different to those used for making the diagnosis of heart failure.

**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. However, the preferred option for patients older than 75 years might be clinical assessment in secondary care. The GDG accepted conclusions of the economic analysis and agreed natriuretic peptide monitoring to be available for specialist use in secondary care in selected patients. In addition, 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.

7.1.8 Recommendations

R71 Ongoing management of patients admitted to hospital with heart failure should be guided by the opinion of a specialist in heart failure. [new 2010].

R74 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

MONIT: What is the efficacy and safety of patient self 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 usually precedes 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 guidance of 2003, complex remote monitoring systems were mentioned, but the experience with them was limited. The guidance commented that tele-monitoring at that stage was in its infancy and therefore 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

MONIT: 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

Outcomes: all cause death up to 5 yrs, hospitalization, unplanned hospitalization, quality of life

Low quality and non-randomised trials were excluded from the review. One prospective cohort study on older adults was included.
a) All chronic heart failure

Eight RCTs were on patients with chronic heart failure. 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANTONICELLI 2008</td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td>CLELAND 2005</td>
<td>Usual care N=85. Individualised written management plan describing medication regimen sent to primary care physician. Patients assessed at research clinic every four months.</td>
<td>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.</td>
</tr>
<tr>
<td>DANSKY 2008</td>
<td>Usual care N=110. Routine home visits. No further details provided.</td>
<td>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.</td>
</tr>
<tr>
<td>DAR 2009</td>
<td>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</td>
<td>Home telemonitoring N=91. Usual care plus telemonitoring including weighing scales, blood pressure, pulse oximeter and symptoms. Data outside of pre-</td>
</tr>
<tr>
<td>Study</td>
<td>Comparison</td>
<td>Intervention</td>
</tr>
<tr>
<td>------------</td>
<td>---------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>GIORDANO 2009</td>
<td>Usual care N=230</td>
<td>Home-based tele-management (HBT) N=230</td>
</tr>
<tr>
<td></td>
<td>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</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>determined triggered a phone call from the nurse</td>
</tr>
<tr>
<td></td>
<td></td>
<td>This included two different procedures: 1) Telemonitoring Scheduled appointments every week or 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. 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</td>
</tr>
<tr>
<td>MORTARA 2009</td>
<td>Usual care N=160</td>
<td>Home telemonitoring N=94</td>
</tr>
<tr>
<td></td>
<td>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</td>
<td>Usual care plus telemonitoring including changes in weight, blood pressure and symptoms weekly PLUS monthly telephone contact from the study nurse</td>
</tr>
<tr>
<td>SCHWARZ 2008</td>
<td>Usual care N=51 No details provided</td>
<td>Telemonitoring N=51</td>
</tr>
<tr>
<td></td>
<td>Weight and symptoms monitored. Values outside range triggered call from nurse</td>
<td></td>
</tr>
<tr>
<td>WAKEFIELD 2008</td>
<td>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.</td>
<td>Telemonitoring N=47</td>
</tr>
<tr>
<td></td>
<td>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</td>
<td></td>
</tr>
</tbody>
</table>
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.  

Table 7.10 below summarises the comparison and intervention for this study.

**Table 7.10: Comparison and intervention for Soran study**

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>SORAN 2008</td>
<td>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 commercially available digital home scale. Patients were instructed to weight themselves daily and record symptoms.</td>
<td>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</td>
</tr>
</tbody>
</table>

Data were reported on the following outcomes:
- All cause mortality (follow-up mean 6 months)
- All cause hospitalisation (follow-up mean 6 months)
### 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 for:

- 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]
- 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]

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**

**Author(s):**

**Date:** 2009-07-08

**Question:** Should telemonitoring vs standard care be used for chronic heart failure?

**Settings:**

**Bibliography:**


<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>No of patients</th>
<th>Summary of findings</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
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</thead>
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<tr>
<td>No of studies</td>
<td>Design</td>
<td>Limitations</td>
<td>Inconsistency</td>
<td>Indirectness</td>
<td>Imprecision</td>
</tr>
<tr>
<td>5</td>
<td>Antiocelli Wakefield Cleland Giordano Danksy</td>
<td>randomised trial</td>
<td>serious¹</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Cleland</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
</tr>
<tr>
<td>6</td>
<td>Antiocelli Schwarz Mortara Dar Giordano Cleland</td>
<td>randomised trial</td>
<td>serious¹</td>
<td>serious²</td>
<td>no serious indirectness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Cleland</td>
<td>randomised trial</td>
<td>no serious limitations</td>
<td>no serious inconsistency</td>
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</table>
## Chronic Heart Failure

### Draft for consultation

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Quality of Life</th>
<th>RR (95% CI)</th>
<th>MD (95% CI)</th>
<th>Rank</th>
<th>P Value</th>
</tr>
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<td>2. Dansky Schwarz</td>
<td>Randomised trial</td>
<td>No serious limitations</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>None</td>
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<tr>
<td>2. Mortara Dar Giodano Cleland</td>
<td>Randomised trial</td>
<td>Serious</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious</td>
<td>None</td>
</tr>
<tr>
<td>1. Cleland</td>
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<td>No serious limitations</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious</td>
<td>None</td>
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### Events

**All cause hospitalisation (no. of events) (follow-up 90-120 days; range of scores: -; Better indicated by less)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Quality of Life</th>
<th>RR (95% CI)</th>
<th>MD (95% CI)</th>
<th>Rank</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Dansky Schwarz</td>
<td>Randomised trial</td>
<td>No serious limitations</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
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<td>None</td>
</tr>
<tr>
<td>2. Mortara Dar Giodano Cleland</td>
<td>Randomised trial</td>
<td>Serious</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious</td>
<td>None</td>
</tr>
<tr>
<td>1. Cleland</td>
<td>Randomised trial</td>
<td>No serious limitations</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious</td>
<td>None</td>
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</tbody>
</table>

### Patients

**Heart failure hospitalisation (no. of patients) (follow-up 6 to 12 months)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Quality of Life</th>
<th>RR (95% CI)</th>
<th>MD (95% CI)</th>
<th>Rank</th>
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</thead>
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<td>No serious limitations</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>None</td>
</tr>
<tr>
<td>2. Mortara Dar Giodano Cleland</td>
<td>Randomised trial</td>
<td>Serious</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious</td>
<td>None</td>
</tr>
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<td>1. Cleland</td>
<td>Randomised trial</td>
<td>No serious limitations</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious</td>
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</tr>
</tbody>
</table>

### Days

**Heart failure hospitalisation (no. of patients), 450 days (follow-up 450 days)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Quality of Life</th>
<th>RR (95% CI)</th>
<th>MD (95% CI)</th>
<th>Rank</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
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<td>Randomised trial</td>
<td>No serious limitations</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>None</td>
</tr>
<tr>
<td>2. Mortara Dar Giodano Cleland</td>
<td>Randomised trial</td>
<td>Serious</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious</td>
<td>None</td>
</tr>
<tr>
<td>1. Cleland</td>
<td>Randomised trial</td>
<td>No serious limitations</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious</td>
<td>None</td>
</tr>
</tbody>
</table>

### Quality of Life

**Quality of life (follow-up 90 days; measured with: MLHF; range of scores: 0-105; Better indicated by less)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Quality of Life</th>
<th>RR (95% CI)</th>
<th>MD (95% CI)</th>
<th>Rank</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>2. Dansky Schwarz</td>
<td>Randomised trial</td>
<td>No serious limitations</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>None</td>
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<tr>
<td>2. Mortara Dar Giodano Cleland</td>
<td>Randomised trial</td>
<td>Serious</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious</td>
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<td>1. Cleland</td>
<td>Randomised trial</td>
<td>No serious limitations</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious</td>
<td>None</td>
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</tbody>
</table>

---

1. 3/5 unclear allocation concealment (>50% total sample size); 5/5 unclear blinding; 5/5 drop reported and < 20%; 5/5 no ITT
2. < 300 events and 95% confidence interval around the pooled estimate of effect includes both negligible effect and appreciable benefit or appreciable harm.
3. The confidence intervals do not overlap, the p value for heterogeneity is less than 0.05, and I² is 76%.
4. 2/4 unclear allocation concealment (>50% sample size); 4/4 unclear blinding; 4/4 drop outs rate stated and less than 20%; 4/4 ITT
5. 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

**Author(s):**

**Date:** 2009-07-13

**Question:** Should telemonitoring vs standard care be used for women and ethnic minorities with CHF?

**Settings:**


<table>
<thead>
<tr>
<th>No of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
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<tr>
<td>all cause mortality (follow-up mean 6 months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Soran 2008</td>
<td>randomised trial</td>
<td>serious¹</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious²</td>
<td>none</td>
</tr>
<tr>
<td>Summary of findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of patients</td>
<td>Relative (95% CI)</td>
<td>Effect</td>
<td>Absolute</td>
<td>Quality</td>
<td>Importance</td>
<td></td>
</tr>
<tr>
<td>Telemonitoring</td>
<td>Standard care</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11/160 (6.9%)</td>
<td>17/155 (11%)</td>
<td>RR 0.63 (0.30 to 1.29)</td>
<td>41 fewer per 1000 (from 77 fewer to 32 more)</td>
<td>LOW</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| all cause hospitalisation (follow-up mean 6 months) |
| 1 Soran 2008 | randomised trial | serious¹ | no serious inconsistency | no serious indirectness | serious² | none |
| Summary of findings |
| No of patients |Relative (95% CI)| Effect| Absolute|Quality|Importance |
| Telemonitoring |Standard care |
| 68/160 (42.5%) | 73/155 (47.1%) | RR 0.90 (0.71 to 1.15) | 47 fewer per 1000 (from 137 fewer to 71 more) | 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\textsuperscript{19}, 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 and presented to the GDG. The first 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)\textsuperscript{134} 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)\textsuperscript{140} 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 (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

<table>
<thead>
<tr>
<th>Study</th>
<th>Study quality*</th>
<th>Study applicability**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dar 2009\textsuperscript{134}</td>
<td>Potentially serious limitations (a)</td>
<td>Directly applicable</td>
</tr>
<tr>
<td>Scalvini 2005\textsuperscript{140}</td>
<td>Very serious limitations (b)</td>
<td>Partially applicable (c)</td>
</tr>
</tbody>
</table>

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

(a) Outcomes were not measured as QALYs; Limited health outcomes for interpreting results
(b) Small cohort size; Outcomes were not measured as QALYs; The analysis did not included 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)\textsuperscript{134}) 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 mortality outcome from this study (reported in the combined outcome ‘days alive and out of hospital’) seems to not differ between cohorts. Finally, quality of life outcomes were not reported, but the author reported no significant difference between cohorts in the change in quality of life 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 economic analysis

<table>
<thead>
<tr>
<th>Cost analysis</th>
<th>Usual care (n=91)</th>
<th>Home telemonitoring (n=91)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean direct NHS cost (SD)</td>
<td>£3,006 (£3,847)</td>
<td>£4,610 (£7,377)</td>
<td>Difference = £1,600 (p=0.2)</td>
</tr>
<tr>
<td>Median direct NHS cost (IQR)</td>
<td>£1,498 (£751-£4,053)</td>
<td>£1,688 (£878-£6,305)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Resource use estimates</th>
<th>Usual care</th>
<th>Home telemonitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause hospitalization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients hospitalized, n (%)</td>
<td>23 (25)</td>
<td>33 (36)</td>
</tr>
<tr>
<td>Number of hospitalisations</td>
<td>39</td>
<td>44</td>
</tr>
<tr>
<td>Duration of hospitalisation, median (IQR)</td>
<td>13 (8-34)</td>
<td>17 (6-25)</td>
</tr>
<tr>
<td>Heart failure hospitalisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients hospitalised, n (%)</td>
<td>10 (11)</td>
<td>17 (19)</td>
</tr>
<tr>
<td>Number of hospitalisations</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td>Duration of hospitalisation, median (IQR)</td>
<td>9 (7-33)</td>
<td>17 (8-25)</td>
</tr>
<tr>
<td>Proportion of emergency heart failure hospitalization, n (%)</td>
<td>13/16 (81)</td>
<td>8/22 (36)</td>
</tr>
<tr>
<td>Number of secondary care outpatient visits</td>
<td>733</td>
<td>622</td>
</tr>
<tr>
<td>Emergency room visits</td>
<td>32</td>
<td>20</td>
</tr>
<tr>
<td>Primary care visits</td>
<td>403</td>
<td>421</td>
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</table>

<table>
<thead>
<tr>
<th>Health outcomes</th>
<th>Usual care</th>
<th>Home telemonitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days alive and out of hospital, median (IQR)</td>
<td>180 (165-180)</td>
<td>178 (90-180)</td>
</tr>
<tr>
<td>Quality of life change</td>
<td></td>
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<td>No significant difference between groups (not reported)</td>
</tr>
<tr>
<td>MLwHF*</td>
<td>No significant difference between groups (not reported)</td>
<td>No significant difference between groups (not reported)</td>
</tr>
</tbody>
</table>

* Minnesota Living with Heart Failure questionnaire

Italian analysis
Cost and clinical outcomes from the Scalvini et al. (2005) analysis 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\textsuperscript{140} economic analysis

<table>
<thead>
<tr>
<th></th>
<th>Usual care (n=179)</th>
<th>Home-based telecardiology (n=230)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>One-year cost outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalisation cost</td>
<td>£121,673</td>
<td>£82,646</td>
<td>N/A</td>
</tr>
<tr>
<td>Telecare service cost</td>
<td>N/A</td>
<td>£10,197</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Total cost</strong></td>
<td>£121,699</td>
<td>£92,863</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>One-year clinical outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization, n (%)</td>
<td>61 (34)</td>
<td>56 (24)</td>
<td>0.62 (0.43-0.81)</td>
</tr>
<tr>
<td>Patients with instability, n (%)</td>
<td>74 (41)</td>
<td>60 (26)</td>
<td>0.50 (0.32-0.68)</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>22 (12)</td>
<td>6 (7)</td>
<td>0.50 (0.20-0.80)</td>
</tr>
</tbody>
</table>

7.2.6 Summary of evidence statements

The use of tele-monitoring in the management of chronic heart failure was reviewed through
eight randomised controlled trials \textsuperscript{131, 132, 133, 134, 135, 136, 137, 138}, and one extra RCT \textsuperscript{139} of a
cohort composed of women and non-Caucasian older male adults.

The outcomes reported were all cause mortality, all-cause hospitalisation (number of
patients), all-cause hospitalisation (number of events), heart failure hospitalisation and
quality of life as assessed by Minnesota Living With Heart Failure questionnaire.

Compared to standard medical care, tele-monitoring led to a significant reduction of all
cause mortality (450 days) and all cause hospitalisation (number of patients, at 8-12 months
of follow up). There was no significant difference between the two strategies with regards to
the remaining measured outcomes.

Importantly, however, it was not clear to most of the authors, as to whether the above effects
were due to tele-monitoring per se or to the improvement in access to care by the patients
assigned to tele-monitoring. The conclusions from many of the studies have pointed towards
the latter being the reason for improvement in the outcomes.

In addition, there was the study by Soran (2008) \textsuperscript{139} that recruited 315 patients who were
women and non-Caucasian males with heart failure. The data on the patients assigned to
the tele-monitoring group was delivered to the specialist team on daily basis.

In this latter study, the authors compared standard care to tele-monitoring in terms of all
cause mortality and all cause hospitalisation. No significant difference was found between
the two groups.

The health economic review identified the study by Scalvini (2005) \textsuperscript{140}. This was based on
the Italian health system (healthcare system reasonably comparable to the UK NHS). It
suggested that tele-cardiology is more efficient and less costly than standard care in the
management of heart failure patients. In this analysis, interactive telemonitoring (including
telephone support and self-monitoring with an ECG portable device) was added to usual
care. It is not clear if telephone support was offered to the usual care cohort.

In addition, a cost analysis was reported as part of the study by Dar (2009) \textsuperscript{134} (included by
the clinical review). This cost assessment was conducted from a UK NHS perspective. The
cost analysis concluded that home telemonitoring is more costly than usual care. In this
study, the addition to usual care of telemonitoring was mainly self-monitoring, and telephone
support was offered to both cohorts of patients. Furthermore, looking at the quality of life
outcomes, mortality outcomes, and the cost analysis reported by Dar (2009) \textsuperscript{134}, home
telemonitoring as was assessed in this trial is not likely to be cost-effective.
7.2.7 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 provide opportunities for the patients to access expert opinion, support and further educational encounters with the specialist team. 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 outpatients appointment with a specialist in heart failure or cardiologist plus primary care visits.

The trials reviewed showed an improvement of the all-cause mortality (450 days) and all cause hospitalisation rates, when the strategy of tele-monitoring, that included intensive reviews and contact with the specialist team, was compared to standard care. On the other hand, there was no evidence of harm caused by applying the former strategy. In some studies, there was an increase in the number of hospitalisations. These, however, were appropriate admissions and they were not prolonged, probably due to early detection of markers of deterioration by the use of the tele-monitoring strategy. The study by Soran while negative, has shown that the intensive care involvement by the nurses including education, made the need for tele-monitoring null.

Quality of evidence

The only evidence of high quality was that of lack of difference in all cause hospitalisation (450 days)

The GDG noted that the tele-monitoring was always associated with augmented opportunity 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 good communication, 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:

1. Whether tele-monitoring will result in more hospitalisations and more referrals to the cardiology services?

2. 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), which was the largest in the review, was associated with slightly more investigations. However, there were fewer interventions and fewer referrals to the cardiologists in the home tele-monitoring arm of the study. At one year, the telemonitoring strategy in this trial was associated with less hospitalisation and lesser cost.
In the home tele-monitoring arm of the Cleland study (2005)\textsuperscript{132}, on the other hand, there was increased uptake of both the aldosterone antagonist spironolactone and beta-blockers. Besides, this trial had older patients, who are probably the more appropriate cohort for such a strategy. The GDG noted though that tele-monitoring will not be appropriate for all older adults with heart failure.

However, the GDG is not convinced that the reduced all cause hospitalisation rate and reduced heart failure hospitalisation rate seen in some trials were direct products of tele-monitoring. The GDG noted that the outcomes could have been related to the more frequent contact with the specialist team. The latter would lead to more uptake and up-titration of therapy, as well as earlier detection of signs of deterioration.

The GDG recommends further research into this topic

\textbf{Trade-off between net health benefits and resource use}

The Italian study\textsuperscript{140} 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)\textsuperscript{134} 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.

\textbf{7.2.8 Recommendations}

Given the limitations of the evidence, the GDG did not find it appropriate to make specific recommendations for home telemonitoring, but agreed that a research recommendation should be made.

\textbf{7.3 Recommendations for monitoring heart failure:}

\textbf{Clinical Review}

<table>
<thead>
<tr>
<th>R67</th>
<th>All patients with chronic heart failure require monitoring. This monitoring should include:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• a clinical assessment of functional capacity, fluid status, cardiac rhythm (minimum of examining the pulse) fluid status, cognitive status and nutritional status</td>
</tr>
<tr>
<td></td>
<td>• a review of medication, including need for changes and possible side effects</td>
</tr>
<tr>
<td></td>
<td>• serum urea, electrolytes and creatinine\textsuperscript{10}. [2003, R60]</td>
</tr>
</tbody>
</table>

\textsuperscript{10} 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
R68 More detailed monitoring will be required if the patient has significant co-morbidity or if their condition has deteriorated since the previous review. [2003, R61]

R69 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, R62]

R70 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, R64].

R71 Ongoing management of patients admitted to hospital with heart failure should be guided by the opinion of a specialist in heart failure. [new 2010].

Serum digoxin

R72 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, R64]

R73 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, R65].

Serum natriuretic peptides

R74 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].
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:  
- Referral (Chapter 12)  
- Supporting patients and carers (Chapter 13)  
- Anxiety and depression (Chapter 14)  
- End of Life (Chapter 15)  
- Prevention (Chapter 16)

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.

R75 Patients with heart failure require specialist advice in the following situations:  
- Initial diagnosis of heart failure with left ventricular systolic dysfunction  
- Heart failure due to valve disease, heart failure with preserved ejection fraction or other cause  
- One or more of the following co-morbidities: COPD, renal dysfunction, anaemia, thyroid disease, peripheral vascular disease, urinary frequency, and gout  
- Angina, atrial fibrillation or other symptomatic arrhythmia  
- Women who are planning a pregnancy or who are pregnant. [new 2010]

R76 The following situations also require specialist advice:  
- severe heart failure  
- heart failure that does not respond to treatment  
- heart failure that can no longer be managed effectively in the home setting. [2003 R67]

Discharge planning

R77 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, R68]

R78 The primary care team, patient and carer must be aware of the management plan. [2003, R69]

R79 Clear instructions should be given as to how the patient/carer can access advice particularly in the high-risk period immediately following discharge. [2003, R70]

Multidisciplinary team approach to heart failure management

R80 Heart failure care should be delivered by a multidisciplinary team with an integrated approach across the healthcare community. [2003, R71]
Non-NHS agencies

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, R72]

R81 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, R73]

R82 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, R74]

R83 The education needs of non-NHS agency carers should be considered. [2003, R75]

Communication

For guidance on Medicines adherence refer to the NICE guideline:


R84 Good communication between healthcare professionals and patients and carers is essential for the best management of heart failure. [2003, R76]

R85 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, R77]

R86 The content, style and timing of information provision should be tailored to the needs of the individual patient. [2003, R78]

R87 Healthcare professionals should assess cognitive ability when sharing information. [2003, R79]

R88 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, R80]

R89 Management of heart failure should be seen as a shared responsibility between patient and healthcare professional. [2003, R81]
**Prognosis**

R91 Prognosis should be discussed with patients and carers in a sensitive, open and honest manner. [2003, R83]

**Support groups**

R92 Healthcare professionals should be aware of local cardiac support networks and provide this information to patients and carers. [2003, R84]

**Anxiety and depression**

For guidance on managing depression refer to the NICE guidelines:


R93 The diagnosis of depression should be considered in all patients with heart failure. [2003, R85]

R94 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, R86]

R95 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, R87]

R96 For patients with heart failure, the potential risks and benefits of drug therapies for depression should be considered carefully. [2003, R88]

R97 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, R89]

**End of life**

R98 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, R90]

R99 The palliative needs of patients and carers should be identified, assessed and managed at the earliest opportunity. [2003, R91]

R100 Patients with heart failure and their carers should have access to professionals with palliative care skills within the heart failure team. [2003, R92]
9 Research recommendations

Having reviewed the current evidence around several diagnostic and therapeutic questions, the Guidelines 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 for the National Institute of Health and Clinical Excellence. 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

<table>
<thead>
<tr>
<th>Research recommendation/question:</th>
</tr>
</thead>
<tbody>
<tr>
<td>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?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure with preserved ejection fraction</td>
<td>Angiotensin converting enzyme and/or Beta-blocker</td>
<td>placebo</td>
<td>Mortality (all cause, heart failure)</td>
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<td>Hospitalisation (heart failure, all cause)</td>
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<td>Change in NYHA class</td>
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<td>Quality of life</td>
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<td>Adverse events</td>
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</table>

Why this is important:

At least half of the people with heart failure in the community have preserved left ventricular ejection fraction. Research has focussed on heart failure with left ventricular systolic dysfunction and found several agents to be beneficial (notably ACEI, 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.

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure due to LVSD</td>
<td>Telemonitoring Or BNP</td>
<td>Clinical care</td>
<td>Mortality (all cause, heart failure)</td>
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<td></td>
<td>Hospitalisation (heart failure, all cause, planned, unplanned)</td>
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<td>Change in NYHA class</td>
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<td>Patient/carer acceptability</td>
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<td></td>
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<td>Quality of life</td>
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<td>Adverse events</td>
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</table>

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 focussed on telemonitoring (the patient's condition is supervised, with electronic support, in the patient's own home) and the use of natriuretic peptides (up titration of drugs is guided by natriuretic peptide levels) 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, where 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 heart failure team.

The role of natriuretic 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?

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>Natriuretic peptides</td>
<td>Clinical care</td>
<td>Mortality (all cause, heart failure)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hospitalisation (heart failure, all cause, planned, unplanned)</td>
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</tbody>
</table>
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 (ARB) in patients with heart failure due to left ventricular systolic dysfunction who are intolerant of angiotensin converting enzyme (ACE) inhibitors?

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure with LVSD and intolerant to ACE inhibitor</td>
<td>Spironolactone</td>
<td>Angiotensin receptor blocker</td>
<td>Mortality (all cause, heart failure)</td>
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<td></td>
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<td>Hospitalisation (heart failure, all cause)</td>
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<td></td>
<td>Adverse events</td>
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</table>

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. However, at least 10% of patients may be intolerant of ACE inhibitors. Current guidance recommends substituting the ACE inhibitor with an ARB,, but this may be less effective. Inhibition of the renin-angiotensin-aldosterone system with spironolactone has also been shown to be beneficial in patients (most of whom were taking an ACE inhibitor). It is therefore important to know whether Aldosterone antagonist or an ARB, in combination with a beta-blocker, is the most effective method for inhibition of the renin-angiotensin-aldosterone system when ACE inhibitors are not tolerated.
Hydralazine and/or nitrates for heart failure with preserved left ventricular ejection fraction

Research recommendation/question:
What is the comparative effectiveness of vasodilator therapy with nitrates, hydralazine or both in patients with heart failure and preserved ventricular ejection fraction?

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure with preserved ventricular ejection fraction</td>
<td>Nitrate and/or hydralazine</td>
<td>Placebo</td>
<td>Mortality (all cause, heart failure)</td>
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<td>Hospitalisation (heart failure, all cause)</td>
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<td>Adverse events</td>
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</table>

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. Studies have indicated that in white patients with left ventricular systolic dysfunction, the combination of nitrate and hydralazine is superior to placebo. In black patients with left ventricular systolic dysfunction the combination has been shown to improve prognosis in patients already taking beta-blockers and ACE inhibitors.

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 (through ventriculo–vascular coupling) 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, alone or in combination, would benefit patients with heart failure and preserved left ventricular ejection fraction.
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