Full version of
NICE Clinical guideline 108

CHRONIC HEART FAILURE

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

Appendices
(except E, F, G, M)

August 2010

Royal College of Physicians
Setting higher medical standards

Chronic heart failure update: Appendices

Appendix A - Scope of partial update

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

SCOPE

1 Guideline title

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

1.1 Short title

Chronic heart failure (partial update)

2 Background

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

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

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

3 Clinical need for the guideline

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

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

4 The guideline

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

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

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

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

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

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

4.1 Population

4.1.1 Groups that will be covered

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

4.1.2 Groups that will not be covered

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

b) Pregnant women.

4.2 Healthcare setting

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

4.3 Clinical management

4.3.1 Topics that will be updated

a) Diagnosing heart failure:

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

b) Pharmacological treatment of heart failure, for example:

- aldosterone antagonists
- angiotensin II receptor antagonists.

c) Invasive procedures:

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

d) Disease monitoring in chronic heart failure:

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

e) Cardiac rehabilitation for heart failure.

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

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

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

4.3.2 Topics that will not be updated

The following topics will not be updated.

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

b) Pharmacological treatments to modify cardiovascular risk.

c) Comorbidities.

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

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

f) Oxygen therapy and continuous positive airways pressure treatment.

g) Review of management plans.

h) Serial cardiac imaging.

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

j) Supporting patients and carers.

k) Anxiety and depression.

l) End of life.

m) Prevention.

4.4 Status

4.4.1 Scope

This is the final scope.

The guideline will partially update the following NICE guidance.

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

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

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

4.4.2 Guideline

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

5 Related NICE guidance

Published

1. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. NICE clinical guideline 67 (2008). Available from www.nice.org.uk/CG67

2. Type 2 diabetes: the management of type 2 diabetes. NICE clinical guideline 66 (2008). Available from www.nice.org.uk/CG66
3. MI secondary prevention: secondary prevention in primary and secondary care for patients following a myocardial infarction. NICE clinical guideline 48 (2007). Available from www.nice.org.uk/CG48
4. Atrial fibrillation: the management of atrial fibrillation. NICE clinical guideline 36 (2006). Available from www.nice.org.uk/CG36
5. Hypertension: management of hypertension in adults in primary care. NICE clinical guideline 34 (2006). Available from www.nice.org.uk/CG34
6. Short term circulatory support with left ventricular assist devices as a bridge to cardiac transplantation or recovery. NICE interventional procedure guidance 177 (2006). Available from www.nice.org.uk/IPG177

6 Further information

The guideline development process is described in:

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

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

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

Appendix: Scope for NICE clinical guideline

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

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

1 Objective

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

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

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

2 Title

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

Clinical Need and Practice[a]

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

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

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

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

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

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

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

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

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

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

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

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

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

Role of lifestyle advice

- Role of surgical interventions to treat or relieve symptoms

Population

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

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

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

Health care setting

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

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

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

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

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

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

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

Interventions and treatment

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

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

The guidelines will consider

2.15 Diagnosis

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

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

2.16 Pharmacological treatments:

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

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

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

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

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

2.17.1 exercise programmes

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

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

Presentation

The guideline will be available in three forms:

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

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

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

Status

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

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

Appendix B – Clinical Questions

DIAG: symptoms and signs vs gold standard

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

BNP1: natriuretic peptides vs gold standard

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

BNP2: natriuretic peptides vs echocardiography

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

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

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

ACE: Angiotensin converting enzyme inhibitors

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

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

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

ARB1: angiotensin II receptor antagonists vs placebo

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

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

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

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

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

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

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

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

MONIT: patient telemonitoring vs out patient monitoring

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

REHAB: exercise based cardiac rehabilitation

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

Appendix C – Review protocols

DIAG: Diagnostic accuracy of symptoms and signs

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

✓ All Chronic Heart failure

☐ Other

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

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

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

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

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

Language:
✓English</td><td>Databases

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

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

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

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

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

D: REVIEW STRATEGY

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

Restricting to systematic reviews

May be updating existing meta-analysis.

Subgroups:

Populations to be identified:

Patients with LVSD

Patients with PLVEF

E. EQUALITIES ISSUES

Possible subgroups may be:

Different age groups; Different ethnicities; male/female

BNP1: Diagnostic accuracy of natriuretic peptides vs gold standard

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

✓ All Chronic Heart failure

☐ Other

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

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

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

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

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

Language:
✓English</td><td>Databases

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

BNP
NT-pro BNP
Natriuretic peptides

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

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

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

D: REVIEW STRATEGY

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

May be updating existing meta-analysis.

Subgroups:

Populations to be identified:

Patients with LVSD

Patients with PLVEF

E. EQUALITIES ISSUES

Possible subgroups may be:

Different age-groups ; Different ethnicities; male/female

BNP2: Diagnostic accuracy of natriuretic peptides vs echocardiography

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

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

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

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

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

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

Language:
✓English</td><td>Databases

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

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

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

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

D: REVIEW STRATEGY

Limit to symptomatic patients

E. EQUALITIES ISSUES

Possible subgroups may be:

Different age-groups; different ethnicities; male/female

BNP3: Natriuretic peptide guided therapy

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

✓ All Chronic Heart failure

☐other

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

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

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

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

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

Language:
✓English</td><td>Databases

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

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

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

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

ACE: Efficacy and safety of Angiotensin converting enzyme inhibitors

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

☐ All Chronic Heart failure

✓HF with PLVEF

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

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

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

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

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

Language:
✓English</td><td>Databases

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

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

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

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

D: REVIEW STRATEGY

Subgroups:

Populations to be identified:

Older people

E. EQUALITIES ISSUES

Possible subgroups may be:

Different age groups; Different ethnicities; male/female

ALDO: Efficacy and safety of Aldosterone antagonists

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

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

B: OBJECTIVES:

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

✓ All Chronic Heart failure

☐ Other

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

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

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

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

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

Language:
✓English</td><td>Databases

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

Aldosterone receptor antagonists
Eplerenone
Spironolactone

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

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

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

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

ARB1: Efficacy and safety of angiotensin II receptor antagonists

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

✓ All Chronic Heart failure

☐ Other

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

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

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

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

☐ All years
☐ 1966-
✓ 1986-
☐ 1995-

Language:
✓English</td><td>Databases

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

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

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

Formatted: German (Germany)

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

D: REVIEW STRATEGY

Note: Papers included in ARB2 will not be included here

Subgroups: Populations to be identified:

patients with PLVEF (preserved left ventricular ejection fraction)

E. EQUALITIES ISSUES

Possible subgroups may be:

Different ethnicities; male/female; Different age groups

ARB2: Efficacy and safety of ARBs + ACEI

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

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

B: OBJECTIVES:

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

✓ All Chronic Heart failure

☐ Other

Exclusions: right heart failure due to

Respiratory disease</td><td>Demographics

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

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

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

☐ All years
☐ 1966-
✓ 1986-
☐ 1995-

Language:
✓English</td><td>Databases

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

Angiotensin-II receptor antagonists/blockers

ARB

Candesartan valsartan losartan irbesartan eprosartan olmesartan telmisartan

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

a)ACE I + placebo

b)Placebo + ACEI + BB

Outcomes

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

2. renal failure

3. qol

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

Formatted: German (Germany)

D: REVIEW STRATEGY

Subgroups:

Populations to be identified:

Patients with LVSD

E. EQUALITIES ISSUES

Possible subgroups may be:

Different age groups; Different ethnicities; male/female

BB: Efficacy and safety of beta blockers

<table>
<tr><td colspan="5">REVIEW PROTOCOL GDG3</td></tr>
<tr><td colspan="5">A: REVIEW QUESTION: BB
What is the efficacy and safety of beta blockers in comparison to placebo, optimal medical management or other beta blockers in people with chronic heart failure?
B: OBJECTIVES:
To assess the role of beta blockers in people with heart failure especially in the following two sub-populations; elderly people; non LVSD population</td></tr>
<tr><td colspan="5">C: SEARCH CRITERIA AND PICO</td></tr>
<tr><td>Population

✓ All Chronic Heart failure

☐ Other

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

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

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

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

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

Language:
✓English</td><td>Databases

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

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

D: REVIEW STRATEGY

Subgroups:

Populations to be identified:

The elderly (BB v placebo)

Non LVSD (BB v placebo)

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

E. EQUALITIES ISSUES

Possible subgroups may be:

Different age groups; Different ethnicities; male/female

ISO: Efficacy and safety of isosorbide/hydralazine

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

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

B: OBJECTIVES:

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

✓ All Chronic Heart failure

☐ Other

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

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

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

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

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

Language:
✓English</td><td>Databases

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

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

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

MONIT: Efficacy and safety of telemonitoring

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

✓ All Chronic Heart failure

☐ Other

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

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

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

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

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

Language:
✓English</td><td>Databases

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

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

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

D: REVIEW STRATEGY

Subgroups:

Populations to be identified: appropriateness/ language barrier issues

Subgroup according to intervention given

E. EQUALITIES ISSUES

Possible subgroups may be:

Different age groups; Different ethnicities; male/female

REHAB: Efficacy and safety of exercise based cardiac rehabilitation

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

✓ All Chronic Heart failure

☐ Other

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

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

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

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

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

Language:
✓English</td><td>Databases

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

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

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

D: REVIEW STRATEGY

Subgroups:

Populations to be identified: All chronic heart failure

E. EQUALITIES ISSUES

Possible subgroups may be :

Different age groups; different ethnicities; male/female

Appendix D Search strategies

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

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

Searches were constructed using the PICO format.

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

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

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

Chronic Heart Failure Population Search strategies

Medline search terms

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

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

Embase search terms

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

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

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

Cinahl search terms

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

Cochrane search terms

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

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

Generic study type search filters

Medline and Embase systematic reviews search terms

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

Medline randomised controlled trials search terms

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

14. or/1-13

Medline observational studies search terms

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

Medline diagnostic studies search terms

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

Medline prognostic studies search terms

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

Embase randomised controlled trials search terms

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

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

Embase observational studies search terms

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

Embase diagnostic studies search terms

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

Embase prognostic studies search terms

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

3.1 or 2

Cinahl and Cochrane generic study type search filters

None used **except** in Question DIAG

Cinahl diagnostic studies search terms (DIAG only)

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

S1 diagnos* or specificity

S2 (MH "Sensitivity and Specificity")

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

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

S5 S1 or S2 or S3 or S4

Cochrane diagnostic studies search terms (DIAG only)

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

Clinical Questions and intervention search strategies

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

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

Intervention search strategies

Medline search terms

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

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

Embase search terms

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

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

Cinahl search terms

S1 (MH "Dyspnea+")

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

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

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

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

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

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

Cochrane search terms

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

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

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

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

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

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

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

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

<u>Intervention search strategies</u>

Medline search terms

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

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

Embase search terms

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

Cinahl search terms

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

Cochrane search terms

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

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

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

<u>Intervention search strategies</u>

Medline search terms

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

4. or/1-3

Embase search terms

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

Cinahl search terms

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

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

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

S4 S1 or S2 or S3

Cochrane search terms

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

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

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

Intervention search strategies

Medline search terms

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

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

Embase search terms

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

Cinahl search strategy

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

Cochrane search terms

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

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

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

Questions ARB1 and ARB2 were run as one search

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

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

Intervention search strategies

Medline search terms

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

Embase search terms

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

Cinahl search terms

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

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

S3 S1 or S2

Cochrane search terms

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

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

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

Intervention search strategies

Medline search terms

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

Embase search terms

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

Cinahl search terms

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

Cochrane search terms

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

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

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

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

Intervention search strategies

Medline search terms

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

Embase search terms

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

9. or/1-8

Cinahl search terms

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

Cochrane search terms

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

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

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

Intervention search strategies

Medline search terms

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

Embase search terms

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

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

Cinahl search terms

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

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

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

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

S5 S1 or S2 or S3 or S4

Cochrane search terms

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

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

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

<u>Intervention search strategies</u>

Medline search terms

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

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

Embase search terms

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

Cinahl search strategy

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

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

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

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

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

S5 S1 or S2 or S3 or S4

Cochrane search terms

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

Economics Search

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

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

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

Medline economic filter search terms

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

Embase economic filter search terms

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

Appendix E – Clinical Evidence Tables **(see separate file)**

See separate file

Appendix F – Forest Plots (see separate file)

See separate file

Appendix G – HE Evidence Tables (see separate file)

Appendix H – Cost-effectiveness analysis

Cost-effectiveness analysis of serial measurement of circulating natriuretic peptide concentration in patients with heart failure

1. Background

Brain natriuretic peptide (BNP) and its aminoterminal portion (N-BNP) are secreted primarily from the left ventricle in response to changes in left ventricular wall stretch[1]. These agents are neurohormonal predictors of left-ventricular function and prognosis[2, 3, 4, 5]. The diagnostic and prognostic value of natriuretic peptide plasma level in heart failure was supported by many studies[6, 7, 8, 9, 10,11]. It was also proven that most drugs used to treat heart failure significantly reduce natriuretic peptide level[12,13,14,15,16,17].

Treatment optimization for patients with heart failure is based on physician assessment and patient tolerance. Circulating natriuretic peptide concentration can be reduced by intensification of drug therapy in heart failure, and monitoring plasma natriuretic peptide level has been proposed for optimizing medical treatment. Four randomised clinical trials were published comparing the management of patients' medical treatment according to natriuretic peptide concentration versus clinical assessment in secondary care and/or usual care in the community[18,19,20,21]. These clinical trials reported that serial measurement of natriuretic peptide concentration improved outcomes compared to clinical assessment or usual care.

In England and Wales, natriuretic peptide measurement is available but its use as a monitoring tool is not widespread. National implementation might significantly affect resource use in the NHS. One cost-effectiveness analysis was published assessing the management of medical treatment in chronic heart failure using BNP measurement compared to clinical assessment[22]. This analysis was based on one clinical trial[18] and it showed that BNP monitoring was cost-effective. However, this analysis was developed from a US perspective, and the generalisation of these results to a UK context is questionable. Furthermore, there is now considerably more trial evidence. Therefore, we undertook an original cost-effectiveness analysis from a UK NHS and personal social services perspective.

2. Objective

The objective of this economic analysis was to assess the cost-effectiveness of three alternative strategies:

- serial measurement in secondary care of circulating natriuretic peptide concentration for optimizing medical therapy
- clinical assessment in secondary care
- usual care in the community

for patients in England and Wales with

1. chronic heart failure (CHF) , or
2. CHF and left ventricular systolic dysfunction (LVSD).

3. Model

In a systematic clinical review[see Section 7.1.2 of Full Guideline (2010)], four clinical trials were identified assessing serial measurement of natriuretic peptide concentration for optimizing the medical therapy in CHF (Troughton 2000[18], Jourdain 2007[20], Pfisterer 2009[19], Lainchbury 2010[21])[b]. Trougton 2000[18], Jourdain 2007[20], and Pfisterer 2009[19] compared serial measurement in secondary care of natriuretic peptide concentration and clinical assessment in secondary care. Lainchbury 2010[21] compared natriuretic peptide measurement in secondary care, clinical assessment in secondary care, and usual care in the community.

The Trougton 2000[18], Jourdain 2007[20], and Pfisterer 2009[19] clinical trials were conducted in patients with CHF and LVSD. Lainchbury 2010 clinical trial[21] was conducted on patients with CHF of any causes. Hence, outcomes of the three clinical trials on patients with LVSD [18], [20], [19] were meta-analysed for use in this economic analysis, and outcomes from the Lainchbury clinical trial[21] were utilized independently. Furthermore, age subgroups were assessed in Pfisterer[19] (<75 years / ≥75 years) and Lainchbury[21] (≤75 years / >75 years), and cost-effectiveness analyses were therefore conducted for these subgroups.

The same mortality rate and yearly cost per patient were assumed for each intervention after the trial periods (Section 4.1.2 and 5.6). A lifetime horizon was used when the number of patients who were alive differed between the compared cohorts at the end of the trial follow-up. When the same number of patient was alive in each trial arm at the end of the trial, the trial period was used as the model time horizon. It was judged that the same number of patient were alive in the three compared cohorts at the end of Lainchbury main analysis, and between the clinical assessment and the usual care cohorts in Lainchbury age-subgroup analyses (≤75 years / >75 years) (Table 1) [21]. Therefore, cost-effectiveness assessments were conducted on these analyses on a three-year time horizon. In addition, for Lainchbury[21] age subgroups, cost-effectiveness assessments were conducted on a lifetime horizon as a higher proportion of patients were alive at the end of the trial in natriuretic peptide cohorts in comparison to clinical assessment or usual care.

Cost-effectiveness analyses were developed from an England and Wales NHS perspective; the health outcome considered was Quality-Adjusted Life Year (QALY), and an annual discount rate of 3.5% was applied to both costs and health outcomes incurred after one year.

Table 1

Mortality (all-cause)* - Risk ratios (95% confidence intervals)				
Analysis	**Trial follow-up**	**Natriuretic peptide vs clinical assessment**	**Usual care vs clinical assessment**	**Natriuretic peptide vs usual care**
Jourdain	15 months	0.64 [0.26; 1.58]	N/A	N/A
Pfisterer all ages	18 months	0.72 [0.5; 1.04]	N/A	N/A
Pfisterer <75 years	18 months	0.47 [0.24; 0.92]	N/A	N/A
Pfisterer ≥75 years	18 months	0.91 [0.61; 1.37]	N/A	N/A
Lainchbury all ages	3 years	1.00 [0.7; 1.43]	0.99 [0.69, 1.42]	1.01 [0.70, 1.44]
Lainchbury ≤75 ages	3 years	0.50 [0.24; 1.03]	1.01 [0.59, 1.73]	0.50 [0.25, 1.00]
Lainchbury >75 ages	3 years	1.41 [0.93; 2.14]	0.99 [0.61, 1.61]	1.43 [0.92; 2.20]

* Troughton did not report all-cause mortality

[b] Beck-da-Silva published in 2005 results from a RCT[23] assessing serial measurement of natriuretic peptide concentration for beta-blocker up-titration as opposed to monitoring the entire drug usage in Troughton 2000[18], Jourdain 2007[20], Pfisterer 2009[19], and Lainchbury 2010[21]. For this reason, and considering that Beck-da-Silva trial[23] has a small cohort size (N=41) and did not reported sensible outcomes for economic modelling (all-cause mortality and heart failure-related hospitalizations), this study was not utilized for this economic analysis.

4. Quality-Adjusted Life Year

Quality-Adjusted Life Years (QALYs) are calculated by multiplying the patients' life expectancy (life years) by a utility score (a quality of life measure on a 0-1 scale).

4.1 Mortality

Within-trial mortality estimates were taken from the clinical trials themselves. Patients' mortality post-trial was assumed the same for each compared cohort in all the analyses. Post-trial mortality estimates were taken from the UK-based study conducted on patients with heart failure by Guili 2005[24].

4.1.1 Mortality within-trial

Two techniques were used to estimate life years for the within-trial periods. When survival curves were available, life years where calculated as the area under the survival curve. Alternatively, risk ratios at the end of trials were used assuming deaths occurred evenly over the trial follow-up period.

The area under the curve was calculated for assessments developed from Lainchbury[21] and Pfisterer[19]. Table 2 shows life years calculated from survival curves. As explained in Section 6, the Pfisterer trial[19] (all ages) was modelled independently as a sensitivity analysis.

Table 2

Within-trial life years* calculated as the area under the survival curve				
Analysis	**Trial follow-up**	**Natriuretic peptide**	**Clinical assessment**	**Usual care**
Lainchbury all ages	3 years	2.51 (2.44)	2.48 (2.41)	2.37 (2.30)
Lainchbury ≤75 years	3 years	2.75 (2.67)	2.46 (2.39)	2.31 (2.25)
Lainchbury >75 years	3 years	2.29 (2.23)	2.47 (2.40)	2.40 (2.33)
Pfisterer all ages	18 months	1.35 (1.34)	1.27 (1.26)	N/A
Pfisterer <75 years	18 months	1.41 (1.40)	1.31 (1.30)	N/A
Pfisterer ≥75 years	18 months	1.28 (1.26)	1.26 (1.24)	N/A

* Undiscounted (discounted); Discounting at 3.5% was applied after one year

Risk ratios were used to calculate life years in the cost-effectiveness assessment based on trials conducted on patients with CHF and LVSD (Troughton[18], Jourdain[20], and Pfisterer[19]). The meta-analysed risk ratio (Table 3) was applied at 18 months (Pfisterer trial[19] follow-up[c]). The baseline risk used was the death risk from Pfisterer[19], the largest trial, in the clinical assessment cohort at 18 months (Table 3). In addition, we modelled as part of the sensitivity analysis (Section 6) Jourdain[20] and Pfisterer[19] independently (Table 3).

Table 3

Mortality all-cause*					
	Risk ratio for natriuretic peptide vs clinical assessment at final follow-up (95% CI) { a }	**Probability of death**		**Mean life years Within trial follow-up period**	
Trial**		**Clinical assessment { b }**	**Natriuretic peptide { c = a x b }**	**Natriuretic peptide**	**Clinical assessment**

[c] The Pfisterer trial[19] follow-up (18 months) was the longest of the meta-analysed trials (15 months for Jourdain[20] and 9.5 months for Troughton[18]). Troughton[21] did not report all-cause mortality but only cardiovascular deaths.

Jourdain (15 months)	0.64 (0.26; 1.58)	0.100	0.064	1.21	1.19
Pfisterer (18 months)	0.72 (0.5; 1.04)	0.222	0.160	1.38	1.33
Meta-analysis	**0.70 (0.5; 0.99)**	**0.222[¥]**	**0.155**	**1.38**	**1.33**

* Discounting has not been applied

** Troughton 2000[18] did not report all-cause mortality

[¥] Assumed to be the same as Pfisterer[19], the largest trial.

4.1.2 Mortality post-trial

Giuli 2005[24] reported outcomes from an observational study using the *General Practice Research Database* in the UK. This study aimed to determine the incidence and prognosis of heart failure (HF) diagnosed by general practitioners. Incident cases of HF in 1991 were selected and followed for three-years. 686,884 patients 45 years and older were classified as definite HF, possible HF, or a prescription of diuretics without a diagnosis of HF. 6478 patients were classified as definite HF[d], and outcomes from this subgroup were considered relevant for this cost-effectiveness analysis.

The mean survival time for definite HF was 23.8 months (95% CI 23.4–24.1), 22.9 months in men and 24.5 months in women (p<0.001). The median survival was 30.8 and 36.5 months in men and women respectively. Sex- and age-group standardised mortality ratios (SMR) were reported. Each SMR was the ratio of the cumulative probability of dying in the study population to the cumulative probability of dying in an age and sex matched sample from the general population in England and Wales. We adjusted the SMRs to account for the effect on survival of ACEI and BB using data from meta-analyses by Flather 2000[25] for ACEI and Shibata 2001[26] for BB assuming no interaction between the two drugs[e]. Table 4 presents both the unadjusted SMR estimates from Guilli 2005[24] (untreated), and our adjusted estimates, which we used in our cost-effectiveness analysis.

Table 4

Standardised mortality ratios (definite HF vs general population)			
		SMR (untreated)	**SMR (treated)**
SMR male	65-74 years	5.73	2.80
	75-84 years*	4.07	2.00
	85+ years	2.41	1.18
SMR female	65-74 years	7.18	3.52
	75-84 years*	4.80	2.35
	85+ years	2.42	1.19

*SMR were presented by Guili 2005[24] for age subgroups 65-74 years and 85+ years at 3 years from diagnosis. Estimates for the age subgroup 75-84 years were assumed to be the unweighted average of the two other age subgroups.

We estimated life expectancy beyond the trial follow-up using the official life tables for England and Wales[27] but adjusting the mortality using the CHF-specific SMRs (Table 4). The life expectancies were based on the mean age at baseline from the trials and were at first calculated for men and women separately[18], [19], [20], [21]. Then, we calculated the average life expectancy for both sexes using the male/female ratio at baseline in clinical trials[18], [19], [20], [21]. Table 5 presents the life expectancies from trial baseline considered for our economic analysis.

Table 5

Life expectancy from baseline						
Analysis		**Mean age at**	**Males**		**Undiscounted**	**Discounted life**

[d] 45% men (n=2884), mean age 75 years (SD=9); 55% women (n=3594), mean age 79 years (SD=9).

[e] Effect of ACEI versus placebo: RR=0.86 (95% CI 0.81-0.91); Effect of BB versus placebo: RR=0.57 (95% CI 0.51-0.64); Combined effect of ACEI and BB = 0.4902.

	Trial follow-up	baseline** (years)	%**	Cohort	life expectancy (years)	expectancy* (years)
Lainchbury all ages	3 years	76	64%	NP	7.14	6.22
				Clinic	7.14	6.22
				UC	7.16	6.24
Lainchbury ≤75 years	3 years	69[¥]	64%[¥¥]	NP	10.34	8.44
				Clinic	9.00	7.45
				UC	8.97	7.43
Lainchbury >75 years	3 years	82[¥]	64%[¥¥]	NP	5.70	5.17
				Clinic	6.46	5.78
				UC	6.48	5.79
LVSD meta-analysis	18 months[Ω]	70	64%	NP	8.90	7.25
				Clinic	8.25	6.73
Jourdain	15 months	66	58%	NP	11.44	8.99
				Clinic	11.02	8.67
Pfisterer all ages	18 months	76	66%	NP	6.99	6.58
				Clinic	6.53	6.15
Pfisterer <75 years	18 months	69	75%	NP	9.64	7.81
				Clinic	8.51	6.91
Pfisterer ≥75 years	18 months	82	59%	NP	5.43	4.77
				Clinic	5.29	4.65

NP=Natriuretic Peptide; Clinic=Clinical assessment; UC=Usual Care
* Discounting at 3.5% applied after one year (except for year 2 in Pfisterer analyses, left undiscounted)
** Weighted average of trial arm estimates from clinical trials at baseline
[¥] Data from Pfisterer[19] age subgroups as not reported by subgroups in Lainchbury[21]
[¥¥] Ratio from Lainchbury main analysis[21] – all ages (not reported by subgroups)
[Ω] Pfisterer trial[19] follow-up which was the longest of meta-analysed trials

4.2 Utility scores

The four clinical trials[18], [19], [20], [21] did not report utility scores. There were some assessments of patients' health-related quality of life (HRQoL) and functional capacities[f], but these could not be used to estimate utility.

Gohler 2009[28] reported mean utility scores stratified by NYHA class for patients with CHF[g]. They used EuroQol 5D (EQ-5D) data collected from the EPHESUS trial[29] (multi-centre and multi-national trial), which assessed the addition of eplerenone to optimal medical treatment in patients with CHF and LVSD post myocardial infarction. During the EPHESUS trial[29], EQ-5D data were collected from a subsample of 1628 patients at baseline, three, six, 12, and 18 months. Gohler 2009[28] estimated utilities using all except the baseline data to mitigate the effect of acute myocardial infarction on the EQ-5D score (Table 6).

[f] Pfisterer assessed patients' quality of life using the Minnesota Living with Heart Failure questionnaire, the Duke Activity Status Index, and the Short Form 12, reporting no significant differences in the magnitude of improvements between strategies. Lainchbury administered the Minnesota Living with Heart Failure questionnaire and showed that Minnesota scores improved significantly and similarly in natriuretic peptide and clinical assessment cohorts. Troughton reported that quality of life scores remained stable for compared cohorts of patients.
[g] Study selected from a non-systematic search for utility scores in CHF. The Gohler paper was selected as being a recent assessment estimating utility scores in CHF using EQ-5D data collected from a well-recognized RCT on patients with CHF.

Table 6

Utility score – Patients with Chronic heart Failure[28]		
NYHA class	**Mean utility score**	**95% CI**
I	0.855	0.845-0.864
II	0.771	0.761-0.781
III	0.673	0.665-0.690
IV	0.532	0.480-0.584

We estimated average utility scores for each of our trials by weighting each of the utility scores in Table 6 with the proportion of patients in each NHYA class at trial baseline (Table 7) [18], [19], [20], [21]. In the absence of evidence to the contrary, we assumed that mean utility scores stayed constant over time and were the same for each intervention.

Table 7

Utility scores used in the economic analysis	
Analysis	**Utility score**
Lainchbury (all ages, ≤75 years, >75 years)*	0.753
Meta-analysis (LVSD)**	0.715
Jourdain[¥]	0.747
Pfisterer all ages[¥¥]	0.698
Pfisterer <75 years	0.707
Pfisterer ≥75 years	0.692

* NYHA classification at baseline was not reported for age subgroups in Lainchbury[21]. We used the main analysis' baseline classification (all ages) and applied it to age subgroups.
** Troughton[18] reported the percentage of patient in class II. We assumed others were in class III.
[¥] Jourdain[20] reported the mean NYHA class per cohort (natriuretic peptide=2.29; clinical assessment=2.21). We assumed that 80% of patients were in class II and others in class III for the clinical assessment cohort, and 70% in class II and others in class III for the natriuretic peptide cohort.
[¥¥] Pfisterer[19] reported the number of patients ≥ class III. We assumed that this proportion was in class III and others in class II.

5. Resource use and cost

Resource use was taken from the clinical trials and was combined with standard UK unit costs. Resource use components considered were hospitalisation, drug usage, outpatient visits, natriuretic peptide assessment, and biochemistry testing to assess renal function. For the post-trial period, a yearly cost per patient was applied.

5.1 Hospitalisation

To estimate hospitalisation costs, we used the risk ratio from the final trial follow-up and we assumed admissions occurred evenly over the follow-up period. The hospitalisation risk for the clinical assessment cohort was used as the baseline risk. For the analysis conducted on patients with CHF and LVSD (based on Troughton[18], Pfisterer[19], and Jourdain[20]), we applied the meta-analysed risk ratio to the baseline risk at 18 months in the Pfisterer[19] trial[h]. Table 8 details the trial hospitalisation data and the probabilities used in this cost-effectiveness analysis.

Table 8

[h] The Pfisterer trial[19] follow-up (18 months) was the longest of the meta-analysed trials (15 months for Jourdain[20] and 9.5 months for Troughton[18]).

Hospitalisation*					
			Probability of hospitalisation		
	RR (95% CI)	Trial follow-up	Natriuretic peptide	Clinical assessment	Usual care
Patients with CHF and LVSD**					
Jourdain	0.46 [0.3; 0.7]	15 months	0.20	0.44	N/A
Pfisterer all ages	0.74 [0.48; 1.15]	18 months	0.12	0.16	N/A
Troughton	0.42 [0.17; 1.05]	9.5 months	0.15	0.36	N/A
Meta-analysis	**0.57 [0.42; 0.76]**	**18 months¥**	**0.09**	**0.16¥¥**	**N/A**
Pfisterer subgroups					
Pfisterer <75	0.53 [0.25; 1.15]	18 months	0.08	0.16	N/A
Pfisterer ≥75	0.92 [0.57; 1.47]	18 months	0.18	0.20	N/A
Lainchbury (Natriuretic peptide versus clinical assessment)					
Lainchbury all	0.9 [0.65; 1.24]	3 years	0.36	0.40	N/A
Lainchbury ≤75	0.73 [0.44; 1.23]	3 years	0.29	0.40	N/A
Lainchbury >75	1.05 [0.7; 1.57]	3 years	0.43	0.41	N/A
Lainchbury (Usual care versus clinical assessment)					
Lainchbury all	0.83 [0.6; 1.15]	3 years	N/A	0.40	0.34
Lainchbury ≤75	0.9 [0.57; 1.42]	3 years	N/A	0.40	0.36
Lainchbury >75	0.76 [0.47; 1.23]	3 years	N/A	0.41	0.31

* No discounting applied

** Troughton 2000[18] was not modelled independently as Pfisterer[19] and Jourdain[20] (Section 6)

¥ Pfisterer trial[19] follow-up which was the longest of meta-analysed trials

¥¥ We used the Pfisterer[19] baseline risk (clinical assessment cohort risk) for the economic assessment on patients with CHF and LVSD based on the meta-analysis

The hospitalisation cost per hospital admission was calculated from reported figures of the NHS reference cost[30] database[i]. This cost was estimated to be £1,725 and was combined with the probabilities in Table 8 to give the hospitalisation cost.

5.2 Drug usage

The change in drug usage was calculated for all clinical trials (Lainchbury[21], Jourdain[20], Pfisterer[19], and Troughton[18]).In the cost-effectiveness assessment for patients with CHF and LVSD (based on Jourdain[20], Pfisterer[19], and Troughton[18]), the Pfisterer[19] drug usage was used for the base case. The drug usage from the other trials was used in sensitivity analyses, to see if the source of this component can affect the results of the analysis (Section 6).

The Lainchbury[21] drug usage was reported for the main analysis only (all ages). In the absence of better evidence, we assumed in our cost-effectiveness analysis that these data also applied to the age subgroups. The Pfisterer[21] drug usage was calculated separately for the main analysis (all ages) and for the age subgroups.

5.2.1 Lainchbury

For the Lainchbury main analysis, mean daily drug doses per patient were reported at every follow-up assessment for furosemide (loop diuretic), enalapril (ACEI), metoprolol[j] (BB), and spironolactone (Table 9).

[i] A weighted average cost was calculated considering elective and non-elective inpatient admissions for heart failure. Excess bed days were added to this calculation[30].

[j] The drug usage was reported for BB in metoprolol equivalent. Metoprolol is an available treatment in the UK, but not licensed for use in heart failure[31]. We costed metoprolol to be consistent with clinical trial outcomes. We consider this is not likely to affect the applicability of our results in a UK context.

Table 9

Lainchbury drug usage (mg/day)[21]											
		Time (months)									
		0		3		6		12		24	
Medications	Treatment Group*	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Furosemide	Natriuretic peptide	128	23	138	20	140	22	182	22	200	27
	Clinical assessment	149	23	144	21	134	21	166	23	197	28
	Usual care	124	22	121	21	119	21	123	22	140	25
Enalapril	Natriuretic peptide	12.7	6	13	6	13.3	6	13.1	6	12.4	7
	Clinical assessment	13.3	6	14.7	6	14.6	6	14.2	6	14	7
	Usual care	10.3	6	11.3	6	11	6	11	6	10.8	6
Metoprolol	Natriuretic peptide	76	11	83	9	95	9	95	10	94	11
	Clinical assessment	80	11	91	9	95	9	99	10	99	12
	Usual care	73	10	74	9	75	9	73	10	72	10
Spironolactone	Natriuretic peptide	20	6	22	4	22	4	20	5	16	7
	Clinical assessment	21	6	22	5	24	5	23	5	20	6
	Usual care	20	2	20	2	21	2	21	2	21	3

* Natriuretic peptide n=121; Clinical assessment n=121; Usual care n=122

We assumed that drug dosages changed at the mid-point between follow-ups. The usage at 24 months was assumed to stay constant up to 36 months (end of trial[21]). We combined these trial data with drug unit costs[31]; Table 10 presents costs of drug treatment for compared cohorts.

Table 10

Lainchbury drug treatment cost per patient*			
	Total 24-month cost per patient	Cost from 24 to 36 months	Total cost per patient
Natriuretic peptide	£289	£126	**£415**
Clinical assessment	£299	£134	**£433**
Usual care	£246	£104	**£350**

* Discounting at 3.5% applied after one year

5.2.2 Pfisterer

Pfisterer[19] presented at baseline the mean percentage of target dose per patient for ACEI/ARB, BB, and loop diuretic. In the absence of better data, these figures at baseline were assumed the same for the main analysis (all ages) and for age subgroups (<75 years, ≥75 years). Changes in drug usage were reported by age subgroups only, in percentage of target doses, for ACEI/ARB and BB. For the cost-effectiveness assessment based on the main analysis (all ages), changes in ACEI/ARB and BB usage were assumed to be the unweighted average of the reported changes for age subgroups. For jointly reported figures for ACEI and ARB, we costed the use of enalapril (ACEI), considering a target dose of 10mg b.i.d.[k] Carvedilol was costed as BB, considering a target dose of 25mg b.i.d.[k] No change in usage was reported for loop diuretic and this treatment was excluded from cost-effectiveness assessments[l]. Table 11 presents data for ACEI and BB used for cost-effectiveness assessments.

Table 11

Pfisterer* drug usage[19]						
	Clinical assessment			Natriuretic peptide		
	Baseline**	Changes	6 months	Baseline**	Changes	6 months

[k] Target doses as recommended by the *European Society of Cardiology*[32], [33], referred to in the RCTs[19], [20].

[l] The baseline usage was the same for compared cohorts

	Mean % target dose	SD / IQR	Mean % target	SE	Mean % target dose	Mean % target dose	SD / IQR	Mean % target	SE	Mean % target dose
All ages										
ACEI	0.5	0.36	0.153	0.063	0.653	0.53	0.41	0.2715	0.067	0.8015
BB	0.25	0.125-0.5	0.1415	0.06	0.3915	0.25	0.05-0.5	0.241	0.054	0.491
< 75 years										
ACEI	0.5	0.36	0.155	0.054	0.655	0.53	0.41	0.292	0.067	0.822
BB	0.25	0.125-0.5	0.162	0.06	0.412	0.25	0.05-0.5	0.281	0.054	0.531
≥ 75 years										
ACEI	0.5	0.36	0.151	0.063	0.651	0.53	0.41	0.251	0.051	0.781
BB	0.25	0.125-0.5	0.121	0.041	0.371	0.25	0.05-0.5	0.201	0.052	0.451

* Clinical assessment: n=248 (all ages); n=102 (<75 years); n=146 (≥75 years). Natriuretic peptide: n=251 (all ages); n=108 (<75 years); n=143 (≥75 years).
** Age subgroups are assumed to be the same as complete cohort.

The number of patients taking spironolactone or eplerenone at baseline and at the end of interventions (6 months) was presented for the Pfisterer main analysis (all ages). In the absence of better data, these figures were also applied to the age-subgroup analyses. We assumed patients were taking spironolactone or eplerenone at a dose of 25mg/day. Table 12 presents drug usage data for spironolactone and eplerenone.

Table 12

Pfisterer drug usage[19]		
	Clinical assessment (no. of patients)	**Natriuretic peptide (no. of patients)**
Spironolactone	56	76
Eplerenone	100	103

* Clinical assessment: n=248; Natriuretic peptide: n=251.

We assumed that drug treatments changed at three months (mid-point between the baseline and the end of interventions), and we assumed that the drug usage at six months stayed constant up to the end of follow-up (18 months)[19]. Table 13 presents costs of drug treatment for the compared cohorts.

Table 13

Pfisterer drug treatment cost per patient*		
	Clinical assessment	**Natriuretic peptide**
All ages		
6-month cost per patient	£86	£92
6 months to 18 months	£291	£313
Total cost per patient	£377	£404
< 75 years		
6-month cost per patient	£86	£93
6 months to 18 months	£293	£317
Total cost per patient	£379	£410
≥75 years		
6-month cost per patient	£85	£91
6 months to 18 months	£290	£308
Total cost per patient	£375	£399

* Discounting at 3.5% applied after one year

5.2.3 Jourdain

Jourdain[20] reported changes in drug usage for ACEI/ARB, BB, and furosemide (loop diuretic). The mean percentage of daily target dose per patient was reported at baseline and 3 months (end of the trial intervention) for ACEI/ARB and BB. The mean daily dose per patient at baseline and 3 months was reported for furosemide. For jointly reported figures for ACEI and ARB, we costed the use of enalapril (ACEI), assuming a target dose of 10mg b.i.d.[k] Carvedilol was costed as the BB, assuming a target dose of 25mg b.i.d.[k] Table 14 presents the drug usage data from Jourdain[20].

Table 14

Jourdain* drug usage[20]					
	Baseline		Changes		3 months
	Mean daily dose (mg)	SD	Increase (mg)	SD	mg
Loop diuretic					
Clinical assessment					
Furosemide	52	60	9	20	61
Natriuretic peptide					
Furosemide	50	48	9	20	59
ACEI and BB					
Clinical assessment	**Baseline (% of recommended daily dose)**				**3 months (% of recommended daily dose)**
Enalapril (ACEI)	94				98
Carvedilol (BB)	57				67
Natriuretic peptide					
Enalapril (ACEI)	94				106**
Carvedilol (BB)	58				77

* Clinical assessment n=110; Natriuretic peptide n=110.

** This means that the mean daily dose was above the recommended dose.

The change in drug usage was assumed at 1.5 months (mid-point between the baseline and the end of interventions). In the absence of better data, we kept constant the drug usage at three months up to the end of Jourdain follow-up (15 months)[20] for the analysis based on this trial alone (sensitivity analysis – Section 6), or up to 18 months, the Pfisterer[19] follow-up period[m], when applying the Jourdain drug usage to the analysis developed on patients with CHF and LVSD (sensitivity analysis – Section 6). Table 15 presents costs of drug treatment for compared cohorts.

Table 15

Jourdain drug treatment cost per patient*		
	Clinical assessment	Natriuretic peptide
3-month cost per patient	£29	£31
3 months to 15 months	£122	£134
15-months cost per patient	**£152**	**£165**
15 months to 18 months	£29	£32
18-months cost per patient	**£181**	**£197**

* Discounting at 3.5% applied after one year

5.2.4 Troughton

Troughton[18] reported the mean dose per patient at baseline and the mean dose increase per patient during the intervention period (6 months) for enalapril (ACEI) and furosemide (loop diuretic). The

[m] In sensitivity analyses, Troughton[18] and Jourdain[20] drug usages were applied to the cost-effectiveness assessment developed on patients with CHF and LVSD based on Pfisterer[19], Jourdain[20], and Troughton[18]. For this assessment, outcomes from trials were assumed at 18 months, the Pfisterer follow-up[19] being the longest one (15 months for Jourdain[20] and 9.5 months for Troughton[18]).

number of patients taking spironolactone and a BB at baseline and six months was also reported. We assumed that spironolactone was taken at a dose of 25mg/day, and that the BB carvedilol was taken at a dose of 25mg bd. Table 16 details the drug usage from Troughton[18].

Table 16

Troughton* drug usage[18]						
	Baseline		Increase		6 months	
	Mean dose (mg)	SD	Mean dose (mg)	SD	Mean dose (mg)	SD
ACEI and loop diuretic						
Clinical assessment						
Enalapril (ACEI)	13.1	6.7	1.2	6.9	14.3	
Furosemide (loop diuretic)	87	119	54		141	263
Natriuretic peptide						
Enalapril (ACEI)	15.3	7.9	4.8	5.9	20.1	
Furosemide (loop diuretic)	123	145	74		197	237
BB and spironolactone						
Clinical assessment	**Baseline (no. of patients)**				**6 months (no. of patients)**	
Spironolactone	0				1	
Carvedilol (BB)	1				2	
Natriuretic peptide						
Spironolactone	0				6	
Carvedilol (BB)	4				4	

* Clinical assessment n=36; Natriuretic peptide n=33.

The change in drug usage was assumed at three months (mid-point between baseline and the end of trial intervention)[18]. We kept constant the drug usage at six months up to 18 months, which was the follow-up time of Pfisterer[19] trial[m]. Table 17 presents costs of drug treatment for the compared cohorts.

Table 17

Troughton drug treatment cost per patient*		
	Clinical assessment	Natriuretic peptide
0 to 6-months	£35	£49
6 months to 9.5 months	£23	£34
0 to 9.5-months**	**£58**	**£83**
9.5 months to 18 months	£55	£80
Total cost (18 months)	**£113**	**£163**

* Discounting at 3.5% applied after one year

** 9.5 months was the follow-up time for Troughton 2000[18]

Drug usages were costed using drug unit costs proposed by the *British National Formulary*[31] (Table 18).

Table 18

Drug prices*			
Drug	**Dose (mg)**	**No. per pack**	**Price per pack**
Furosemide	40	28	£0.85
Enalapril	5	28	£1.03
Carvedilol**	12.5	28	£1.54
Carvedilol**	25	28	£2.17
Metoprolol	50	28	£1.28
Spironolactone	25	28	£1.79

Eplerenone	25	28	£42.72

* BNF No. 58[31]

** When carvedilol was costed per 25mg dose, we used the 25mg tablet cost. Otherwise, we used the 12.5mg cost (when carvedilol usage was reported in percentage of target dose)[31].

5.3 Outpatient visits

Table 19 presents numbers of outpatient visits attended from each of the four clinical trials. Troughton[18] was the only clinical trial reporting additional (unplanned) outpatient visits. In the absence of better data, we assumed the Troughton figures for additional visits in our analyses of the Jourdain and Pfisterer trials. For Lainchbury, we assumed Troughton figures of additional visits for natriuretic peptide and clinical assessment cohorts, and no additional visit was assumed for the usual care cohort.

Table 19

Outpatient visits				
	Troughton[18]	**Jourdain[20]**	**Pfisterer[19]**	**Lainchbury[21]**
Therapy frequency	Every 3 months; Every 2 weeks when target not met; Intervention at every visit	Every month for 3 months (intervention); Then every 3 months as follow-up	Visits at 1, 3, 6 months (intervention); Visits at 12 and 18 months as follow-up	Every 3 months for 2 years (intervention); Additional visit for NP and Clinic cohorts triggered by symptoms / measurement (not usual care)
Trial follow-up	Median 9.5 months	Median 15 months	18 months	3 years
Planned outpatient visits (for intervention)	4	4	4	9
Additional outpatient visit (for intervention)	NP = 0.9 per patient; Clinic = 0.3 per patient*	NR	NR	NP = Clinic NP & Clinic > Usual care **
Total	NP = 4.9 Clinic = 4.3	NR	NR	NR
Number of visit assumed in the model	**NP = 4.9** **Clinic = 4.3**	**NP = 4.9** **Clinic = 4.3**	**NP = 4.9** **Clinic = 4.3**	**NP = 9.9[¥]** **Clinic = 9.3** **Usual care = 9**

NP = Natriuretic peptide cohort; Clinic = Clinical assessment cohort

* Additional visits to intensify drug therapy were needed in 18/33 patients in the natriuretic peptide cohort and 14/36 patients in the clinical assessment cohort (p=0.34). The average number of extra visits per patient was 1.7 in the natriuretic peptide cohort and 0.8 in the clinical assessment cohort (p=0.19)[18].

** Data not presented

[¥] For all Lainchbury cohorts, four outpatient visits were assumed during the second year and were discounted.

Natriuretic peptide and clinical assessment interventions were offered in secondary care at a specialist level in every clinical trial. The outpatient visit cost for these cohorts was calculated using figures reported by the National reference cost[30] database[n], and was estimated to be £98 per visit. In the Lainchbury usual care cohort, it was conservatively assumed that all attendances were with the general practitioner. The mean cost per GP visit in the community was estimated nationally to be £52[34].

[n] A weighted average cost was calculated considering cardiology follow-up visits (not leading to admission), by consultant and non-consultant, with or without a multiprofessional approach.

5.4 Natriuretic peptide assessment

Natriuretic peptide assessments were undertaken at every outpatient visit in the natriuretic peptide cohort. There is no national price for this test in England and Wales. The tariff price at St George's Healthcare Trust (London) is £27.71 for NT-proBNP testing[o]. This cost was used for base-case cost-effectiveness assessments and added to the cost of an outpatient visit (Section 5.3)[p]. To allow for a potentially lower cost for natriuretic peptide testing, for example if this test is made available to a large number of patients, we used in the sensitivity analysis a cost of £20 (Section 6).

5.5 Biochemistry testing

When initiating or modifying dosages of ACEI, diuretic, and spironolactone/eplerenone, biochemistry testing for renal function is current practice. Numbers of treatment modifications per cohort were reported by Jourdain[20] for these drugs (Table 20). Pfisterer[19] reported the number of patients per cohort adding spironolactone/eplerenone to their drug therapy during interventions (none were taking spironolactone/eplerenone at baseline) (Table 20). We calculated probabilities of treatment modifications for natriuretic peptide and clinical assessment cohorts using data from Jourdain[20] for ACEI, and diuretic, and pooled data from Jourdain[20] and Pfisterer[19] for spironolacone/eplerenone (Table 20). In the absence of data for Lainchbury usual care cohort, we assumed no biochemistry testing for this group of patients.

The probability of treatment modification was multiplied by the average cost of a biochemistry test: £1.34 from the NHS Reference costs[30]. The cost of biochemistry testing may have been overestimated for natriuretic peptide and clinical assessment cohorts, as multiple treatment modifications may occur during a single physician visit. However, since the cost of biochemistry testing is so small, the impact on the results of our cost-effectiveness analysis is minimal.

Table 20

Treatment modifications			
	Natriuretic peptide	**Clinical assessment**	
Jourdain[20] - Number of treatment modifications			
	Treatment modification		
Drug	**Natriuretic peptide (n=110)**	**Clinical assessment (n=110)**	**p-value**
Diuretic	55	26	<0.05
ACEI	21	9	<0.05
Spironolactone	17	7	<0.05
Pfisterer[19] - Addition of spironolactone/eplerenone			
	Number of patient		
Drug	**Natriuretic peptide (n=251)**	**Clinical assessment (n=248)**	
Spironolactone or eplerenone	179	156	
Probabilities of treatment modification* - Jourdain and Pfisterer**			
Drug	**Natriuretic peptide**	**Clinical assessment**	
Diuretic	50.0%	23.6%	
ACEI	19.1%	8.2%	
Spironolactone/eplerenone**	54.3%	45.5%	

* We assumed all treatment modifications during year one and therefore no discounting was applied
** Data from Jourdain[20] and Pfisterer[19] were combined for spironolactone/eplerenone only.

[o] Test costs are equivalent for BNP and NT-proBNP
[p] For cost-effectiveness assessments based on Lainchbury[21], four natriuretic peptide tests were assumed during year two and were discounted (as for outpatient visits – Section 5.3)

5.6 Post-trial cost

Stewart 2002[35] published a cost-of-illness analysis of heart failure developed from a UK NHS perspective. Cost components incorporated in the analysis were hospitalisation, hospital-based outpatient consultations, GP consultations, drug treatment, and nursing-home care. The yearly cost per patient was estimated in 2000 to be £896[q]. Using the prices index for hospital and community health services[34], we estimated this cost in 2008 GBP to be £1,171 per patient per year. This yearly cost per patient was used in the post-trial period of the model was assumed the same for the different cohorts.

6. Sensitivity analysis

Sensitivity analyses were performed to assess the robustness of the cost-effectiveness results to plausible variations in model parameters. First, for the cost-effectiveness assessment conducted on patients with CHF and LVSD, the Pfisterer[19] drug usage was used for the base case, and drug usages from Jourdain[20] and Troughton[18] (Section 5.2) were applied to sensitivity analyses.

Secondly, Jourdain[20] and Pfisterer[19] clinical trials were modelled independently in addition to the assessment combining outcomes from Pfisterer[19], Jourdain[20], and Troughton[18], because of some inconsistencies in outcomes[r]. Troughton[18] was not modelled independently since it was small and did not report all-cause mortality[s].

Furthermore, as discussed in Section 3, the same number of patients was alive in the three compared cohorts at the end of Lainchbury main analysis, and between the clinical assessment and the usual care cohorts in Lainchbury age-subgroup analyses (≤75 years / >75 years) (Table 1)[21]. Thereby, the cost-effectiveness assessment from Lainchbury[21] main analysis was conducted on a three-year time horizon, and cost-effectiveness assessments from Lainchbury[21] age-subgroup analyses were conducted on both a three-year and a lifetime horizons. Moreover, cost-effectiveness assessments conducted on patients with CHF and LVSD were developed on a lifetime horizon in the base-case analysis. These cost-effectiveness assessments were based on trial follow-ups shorter than three years (18 months[19] and 15 months[20]). Considering that mortality ratios in natriuretic peptide and clinical assessment cohorts for all-age analyses might be the same at three years as in Lainchbury[21] main analysis, we conducted additional analyses on patients with CHF and LVSD on a three-year time horizon[t].

Finally, as discussed in Section 5.4, we used in the sensitivity analysis a cost of £20 for natriuretic peptide testing in all cost-effectiveness analyses in addition to the £27.71 used in the base case.

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[q] £905 million (1.91% of total NHS expenditure); 1.01 million cases[35].

[r] (1) Hospitalisation data: (a) Pfisterer[19] (all ages) baseline risk (clinical assessment cohort) = 0.16; RR (natriuretic peptide vs clinical assessment) = 0.74 [0.48; 1.15]. (b) Jourdain[20] baseline risk = 0.44; RR = 0.46 [0.3; 0.7]. (2) Mortality: (a) Pfisterer[19] baseline risk = 0.22; RR = 0.72 [0.5; 1.04]. (b) Jourdain[20] baseline risk = 0.10; RR = 0.64 [0.26; 1.58]. (c) We used area under curves for Pfisterer[19] main analysis (all ages) to estimate life years instead of end-of-trial RR as in the combined analysis (CHF and LVSD – Section 4.1.1).

[s] Troughton[18] did not report all-cause mortality; has a small cohort size (N=69); and this trial was conducted before BB were commonly used in CHF. We considered that modelling Troughton[18] independently would not add value to this economic analysis.

[t] We assumed the same mortality rate and yearly cost per patient up to three years after trial periods.

7. Probabilistic analysis

This economic analysis presents probabilistic results. A probabilistic analysis applies probability distributions to each model parameter and therefore allows us to calculate a distribution for the results of the cost-effectiveness analysis, equivalent to a confidence interval. A gamma distribution (bounded at 0) was applied to cost estimates and to standardized mortality ratios. A beta distribution (bounded between 0 and 1) was applied to utility scores and probabilities. Finally, a lognormal distribution (bounded at 0) was applied to risk ratios, mean drug dosage[u] and mean number of outpatient visits (refer to Table 25 on Section 11). The results of each analysis (base-case analyses and sensitivity analyses) were re-calculated 5000 times, with all the model parameters set simultaneously, selected at random from the respective parameter distribution. We present the results in terms of the mean of the 5000 computed simulations.

8. Results

This economic analysis assessed two populations of patients: patients with CHF and LVSD; and patients with heart failure of any cause. For these two populations, age subgroups were also assessed (Pfisterer <75 years, ≥75 years; Lainchbury ≤75 years, >75 years).

8.1 Patients with CHF and LVSD

Table 21 presents the breakdown of resource use components, life years, and QALYs for the base-case cost-effectiveness analysis developed on patients with CHF and LVSD based on the Pfisterer[19], Jourdain[20], and Troughton[18] trials. Table 22 presents cost-effectiveness results for the base-case analysis, subgroup analyses, and sensitivity analysis in this population. Results show that serial measurement of natriuretic peptide concentration in secondary care is clearly cost-effective compared to clinical assessment in secondary care, for the base-case population and both age subgroups (<75 years, ≥75 years). The probability of natriuretic peptide being cost-effective was high (98% for the base case, 99% for <75 years, and 68% for ≥75 years). The conclusion was the same in all the sensitivity analyses. In the sensitivity analysis based on Jourdain[20] with a three-year time horizon, the natriuretic peptide option was actually cost-saving compared to clinical assessment.

Table 21

Cost and QALY results*: Patients with CHF and LVSD (lifetime horizon)			
Resource use	**Natriuretic peptide**	**Clinical assessment**	**Difference NP-Clinic**
Natriuretic peptide test	£136	£0	£136
Drugs	£404	£377	£27
Biochemistry test	£1.66	£1.04	£0.62
Outpatient visit	£482	£422	£60
Hospitalisation	£161	£279	-£118
Post-trial cost	£8,337	£7,698	£639
Total cost	**£9,521**	**£8,777**	**£744**
Life years	**7.23**	**6.74**	**0.49**
QALYs	**5.18**	**4.82**	**0.36**

NP = Natriuretic Peptide; Clinic = Clinical assessment

* Discounting at 3.5% applied after one year

[u] Due to a 'bug', excel cannot calculate the gamma distribution when the standard error is very small compared with the mean. This was the case with some mean drug dosage and therefore we used the lognormal distribution instead.

Table 22

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

NP = Natriuretic Peptide; Clinic = Clinical assessment; INMB = Incremental Net Monetary Benefit; ICER = Incremental Cost-Effectiveness Ratio

* Natriuretic peptide is more effective and less costly than clinical assessment

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8.2 Patients with CHF due to any cause

The population assessed in Lainchbury[21] was patients with CHF due to any cause. Based on Lainchbury[21], we assessed the cost-effectiveness of serial measurement in secondary care of natriuretic peptide concentration compared to a) clinical assessment in secondary care and to b) usual care in the community. In addition to the base-case cost-effectiveness assessment developed from the main Lainchbury results, age subgroups analyses were also conducted (<75 years, ≥75 years)[21].

Table 23 presents a breakdown of cost components, life years, and QALYs for the base-case cost-effectiveness analysis developed from Lainchbury[21]. Table 24 shows results of this cost-effectiveness analysis modelled on a three-year time horizon (Section 3). Comparing an intervention with the next

best alternative (Figure 1), and applying a threshold of £20,000 per QALY gained, clinical assessment is cost-effective compared to usual care (ICER = £7,188/QALY) and natriuretic peptide is cost-effective compared to clinical assessment (ICER = £11,861/QALY). Serial measurement of natriuretic peptide is therefore the preferred option from a cost-effectiveness perspective.

For the age-subgroup cost-effectiveness assessment conducted on patients *75 years old and younger* and developed on three-year and lifetime horizons (Section 3), the diagram of the cost-effectiveness plane (Figure 2) shows that clinical assessment is ruled out due to 'extended dominance'. Extended dominance exists when an option is less effective and more costly than a linear combination of two other strategies. The results show that serial measurement in secondary care of natriuretic peptide is highly cost-effective compared to usual care in the community for patients with CHF 75 years old and younger (Table 24).

For the age-subgroup cost-effectiveness assessment conducted on patients *older than 75 years* and developed on three-year and lifetime horizons (Section 3), the natriuretic peptide option is dominated by usual care (usual care is more effective and less costly – Figure 2). However, clinical assessment is cost-effective compared to usual care (Table 24). Therefore, clinical assessment in secondary care is the preferred options for patients with CHF older than 75 years.

Finally, the results of all analyses stayed the same when using a cost of £20 for natriuretic peptide testing (instead of £27 – Section 5.4).

Table 23

Cost and QALY results*: Patients with CHF of any cause - Lainchbury (3 years time horizon)					
Resource use	**Natriuretic peptide**	**Clinical assessment**	**Usual care**	**Difference NP-Clinic**	**Difference Clinic-UC**
Natriuretic peptide test	£270	£0	£0	£270	£0
Drugs	£415	£433	£349	-£18	£84
Biochemistry test	£1.65	£1.03	£0	£0.62	£1.03
Outpatient visit	£951	£894	£461	£57	£433
Hospitalisation	£638	£699	£588	-£61	£111
Total cost	**£2,276**	**£2,027**	**£1,399**	**£249**	**£628**
Life years	**2.44**	**2.41**	**2.30**	**0.03**	**0.11**
QALYs	**1.84**	**1.82**	**1.73**	**0.02**	**0.09**

NP = Natriuretic Peptide; Clinic = Clinical assessment; UC = Usual Care

* Discounting at 3.5% applied after one year

Figure 1: Cost-effectiveness results (CHF any cause; base case)

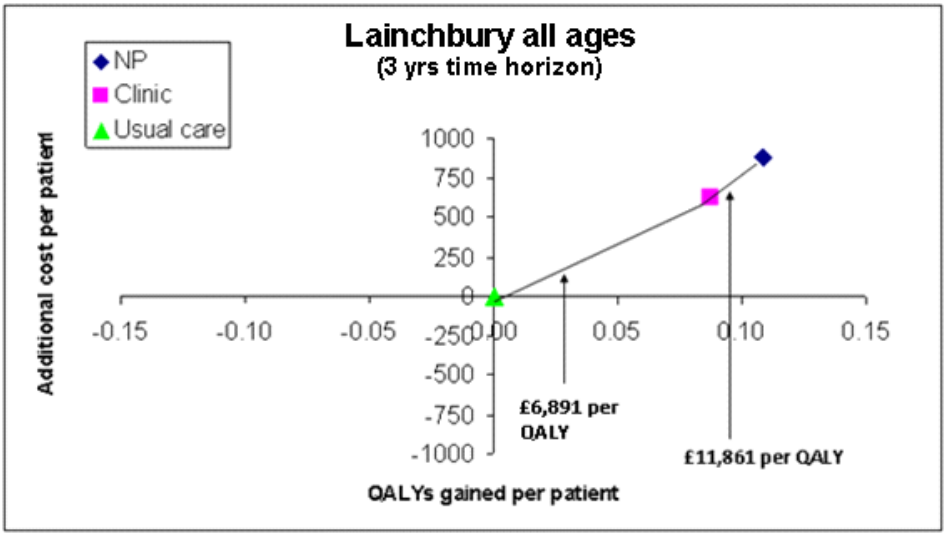


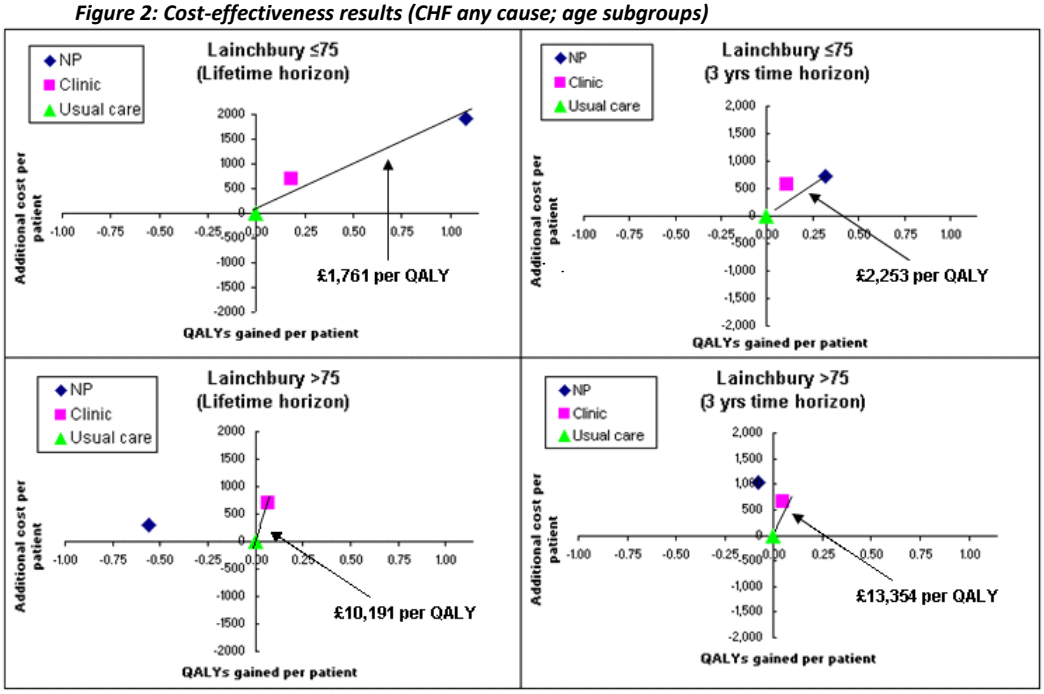
Table 24

Cost-effectiveness: CHF of any cause - Lainchbury							
Time horizon	**Compared interventions**	**Cost difference (Clinic-UC) (NP-Clinic) (NP-UC)**	**QALY difference (Clinic-UC) (NP-Clinic) (NP-UC)**	**INMB (20k/QALY)**	**Probability NP/Clinic* being cost-effective**	**ICER**	**Sensitivity analysis - NP measurement £20 (ICER)**
Lainchbury all ages							
3 years	Clinic vs Usual care	£628	0.09	£1,120	99.9%	£6,891	£7,188
3 years	NP vs Clinic	£249	0.02	£171	90.9%	£11,861	£8,278
Lainchbury ≤75 years							
Lifetime	NP vs Usual care	£1,905	1.08	£19,734	97.9%	£1,761	£1,692
3 years	NP vs Usual care	£720	0.32	£5,671	100.0%	£2,253	£2,018
Lainchbury >75 years							
Lifetime	Clinic vs Usual care	£697	0.07	£670	50.1%	£10,191	N/A
3 years	Clinic vs Usual care	£668	0.05	£333	86.8%	£13,354	N/A

NP = Natriuretic Peptide; Clinic = Clinical assessment; UC = Usual Care; INMB = Incremental Net Monetary Benefit; ICER = Incremental Cost-Effectiveness Ratio

* Clinic for Clinic vs Usual care; NP for NP vs Clinic; NP for NP vs Usual care

Figure 2: Cost-effectiveness results (CHF any cause; age subgroups)



9. Discussion

We assessed the use of serial measurement in secondary care of natriuretic peptide for optimizing medical therapy in patients admitted to hospital because of chronic heart failure, compared to both clinical assessment in secondary care and to usual care in the community:

- Clinical assessment was more costly than usual care
- Clinical assessment was more effective and cost-effective compared to usual care
- Natriuretic peptide monitoring was more costly than clinical assessment (with exception of the analysis based on Jourdain[20] and the one based on Lainchbury[21] >75)
- Natriuretic peptide monitoring was more effective and cost-effective compared to clinical assessment (with exception of the analysis based on Lainchbury[21] >75)
- Conclusions stayed consistent for age subgroups for patients with CHF and LVSD
- Clinical assessment was the preferred option in patients older than 75 years with CHF due to any cause
- Results were robust to sensitivity analyses

At the end of the Lainchbury trial[21], the same number of patients was alive in the three compared cohorts. In the base-case cost-effectiveness analysis based on Lainchbury[21] (patient with CHF due to any cause), the natriuretic peptide option being cost-effective relates to the calculation of life years using survival curves, which is more precise than using end-of-trial risk ratios. However, where we used survival curves to calculate life years, sampling error was not accounted for and uncertainty was underestimated. Nevertheless, for the analysis of patients with CHF and LVSD, which did not use this approach, the probability that natriuretic peptide monitoring is cost-effective was still convincingly high (98.3%).

Additional outpatient visits for up titrating medical therapy were reported by Troughton[18] only and were applied to all cost-effectiveness analyses for natriuretic peptide and clinical assessment cohorts. Troughton[18] was conducted before beta blockers were commonly used in heart failure and this may mean that we have under-estimated the additional outpatient visits associated with natriuretic peptide monitoring and therefore under-estimated the cost-effectiveness ratio.

In cost-effectiveness assessments of Lainchbury's age subgroups, using lifetime or three-year time horizons did not change conclusions. However, when comparing clinical assessment and usual care in patients older than 75 years, the probability of clinical assessment being cost-effective compared to usual care was 50% on a lifetime horizon and 87% on a three-year time horizon. As the same number of patients were alive at the end of Lainchbury trial[21] (3 years) in usual care and clinical assessment cohorts (in patients older than 75 years), the three-year time horizon results with the probability of cost-effectiveness of 87% are more relevant.

Results from cost-effectiveness assessments conducted on patients 75 years and older differed using outcomes from Lainchbury[21] (>75) or from Pfisterer[19] (≥75). The natriuretic peptide intervention improved survival in Pfisterer[19] and decreased it in Lainchbury[21] (compared to clinical assessment). It might be because patients with heart failure and preserved ejection fraction (HFPEF) were included in Lainchbury[21] and excluded in Pfisterer[19], and drug treatments in CHF were not shown to be as effective in HFPEF as they were in CHF with LVSD. The GDG also postulated that interventions in older CHF patients driven by raised natriuretic peptide can also increase the risk of renal impairment, thus adding to the potential risk of the NP-guided strategy in this age group.

Results presented are related to this population of patients, and may not be applied to patients excluded from clinical trials on which we based our cost-effectiveness analysis. The use of natriuretic peptide guided intervention in general practices was not assessed in clinical trials and no conclusion can be drawn. Considering the influence of the outpatient visit cost in the Lainchbury cost-effectiveness analyses, it might be advantageous to implement serial measurement of natriuretic peptide concentration for optimizing CHF medical therapy in general practices. Additional research is needed.

10. Conclusion

The optimization of drug therapy in chronic heart failure using serial measurement in secondary care of natriuretic peptide concentration is cost-effective compared to clinical assessment in secondary care and to usual care in the community. However, the use of natriuretic peptide measurement in patients older than 75 years may be harmful and not cost-effective, which suggests that careful patient selection is important. However, for patients older than 75 years, the optimization of drug therapy in chronic heart failure by clinical assessment in secondary care without natriuretic peptide monitoring was still cost-effective compared to usual care in the community.

11. Parameters used in probabilistic analyses

Table 25

Parameters used in probabilistic analyses				
Description of variable	**Mean value**	**Probability distribution**	**Parameters**	**Source**
Lainchbury				
Mortality risk ratio				
Lainchbury (all ages) NP vs Clinic	1.00	lognormal	95% CI = 0.7; 1.43	Lainchbury[21]
Lainchbury (all ages) UC	0.99	lognormal	95% CI = 0.69; 1.42	Lainchbury[21]

vs Clinic				
Lainchbury (≤75 yrs) NP vs Clinic	0.50	lognormal	95% CI = 0.24; 1.03	Lainchbury[21]
Lainchbury (≤75 yrs) UC vs Clinic	1.01	lognormal	95% CI = 0.59; 1.73	Lainchbury[21]
Lainchbury (>75 yrs) NP vs Clinic	1.41	lognormal	95% CI = 0.93; 2.14	Lainchbury[21]
Lainchbury (>75 yrs) UC vs Clinic	0.99	lognormal	95% CI = 0.61; 1.61	Lainchbury[21]
Mortality baseline risk				
Lainchbury (all ages)	0.33	Beta	α = 40; β = 81	Lainchbury[21]; clinic cohort
Lainchbury (≤75 years)	0.31	Beta	α = 17; β = 38	Lainchbury[21]; clinic cohort
Lainchbury (>75 years)	0.35	Beta	α = 23; β = 43	Lainchbury[21]; clinic cohort
Hospitalisation for heart failure risk ratio				
Lainchbury all ages - NP vs Clinic	0.90	lognormal	95% CI = 0.65; 1.24	Lainchbury[21]
Lainchbury ≤75 - NP vs Clinic	0.73	lognormal	95% CI = 0.44; 1.23	Lainchbury[21]
Lainchbury >75 - NP vs Clinic	1.05	lognormal	95% CI = 0.7; 1.57	Lainchbury[21]
Lainchbury all ages - UC vs Clinic	0.83	lognormal	95% CI = 0.6; 1.15	Lainchbury[21]
Lainchbury ≤75 - UC vs Clinic	0.90	lognormal	95% CI = 0.57; 1.42	Lainchbury[21]
Lainchbury >75 - UC vs Clinic	0.76	lognormal	95% CI = 0.47; 1.23	Lainchbury[21]
Hospitalisation for heart failure; Baseline risk				
Lainchbury all ages	0.40	beta	α = 49; β = 72	Lainchbury[21]; clinic cohort
Lainchbury ≤75 yrs	0.40	beta	α = 22; β = 33	Lainchbury[21]; clinic cohort
Lainchbury >75 yrs	0.41	beta	α = 27; β = 39	Lainchbury[21]; clinic cohort
Drug usage (mg)				
Furosemide				
NP baseline	128	lognormal	SE = 2.09	Lainchbury[21]
Clinic baseline	149	lognormal	SE = 2.09	Lainchbury[21]
UC baseline	124	lognormal	SE = 1.99	Lainchbury[21]
NP 3 months	138	lognormal	SE = 1.82	Lainchbury[21]
Clinic 3 months	144	lognormal	SE = 1.91	Lainchbury[21]
UC 3 months	121	lognormal	SE = 1.9	Lainchbury[21]
NP 6 months	140	lognormal	SE = 2	Lainchbury[21]
Clinic 6 months	134	lognormal	SE = 1.91	Lainchbury[21]
UC 6 months	119	lognormal	SE = 1.9	Lainchbury[21]
NP 12 months	182	lognormal	SE = 2	Lainchbury[21]
Clinic 12 months	166	lognormal	SE = 2.09	Lainchbury[21]
UC 12 months	123	lognormal	SE = 1.99	Lainchbury[21]
NP 24 months	200	lognormal	SE = 2.45	Lainchbury[21]
Clinic 24 months	197	lognormal	SE = 2.55	Lainchbury[21]

UC 24 months	140	lognormal	SE = 2.26	Lainchbury[21]
Enalapril				
NP baseline	12.7	lognormal	SE = 0.55	Lainchbury[21]
Clinic baseline	13.3	lognormal	SE = 0.55	Lainchbury[21]
UC baseline	10.3	lognormal	SE = 0.54	Lainchbury[21]
NP 3 months	13.0	lognormal	SE = 0.55	Lainchbury[21]
Clinic 3 months	14.7	lognormal	SE = 0.55	Lainchbury[21]
UC 3 months	11.3	lognormal	SE = 0.54	Lainchbury[21]
NP 6 months	13.3	lognormal	SE = 0.55	Lainchbury[21]
Clinic 6 months	14.6	lognormal	SE = 0.55	Lainchbury[21]
UC 6 months	11.0	lognormal	SE = 0.54	Lainchbury[21]
NP 12 months	13.1	lognormal	SE = 0.55	Lainchbury[21]
Clinic 12 months	14.2	lognormal	SE = 0.55	Lainchbury[21]
UC 12 months	11.0	lognormal	SE = 0.54	Lainchbury[21]
NP 24 months	12.4	lognormal	SE = 0.64	Lainchbury[21]
Clinic 24 months	14.0	lognormal	SE = 0.64	Lainchbury[21]
UC 24 months	10.8	lognormal	SE = 0.54	Lainchbury[21]
Sprionolactone				
NP baseline	20	lognormal	SE = 0.55	Lainchbury[21]
Clinic baseline	21	lognormal	SE = 0.55	Lainchbury[21]
UC baseline	20	lognormal	SE = 0.18	Lainchbury[21]
NP 3 months	22	lognormal	SE = 0.36	Lainchbury[21]
Clinic 3 months	22	lognormal	SE = 0.45	Lainchbury[21]
UC 3 months	20	lognormal	SE = 0.18	Lainchbury[21]
NP 6 months	22	lognormal	SE = 0.36	Lainchbury[21]
Clinic 6 months	24	lognormal	SE = 0.45	Lainchbury[21]
UC 6 months	21	lognormal	SE = 0.18	Lainchbury[21]
NP 12 months	20	lognormal	SE = 0.45	Lainchbury[21]
Clinic 12 months	23	lognormal	SE = 0.45	Lainchbury[21]
UC 12 months	21	lognormal	SE = 0.18	Lainchbury[21]
NP 24 months	16	lognormal	SE = 0.64	Lainchbury[21]
Clinic 24 months	20	lognormal	SE = 0.55	Lainchbury[21]
UC 24 months	21	lognormal	SE = 0.27	Lainchbury[21]
Sprionolactone				
NP baseline	76	lognormal	SE = 11	Lainchbury[21]
Clinic baseline	80	lognormal	SE = 11	Lainchbury[21]
UC baseline	73	lognormal	SE = 10	Lainchbury[21]
NP 3 months	83	lognormal	SE = 9	Lainchbury[21]
Clinic 3 months	91	lognormal	SE = 9	Lainchbury[21]
UC 3 months	74	lognormal	SE = 9	Lainchbury[21]
NP 6 months	95	lognormal	SE = 9	Lainchbury[21]
Clinic 6 months	95	lognormal	SE = 9	Lainchbury[21]
UC 6 months	75	lognormal	SE = 9	Lainchbury[21]
NP 12 months	95	lognormal	SE = 10	Lainchbury[21]
Clinic 12 months	99	lognormal	SE = 10	Lainchbury[21]
UC 12 months	73	lognormal	SE = 10	Lainchbury[21]
NP 24 months	94	lognormal	SE = 11	Lainchbury[21]
Clinic 24 months	99	lognormal	SE = 12	Lainchbury[21]
UC 24 months	72	lognormal	SE = 10	Lainchbury[21]
Pfisterer				
Mortality risk ratio				
Pfisterer (all ages)	0.72	lognormal	95% CI = 0.5; 1.04	Pfisterer[19]
Pfisterer (<75 yrs)	0.47	lognormal	95% CI = 0.24; 0.92	Pfisterer[19]

Pfisterer (≥75 yrs)	0.91	lognormal	95% CI = 0.61; 1.37	Pfisterer[19]
Mortality baseline risk				
Pfisterer (all ages)	0.22	Beta	α = 55; β = 193	Pfisterer[19]; clinic cohort
Pfisterer (<75 years)	0.22	Beta	α = 22; β = 80	Pfisterer[19]; clinic cohort
Pfisterer (≥75 years)	0.25	Beta	α = 37; β = 109	Pfisterer[19]; clinic cohort
Hospitalisation for heart failure risk ratio				
Pfisterer (all ages)	0.74	lognormal	95% CI = 0.48; 1.15	Pfisterer[19]
Pfisterer <75 yrs	0.53	lognormal	95% CI = 0.25; 1.15	Pfisterer[19]
Pfisterer ≥75 yrs	0.92	lognormal	95% CI = 0.57; 1.47	Pfisterer[19]
Hospitalisation for heart failure; Baseline risk				
Pfisterer all ages	0.16	beta	α = 40; β = 208	Pfisterer[19]; clinic cohort
Pfisterer <75 yrs	0.16	beta	α = 16; β = 86	Pfisterer[19]; clinic cohort
Pristerer ≥75 yrs	0.20	beta	α = 29; β = 117	Pfisterer[19]; clinic cohort
Drug usage				
All ages				
ACEI\ARB, baseline dose, Clinic	0.50	lognormal	SE = 0.023	Pfisterer[19]
ACEI\ARB, dose change, Clinic	0.15	lognormal	SE = 0.063	Pfisterer[19]
BB, dose change, Clinic	0.14	lognormal	SE = 0.06	Pfisterer[19]
ACEI\ARB, baseline dose, NP	0.53	lognormal	SE = 0.026	Pfisterer[19]
ACEI\ARB, dose change, NP	0.27	lognormal	SE = 0.067	Pfisterer[19]
BB, dose change, NP	0.24	lognormal	SE = 0.054	Pfisterer[19]
BB, baseline dose, Clinic	0.25	beta	α = 62; β = 186	Pfisterer[19]
BB, baseline dose, NP	0.25	beta	α = 62.75; β = 188.25	Pfisterer[19]
< 75 years				
ACEI\ARB, dose change, Clinic	0.16	lognormal	SE = 0.054	Pfisterer[19]
BB, dose change, Clinic	0.16	lognormal	SE = 0.06	Pfisterer[19]
ACEI\ARB, dose change, NP	0.29	lognormal	SE = 0.067	Pfisterer[19]
BB, dose change, NP	0.28	lognormal	SE = 0.054	Pfisterer[19]
≥ 75 years				
ACEI\ARB, dose change, Clinic	0.15	lognormal	SE = 0.063	Pfisterer[19]
BB, dose change, Clinic	0.12	lognormal	SE = 0.041	Pfisterer[19]
ACEI\ARB, dose change, NP	0.25	lognormal	SE = 0.051	Pfisterer[19]
BB, dose change, NP	0.20	lognormal	SE = 0.052	Pfisterer[19]
All patients / <75 years / ≥75 years				
Spironolactone, probability of use, Clinic	0.23	beta	α = 56; β = 192	Pfisterer[19]
Eplerenone, probability of use, Clinic	0.40	beta	α = 100; β = 148	Pfisterer[19]

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Spironolactone, probability of use, NP	0.30	beta	α = 76; β = 175	Pfisterer[19]
Eplerenone, probability of use, NP	0.41	beta	α = 103; β = 148	Pfisterer[19]
Jourdain				
Mortality risk ratio	0.64	lognormal	95% CI = 0.26; 1.58	Jourdain[20]
Mortality baseline risk	0.10	Beta	α = 11; β = 99	Jourdain[20]; clinic cohort
Hospitalisation for heart failure risk ratio	0.46	lognormal	95% CI = 0.3; 0.7	Jourdain[20]
Hospitalisation for heart failure; Baseline risk	0.44	beta	α = 48; β = 62	Jourdain[20]; clinic cohort
Treatement modification (biochemistry testing)				
Diuretic, NP group	0.5	beta	α = 55; β = 55	Jourdain[20]
ACEI, NP group	0.19	beta	α = 21; β = 89	Jourdain[20]
Spironolactone\eplereno ne, NP group	0.54	beta	α = 196; β = 165	Combined data from Jourdain[20] and Pfisterer[19]
Diuretic, Clinic group	0.24	beta	α = 26; β = 84	Pfisterer[19]
ACEI ,Clinic group	0.08	beta	α = 9; β = 101	Pfisterer[19]
Spironolactone\eplereno ne, Clinic group	0.46	beta	α = 163; β = 195	Combined data from Jourdain[20] and Pfisterer[19]
Drug usage				
ACEI\ARB, baseline dose, Clinic	18.8	lognormal	SE = 10 (assumed 50% of target dose as SE)	Jourdain[20]
BB, baseline dose, Clinic	28.5	lognormal	SE = 25 (assumed 50% of target dose as SE)	Jourdain[20]
ACEI\ARB, 3 months dose, Clinic	19.6	lognormal	SE = 10 (assumed 50% of target dose as SE)	Jourdain[20]
BB, 3 months dose, Clinic	33.5	lognormal	SE = 25 (assumed 50% of target dose as SE)	Jourdain[20]
ACEI\ARB, baseline dose, NP	18.8	lognormal	SE = 10 (assumed 50% of target dose as SE)	Jourdain[20]
BB, baseline dose, NP	29.0	lognormal	SE = 25 (assumed 50% of target dose as SE)	Jourdain[20]
ACEI\ARB, 3 months dose, NP	21.2	lognormal	SE = 10 (assumed 50% of target dose as SE)	Jourdain[20]
BB, 3 months dose, NP	38.5	lognormal	SE = 25 (assumed 50% of target dose as SE)	Jourdain[20]
Furosemide, baseline dose, Clinic	52.0	lognormal	SE = 5.72	Jourdain[20]
Furosemide, dose change, Clinic	9.0	lognormal	SE = 1.91	Jourdain[20]
Furosemide, baseline dose, NP	50.0	lognormal	SE = 4.58	Jourdain[20]
Furosemide, dose change, NP	9.0	lognormal	SE = 1.91	Jourdain[20]
Troughton				
Hospitalisation for heart failure (Risk ratio)	0.42	lognormal	95% CI = 0.17; 1.05	Troughton[18]
Outpatient visits				
Additional outpatient visit per patient; Clinic	0.30	lognormal	SE = 0.15	Troughton[18]

group				
Additional outpatient visit per patient; NP group	0.90	lognormal	SE = 0.45	Troughton[18]
Drug usage				
ACEI\ARB, baseline dose, Clinic	13.1	lognormal	SE = 1.12	Troughton[18]
Furosemide, baseline dose, Clinic	87.0	lognormal	SE = 19.83	Troughton[18]
ACEI\ARB, dose change, Clinic	1.2	lognormal	SE = 1.15	Troughton[18]
Furosemide, 6 months, Clinic	141.0	lognormal	SE = 43.83	Troughton[18]
ACEI\ARB, baseline dose, NP	15.3	lognormal	SE = 1.38	Troughton[18]
Furosemide, baseline dose, NP	123.0	lognormal	SE = 25.24	Troughton[18]
ACEI\ARB, dose change, NP	4.8	lognormal	SE = 1.03	Troughton[18]
Furosemide, 6 months, NP	197.0	lognormal	SE = 41.26	Troughton[18]
Spironolactone, probability of use, 6 months, Clinic	0.028	beta	α = 1; β = 35	Troughton[18]
BB, probability of use, baseline, Clinic	0.028	beta	α = 1; β = 35	Troughton[18]
BB, probability of use, 6 months, Clinic	0.056	beta	α = 2; β = 34	Troughton[18]
Spironolactone, probability of use, 6 months, NP	0.18	beta	α = 6; β = 27	Troughton[18]
BB, probability of use, baseline, NP	0.12	beta	α = 4; β = 29	Troughton[18]
BB, probability of use, 6 months, NP	0.12	beta	α = 4; β = 29	Troughton[18]
Patient with CHF and LVSD (meta-analysis of Pfisterer, Jourdain, and Troughton)				
Mortality risk ratio				
Meta-analysis of Pfisterer (all ages) and Jourdain	0.70	lognormal	95% CI = 0.5; 0.99	Pfisterer and Jourdain
Hospitalisation for heart failure risk ratio				
Meta-analysis (Jourdain, Pfisterer, and Troughton)	0.57	lognormal	95% CI = 0.42; 0.76	Jourdain[20], Pfisterer[19], and Troughton[18]
Mean cost (£)				
Hospitalisation cost				
Elective Inpatient				
Heart Failure or Shock with CC	3954	gamma	SE = 2114 / α = 3.50; β = 1130.34 / Using interquartile range (20001; 4703)	NHS reference cost[30]
Heart Failure or Shock without CC	2756	gamma	SE = 1862 / α = 2.19; β = 1258.09 / Using interquartile range (1262; 3562)	NHS reference cost[30]
Elective Inpatient Excess Bed Day				
Heart Failure or Shock	186	gamma	SE = 56.5 / α = 10.79; β = 17.20 /	NHS reference cost[30]

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with CC			Using interquartile range (113; 187)	
Heart Failure or Shock without CC	238	gamma	SE = 95.5 / α = 6.22; β = 38.29 / Using interquartile range (177; 302)	NHS reference cost[30]
Non-Elective Inpatient (Long Stay) HRG Data				
Heart Failure or Shock with CC	2608	gamma	SE = 774 / α = 11.35; β = 229.73 / Using interquartile range (1949; 2976)	NHS reference cost[30]
Heart Failure or Shock without CC	1692	gamma	SE = 508 / α = 11.10; β = 152.50 / Using interquartile range (1268; 1942)	NHS reference cost[30]
Non-Elective Inpatient (Long Stay) Excess Bed Days HRG Data				
Heart Failure or Shock with CC	193	gamma	SE = 59 / α = 10.67; β = 18.06 / Using interquartile range (152; 230)	NHS reference cost[30]
Heart Failure or Shock without CC	189	gamma	SE = 57 / α = 11.01; β = 17.18 / Using interquartile range (151; 228)	NHS reference cost[30]
Non-Elective Inpatient (Short Stay) HRG Data				
Heart Failure or Shock with CC	356	gamma	SE = 120 / α = 8.81; β = 40.44 / Using interquartile range (248; 406)	NHS reference cost[30]
Heart Failure or Shock without CC	340	gamma	SE = 106 / α = 10.29; β = 33.04 / Using interquartile range (248; 388)	NHS reference cost[30]
Cardiologist outpatient visit cost				
Consultant Led: Follow up Attendance Non-Admitted Face to Face	105	gamma	SE = 35.5 / α = 8.80; β = 11.97 / Using interquartile range (75; 122)	NHS reference cost[30]
Consultant Led: Follow up Attendance Multiprofessional Non-Admitted Face to Face	125	gamma	SE = 11 / α = 129.01; β = 0.97 / Using interquartile range (123; 138)	NHS reference cost[30]
Non-Consultant Led: Follow up Attendance Non-Admitted Face to Face	71	gamma	SE = 44 / α = 2.62; β = 27.19 / Using interquartile range (38; 93)	NHS reference cost[30]
Non-Consultant Led: Follow up Attendance Multiprofessional Non-Admitted Face to Face	117	gamma	SE = 27 / α = 18.85; β = 6.22 / Using interquartile range (85; 121)	NHS reference cost[30]
Mean utility scores				
NYHA class I	0.855	Beta	95% CI = 0.845; 0.864 / α = 1391.94; β = 236.06	Gohler 2009[28]
NYHA class II	0.771	Beta	95% CI = 0.761; 0.781 / α = 1255.19; β = 372.81	Gohler 2009[28]
NYHA class III	0.673	Beta	95% CI = 0.665; 0.690 / α = 1095.64; β = 532.36	Gohler 2009[28]
NYHA class IV	0.532	Beta	95% CI = 0.480; 0.584 / α = 866.1; β = 761.9	Gohler 2009[28]
Other				
Standard Mortality ratios (Mean %)				
Male, 65-74 years	573	Gamma	95% CI = 521; 631 / SE = 30 / α = 364.81; β = 1.57	Guili 2005[24]
Male, 85+ years	241	Gamma	213; 272 / SE = 15 / α = 258.14; β =	Guili 2005[24]

			0.93	
Female, 65-74 years	718	Gamma	641; 804 / SE = 42 / α = 292.25; β = 2.46	Guili 2005[24]
Female, 85+ years	242	Gamma	223; 262 / SE = 14 / α = 298.80; β = 0.81	Guili 2005[24]
Effect of ACEI on survival (Risk ratio)	0.86	lognormal	95% CI = 0.81; 0.91	Flather 2000[25]
Effect of BB on survival (Risk ratio)	0.57	lognormal	95% CI = 0.51; 0.64	Shibata 2001[26]
Biochemistry test cost (£)	1.34	gamma	SE = 0.59 / α = 5.16; β = 0.26 / Using interquartile range (0.79; 1.56)	NHS reference cost[30]

NP = Natriuretic Peptide; Clinic = Clinical assessment; UC = Usual Care

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Appendix J – Practical notes

Background:

The course of heart failure patients is characterised by periods of clinical deterioration and potential need for changes to pharmacological therapy to be made. It is essential to maintain patients on therapy proven to reduce the risks of hospitalisation and improve the chances of survival. The adherence to this general advice is made difficult by practitioners' concerns about side effects of therapy. In particular, many clinicians are concerned about renal impairment and reduced blood pressure in patients with heart failure.

The 2003 guideline included tables of practical recommendations that were based on the publication by McMurray {McMurray, 2001 1466 /id}). These covered aspects of clinical management that were not included in the evidence reviewed but which the GDG considered important.

In updating the guideline the GDG reviewed these recommendations and agreed that they were helpful to all practitioners caring for patients with heart failure, and would enable patients and practitioners avoid the frequent scenario where essential medications for heart failure are inappropriately discontinued. Where appropriate, the GDG adopted the advice from Chronic Kidney Disease: Early identification and management of chronic kidney disease in adults in primary and secondary care. NICE clinical guideline 73 (2008).

These practical notes were written by the Guideline Development Group for publication in August 2010. They will not be revised before the guideline is considered for review in 2013. For all current NICE guidance, see www.nice.org.uk

General Advice:

For optimal prognostic and symptomatic benefit doses of ACEI and β blocker should be up-titrated to the maximum tolerated. This may require repeated or prolonged supervision in some patients.

The dose of diuretic should be the minimum necessary to control oedema.

Communication with Patients:

Identify a clinician from whom patients may seek advice regarding heart failure.

Explain the purpose of the medication prescribed and the importance of up-titration to optimal dose.

Explain the need for regular monitoring and at times alteration of medication.

Explain that improvement with ACEI or β blockers may take time to accrue.

Explain that minor worsening of symptoms may occur when β blockers are being initiated.

Encourage individuals to monitor their weight and to report any change

Renal function:

Monitor in all patients routinely. Check the renal function before the initiation of ACEI/ARB, and monitor the urea, creatinine, eGFR and electrolytes following each dose increment, and then at regular intervals every three months.

Measure serum urea, creatinine and electrolytes at initiation of an ACE inhibitor/ARB and after each dose increment.

Monitor more frequently patients taking combined loop and thiazide diuretic therapy, and in those taking aldosterone antagonists.

In people with CKD, measure serum potassium concentrations and estimate the GFR before starting ACEI/ARB therapy. Repeat these measurements between 1 and 2 weeks after starting ACEI/ARB therapy and after each dose increase. (Chronic Kidney Disease: Early identification and management of chronic kidney disease in adults in primary and secondary care. NICE clinical guideline 73 (2008). R48

ACEI/ARB therapy should not normally be started if the pre-treatment serum potassium concentration is significantly above the normal reference range (typically >5.0 mmol/l). (Chronic Kidney Disease: Early identification and management of chronic kidney diseae in adults in primary and secondary care. NICE clinical guideline 73 (2008). R49.

Stop ACEI/ARB therapy if the serum potassium concentration rises to above 6.0 mmol/l and other drugs known to promote hyperkalaemia have been discontinued. (Chronic Kidney Disease: Early identification and management of chronic kidney diseae in adults in primary and secondary care. NICE clinical guideline 73 (2008). R52

Following the introduction or dose increase of ACEI/ARB, do not modify the dose if either the GFR decrease from pre-treatment baseline is <25% or the plasma creatinine increase from baseline is <30%. (Chronic Kidney Disease: Early identification and management of chronic kidney disease in adults in primary and secondary care. NICE clinical guideline 73 (2008). R53

If there is a fall in eGFR or rise in plasma creatinine after starting or increasing the dose of ACEI/ARB, but it is less than 25% (eGFR) or 30% (serum creatinine) of baseline, the test should be repeated in a further 1–2 weeks. Do not modify the ACE/ARB dose if the change in eGFR <25% or change in plasma creatinine is <30%. (Chronic Kidney Disease: Early identification and management of chronic kidney diseae in adults in primary and secondary care. NICE clinical guideline 73 (2008). R54.

If the eGFR change is ≥25% or change in plasma creatinine is ≥30%:

1. investigate other causes of a deterioration in renal function such as volume depletion or concurrent medication (e.g. non-steroidal anti-inflammatory drugs (NSAIDS)
2. if no other cause for the deterioration in renal function is found, stop the ACEI/ARB therapy or reduce the dose to a previously tolerated lower dose. (Chronic Kidney Disease: Early identification and management of chronic kidney disease in adults in primary and secondary care. NICE clinical guideline 73 (2008). R55.

Before starting aldosterone antagonists, measure urea, creatinine, eGFR and electrolytes.

Comment [AA1]:

Comment [AA2]: Nan, there is no need to remove this. I am re-instating it:

In patients taking aldosterone antagonists, measure urea, creatinine, eGFR and electrolytes at 1 week, and at 1, 2, 3, and 6 months and 6 monthly thereafter.

Halve the aldosterone antagonist dose if the potassium rose to 5-5-5.9 mmol/l.

Stop the aldosterone antagonist if the potassium rises above 6 mmol/l or the creatinine above 220 µmol/l.

Blood pressure:

Monitor in all patients routinely.

If blood pressure is low, first consider discontinuing nitrates, calcium channel blockers and other vasodilators.

If blood pressure is low, reduce diuretics in patients who do not have signs of congestion.

In asymptomatic hypotension do not alter dose of ACEI or β blockers.

Where at all possible maintain treatment with both ACEI and BB, at reduced dose if necessary.

Increasing congestion/fatigue:

If Temporary deterioration occurs during the initiation or up-titration of β blockers

diuretic dose may need to be briefly increased.

If congestion occurs increase diuretics and consider reducing dose of β blocker (but not discontinuing).

Where there is extreme fatigue (or bradycardia < 50bpm) consider reducing the dose of β blocker.

Seek specialist advice if serious deterioration (fatigue, oedema, weight gain and dyspnoea) does not improve

Consider Specialist review (see above):

Where fluid retention is resistant.

When commencing ACEI in patients taking large doses of diuretics.

Where renal function continues to deteriorate or deteriorated rapidly.

Where there are concerns about low blood pressure.

Where fatigue, oedema, weight gain and dyspnoea do not rapidly improve**.**

Appendix K - Criteria for selecting high priority research recommendations

Criterion	RP1 Beta Blocker or ACEI in Heart Failure with Preserved Left Ventricular Ejection Fraction	RP2 Telemonitoring, Natriuretic Peptide Monitoring or Clinical Monitoring in HF with LVSD	RP3 The use of natriuretic peptides in determining prognosis and resource allocation in the heart failure team	RP4 SPIRONOLACTONE OR Angiotensin receptor blocker in HF patients intolerant of ACEI	RP5 Hydralazine and or Nitrates in HFPEF
Importance to patients or the population	This is of major importance to a large population of patients with heart failure.	Efficient affordable strategies for optimal management of heart failure afford the best opportunity to maintain or improve patient quality of life and independence.	A population with heart failure is best served by alignment of resource with need. The ability to stratify need (and prognosis) would allow targeting of limited resource where patient need is greatest	We do not currently know which regimen would optimise RAAS inhibition in those intolerant of ACE inhibitors. It is important that this is clarified.	Therapeutic intervention has been found to significantly improve the prognosis of heart failure and LVSD. It would be of great advantage to see if either agent or the combination would be effective in HF with preserved LV ejection fraction.
Relevance to NICE guidance	High. Current NICE guidance highlights lack of evidence of benefit.	High The research is essential to inform future updates of key recommendations in the guidelines.	High: Facilitate implementation of existing guidance.	High: Research would inform future recommendations.	High. Would inform future guidance.
Relevance to the NHS	Heart failure with preserved ejection fraction is responsible for repeated hospital admissions and significant	Financial strategy and management of heart failure in the community	Financial advantage by alignment of resource allocation with clinical need and therefore reducing redundancy in care input.	Would streamline care for the patients intolerant of one of the cornerstones of therapy for HF with LVSD	Unmet treatment need.

Criterion	RP1 Beta Blocker or ACEI in Heart Failure with Preserved Left Ventricular Ejection Fraction	RP2 Telemonitoring, Natriuretic Peptide Monitoring or Clinical Monitoring in HF with LVSD	RP3 The use of natriuretic peptides in determining prognosis and resource allocation in the heart failure team	RP4 SPIRONOLACTONE OR Angiotensin receptor blocker in HF patients intolerant of ACEI	RP5 Hydralazine and or Nitrates in HFPEF
	impairment of quality of life. Improvement in both would be beneficial to healthcare planning and to patient quality of life.				
National priorities	National priorities and national strategy emphasise on reduction of hospitalisation use.	National priorities and national strategy emphasise on reduction of hospitalisation use	National priorities and national strategy emphasise on reduction of hospitalisation use		National priorities and national strategy emphasise on reduction of hospitalisation use
Current evidence base	Current evidence is limited but shows potential benefit of beta-blocker and ACE inhibitors in preserved ejection fraction population A large study with clearly defined population is required. (See Section 2.2.1)	Interpretation of current studies available is difficult because of differing research methodologies used and differences in what constitutes 'usual care'. (See Chapter 7 - Monitoring)	Studies show potential reduction in mortality in some groups when natriuretic peptides are used to guide titration. The overall utility of BNP in the broader HF population is unclear. (See Section 6.1 and Section 4.2)	It is currently unclear whether angiotensin receptor blocker or spironolcatone are the most effective treatments in those intolerant to ACEI. (See Sections 2.2.1)	There is evidence of benefit of nitrate and hydralazine in combination compared to placebo in caucasian LVSD population and of hydralazine and nitrates in black LVSD population on therapy with ACEI and beta blockers. (See Section 5.2.4)
Equality	There is a lack of effective treatments for			It is not known in this population how to replace an essential agent in treating HF	There is a lack of effective treatments for

Criterion	RP1 Beta Blocker or ACEI in Heart Failure with Preserved Left Ventricular Ejection Fraction	RP2 Telemonitoring, Natriuretic Peptide Monitoring or Clinical Monitoring in HF with LVSD	RP3 The use of natriuretic peptides in determining prognosis and resource allocation in the heart failure team	RP4 SPIRONOLACTONE OR Angiotensin receptor blocker in HF patients intolerant of ACEI	RP5 Hydralazine and or Nitrates in HFPEF
	this population			with LVSD	this population
Feasibility	Highly feasible	Highly feasible	Highly feasible	Feasible, but there is the difficulty of overcoming the current practice of automatically commence ARB whenever there is intolerance of ACEI	Highly feasible
Other comments					

Appendix L - Declarations of Interest

Introduction

All members of the GDG and all members of the NCGC staff were required to make formal declarations of interest at the outset, and these were updated at every subsequent meeting throughout the development process. The chair reviewed the declarations of interest at the start of each meeting and, with one exception, none were deemed in conflict with the agenda topics and clinical questions under discussion at the meetings. Dr Fuat (deputy for Dr Davis) did not take part in the discussions on Angiotensin Receptor Blockers as he has been a member of an Advisory Board on the use of Candesartan for heart failure for Takeda Pharmaceuticals since February 2009.

Declarations of interests of the GDG members

Dr Abdallah Al-Mohammad

GDG meeting	Declaration of Interests
GDG Application (14th November 2008)	AAM declared the following items of **personal pecuniary interest**: • Hospitality from Novartis in March 2008 to attend the American College of Cardiology meeting in Chicago (Conference registration fee, flights and hotel). • Honoraria for delivering educational lectures to general practitioners, heart failure nurses and Matrons on three occasions in the 12 months to the 14th of November 2008: AAM declared the following items of **personal non-pecuniary interest**: • Authored and co-authored papers on issues related to heart failure and imaging. • Investigator in several projects (funded by the industry and by scientific grants) on heart failure that are ongoing. • Honorary senior clinical lecturer in the University of Sheffield • Fellow of the Royal Colleges of Physicians of Edinburgh and London. • Member of the British Cardiovascular Society, the British Society of Heart Failure, the British Nuclear Cardiology Society, the European Association of Echocardiography, the European Society of Cardiology and the British Medical Association. AAM did not declare any items of **personal family interest or personal non-pecuniary interest**
GDG Induction meeting **(30th January 2009)**	No change in declaration
First GDG meeting (27th February 2009)	No change in declaration
Second GDG Meeting **(27th March 2009)**	No change in declaration
Third GDG Meeting **(1st May 2009)**	No change in declaration
Fourth GDG Meeting **(5th June 2009)**	No change in declaration
Fifth GDG Meeting	No change in declaration

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(3rd July 2009)	
Sixth GDG Meeting **(31st July 2009)**	No change in declaration.
Seventh GDG Meeting **(18th September 2009)**	No change in declaration
Eighth GDG Meeting **(16th October 2009)**	No change in declaration
Ninth GDG Meeting **(13th November 2009)**	No change in declaration
Tenth GDG Meeting (9th April 2010)	No change in declaration
Eleventh GDG meeting (June 2010)	No change in declaration

Dr Mark Davis

GDG meeting	Declaration of Interests
GDG Application 23/10/08	MD declared the following item of **personal pecuniary interest** • (Honorarium from Menarini for taking part in an Advisory Board (Feb 2008) MD did not declare any items of **personal pecuniary interest, personal family interest, non-personal pecuniary interest** or **personal non-pecuniary interest**
GDG Induction meeting **(30th January 2009)**	No change in declaration
First GDG meeting (27th February 2009)	DNA Potential conflict of interest from attending Advisory Board for Menarini expires.
Second GDG Meeting **(27th March 2009)**	As above plus: MD declared the following item of **personal pecuniary interest:** • Received a fee to attend a Takeda meeting on Practice Based Commissioning at which the role of ARBs in heart failure was discussed (6/3/09)
Third GDG Meeting **(1st May 2009)**	No change in declaration
Fourth GDG Meeting **(5th June 2009)**	No change in declaration
Fifth GDG Meeting **(3rd July 2009)**	DNA
Sixth GDG Meeting **(31st July 2009)**	DNA
Seventh GDG Meeting **(18th September 2009)**	No change in declaration
Eighth GDG Meeting **(16th October 2009)**	No change in declaration
Ninth GDG Meeting **(13th November 2009)**	No change in declaration
Tenth GDG Meeting (9th April 2010)	As above, plus: MD declared the following item of **personal pecuniary interest:** • Attended Takeda advisory board to discuss substitutions within ARB class
Eleventh GDG meeting (June 2010)	No change in declaration

Dr Paresh Dawda

GDG meeting	Declaration of Interests
GDG Application	PD did not declare any items of personal pecuniary interest, **personal family interest, non-personal pecuniary interest** or **personal non-pecuniary interest**
GDG Induction meeting **(30th January 2009)**	No change to declaration
First GDG meeting (27th February 2009)	PD declared the following item of **personal family interest:** • Sister is employed by Takeda Pharmaceuticals
Second GDG Meeting **(27th March 2009)**	No change to declaration
Third GDG Meeting **(1st May 2009)**	No change to declaration
Fourth GDG Meeting **(5th June 2009)**	No change to declaration
Fifth GDG Meeting **(3rd July 2009)**	As above plus: PD declared the following item of **non-personal pecuniary interest:** • His organisation was paid backfill by the NHS National Institute for Innovation and Improvement to cover his attendance at a Leadership in Patient Safety Course for 1 week (22/6/09-26/6/09).
Sixth GDG Meeting **(31st July 2009)**	No change to declaration
Seventh GDG Meeting **(18th September 2009)**	As above plus: PD declared the following item of **personal pecuniary interest:** • Supported by NHS Institute for Innovation and Improvement to attend a patient safety course at Institute for Healthcare Improvement in Boston USA (10-16 Sept 09)
Eighth GDG Meeting **(16th October 2009)**	As above plus: PD declared the following item of **personal pecuniary interest:** • Consultancy work for NHS Institute for Innovation and Improvement (from 7/10/09)
Ninth GDG Meeting **(13th November 2009)**	No change to declaration
Tenth GDG Meeting (9th April 2010)	No change to declaration
Eleventh GDG meeting (June 2010)	No change in declaration

Dr Paul Foley (Deputy for Dr Leyva)

GDG meeting	Declaration of Interests
GDG Application	Not applicable
GDG Induction meeting **(30th January 2009)**	DNA
First GDG meeting (27th February 2009)	DNA
Second GDG Meeting **(27th March 2009)**	DNA
Third GDG Meeting **(1st May 2009)**	DNA
Fourth GDG Meeting **(5th June 2009)**	DNA
Fifth GDG Meeting **(3rd July 2009)**	DNA
Sixth GDG Meeting **(31st July 2009)**	FL declared the following item of **personal pecuniary interest:** • The Heart of England NHS Foundation Trust receives payment from Medtronic Inc which goes towards his Research Fellow's salary PF declared no items of **personal family interest, non-personal pecuniary interest** or **personal non-pecuniary interest**
Seventh GDG Meeting **(18th September 2009)**	DNA
Eighth GDG Meeting **(16th October 2009)**	DNA
Ninth GDG Meeting **(13th November 2009)**	DNA
Tenth GDG Meeting (9th April 2010)	As above plus; PF declared the following item of **personal pecuniary interest:** • Chaired research meeting for Medtronic at which clinical research fellow presented data And the following item of personal non-pecuniary interest: • ongoing research into CRT
Eleventh GDG meeting (June 2010)	DNA

Dr Ahmet Fuat – Deputy for Dr Davis

GDG meeting	Declaration of Interests
GDG Application	Not applicable
GDG Induction meeting **(30th January 2009)**	DNA
First GDG meeting (27th February 2009)	AF declared the following items of **personal non-pecuniary interest:** • Chair of National GPs with specialist interest in Cardiology National Forum • Hon Sec of Primary care Cardiovascular Society AF did not declare any items of **personal pecuniary interest, personal family interest,** or **non-personal pecuniary interest**
Second GDG Meeting **(27th March 2009)**	DNA
Third GDG Meeting **(1st May 2009)**	DNA
Fourth GDG Meeting **(5th June 2009)**	DNA
Fifth GDG Meeting **(3rd July 2009)**	AF declared the following item of **personal pecuniary interest:** • Member of an Advisory Board on use of Candesartan for heart failure for Takeda Pharmaceuticals since February 2009. The chair reviewed the declarations of interest and noted the declarations of interest.
Sixth GDG Meeting **(31st July 2009)**	DNA
Seventh GDG Meeting **(18th September 2009)**	DNA
Eighth GDG Meeting **(16th October 2009)**	DNA
Ninth GDG Meeting **(13th November 2009)**	DNA AF declared the following item of **personal pecuniary interest:** • Honoraria from Pfizer for lecturing (Nov 2010).
Future commitments	AF declared the following item of **personal pecuniary interest:** • Honoraria from Pfizer for lecturing (Feb 2010).
Tenth GDG Meeting (9th April 2010)	DNA
Eleventh GDG meeting (June 2010)	DNA

Ms Jane Gilmour

GDG meeting	Declaration of Interests
GDG Application **(5th Nov 2008)**	JG did not declare any items of **personal pecuniary interest, personal family interest, non-personal pecuniary interest, personal non-pecuniary interest**
GDG Induction meeting **(30th January 2009)**	No change to declaration
First GDG meeting (27th February 2009)	No change to declaration
Second GDG Meeting **(27th March 2009)**	No change to declaration
Third GDG Meeting **(1st May 2009)**	No change to declaration
Fourth GDG Meeting **(5th June 2009)**	No change to declaration
Fifth GDG Meeting **(3rd July 2009)**	No change to declaration
Sixth GDG Meeting **(31st July 2009)**	No change to declaration
Seventh GDG Meeting **(18th September 2009)**	No change to declaration
Eighth GDG Meeting **(16th October 2009)**	No change to declaration
Ninth GDG Meeting **(13th November 2009)**	No change to declaration
Tenth GDG Meeting (9th April 2010)	JG declared an item of **non-personal non-pecuniary interest:** • Panel member at heart failure education event sponsored by Takeda (22/4/10)
Eleventh GDG meeting (June 2010)	No change in declaration

Dr Suzanna Hardman

GDG meeting	Declaration of Interests
GDG Application 19/11/08	SH declared the following items of **personal pecuniary interest:** • Share holdings in Glaxo and Astra Zeneca • Honorarium from Otsuku for taking part in an Advisory Board.(June 2008) • Travel expenses/accommodation from Takeda to attend ESC meeting (June 2008) • Honorarium from Menarini for taking part in an Advisory Board (Feb 2008) SH also declared the following item of **personal family interest:** • Husband has an investment with Glaxo Welcome SH declared the following item of **personal non-pecuniary interest** • Chair–elect of the British Society for Heart Failure SH did not declare any item of **non-personal pecuniary interest**
GDG Induction meeting **(30th January 2009)**	No change to declaration
First GDG meeting **(27th February 2009)**	Potential conflict of interest from attending Advisory Board for Menarini expires.
Second GDG Meeting **(27th March 2009)**	DNA
Third GDG Meeting **(1st May 2009)**	No change to declaration
Fourth GDG Meeting **(5th June 2009)**	No change to declaration
Fifth GDG Meeting **(3rd July 2009)**	No change to declaration
Sixth GDG Meeting **(31st July 2009)**	No change to declaration
Seventh GDG Meeting **(18th September 2009)**	No change to declaration
Eighth GDG Meeting **(16th October 2009)**	No change to declaration
Ninth GDG Meeting **(13th November 2009)**	No change to declaration
Tenth GDG Meeting (9th April 2010)	As above plus: SH declared the following item of **personal non-pecuniary interest:** • Speaker at Acute to Chronic Cardiovascular disease meeting on 25th March 2010 (Supported by Pfizer).
Eleventh GDG meeting (June 2010)	SH declared an item of **personal non-pecuniary interest:**

	• Discussions with Milliman re development of an ICP for heart failure

Dr Francisco Leyva

GDG meeting	Declaration of Interests
GDG Application 12/11/08	FL declared the following item of **non-personal pecuniary interest:** • The pacemaker industry (Medtronic Inc and St Jude Medical) provide funding for the salary of two of his research fellows who are involved in pacemaker and imaging research. Medtronic Inc has also funded a pacemaker research trial under his direction FL did not declare any items of **personal pecuniary interest, personal family interest or personal non-pecuniary interest**.
GDG Induction meeting **(30th January 2009)**	No change in declaration
First GDG meeting (27th February 2009)	No change in declaration
Second GDG Meeting **(27th March 2009)**	No change in declaration
Third GDG Meeting **(1st May 2009)**	No change in declaration
Fourth GDG Meeting **(5th June 2009)**	As above plus: FL declared an item of **personal pecuniary interest:** • Menarini provided funding for travel and accommodation for a conference in Barcelona
Fifth GDG Meeting **(3rd July 2009)**	No change in declaration
Sixth GDG Meeting **(31st July 2009)**	DNA
Seventh GDG Meeting **(18th September 2009)**	No change in declaration
Eighth GDG Meeting **(16th October 2009)**	No change in declaration
Ninth GDG Meeting **(13th November 2009)**	No change to declaration
Tenth GDG Meeting (9th April 2010)	No change to declaration
Eleventh GDG meeting (June 2010)	No change in declaration

Dr Hugh McIntyre

GDG meeting	Declaration of Interests
GDG Application 14/11/08	HM declared the following items of **personal pecuniary interest:** • Member of Advisory Board for Otsuku (Tolvaptan- prelicence product – possibly of heart failure) (June 2008) • Member of Advisory Board for Servier (Ivabradine – Angina) Oct 2009 • Reimbursement from Novartis, MSD, Pfizer for lecturing, in the 12montsh prior to Nov 2008 • Reimbursement from Servier (July 2008) and MSD (Jan 2008) for programme development and event chairing. • Expenses and hospitality to attend meetings and conferences 12 months before the GDG started HM declared the following item of **personal non-pecuniary interest:** • Consultancy (unpaid) to Extralife (independent provider of left ventricular assist devices) • Member of the Editorial board of the European Journal of Heart Failure (2008 onwards) HM declared the following item of **non-personal pecuniary interest:** • Educational grant from Takeda to support two year doctorate Research Fellow investigating socioeconomic gradient in heart failure (From Jan 2009). This does not involve any medical or product application or research • Member of ESC heart failure association committee on heart failure with preserved ejection fraction (From 2008) • Member of ESC heart failure association committee on education (From 2008) HM did not declare any items of **personal family interest**
GDG Induction meeting **(30th January 2009)**	No change to declaration
First GDG meeting (27th February 2009)	No change to declaration
Second GDG Meeting **(27th March 2009)**	No change to declaration
Third GDG Meeting **(1st May 2009)**	No change to declaration
Fourth GDG Meeting **(5th June 2009)**	As above plus: HM declared the following item of **personal pecuniary interest:** • Meeting fees, travel and accommodation for the Heart Failure Update meeting of the European Society of cardiology (NICE, May 30 – June 2nd) provided by Takeda pharmaceuticals • Meeting fees, travel and accommodation for the annual meeting of the European Society of Cardiology (Aug 30th – Sept 2nd) – provided by Servier pharmaceuticals
Fifth GDG Meeting **(3rd July 2009)**	No change to declaration
Sixth GDG Meeting **(31st July 2009)**	No change to declaration

Seventh GDG Meeting **(18th September 2009)**	No change to declaration
Eighth GDG Meeting **(16th October 2009)**	HM declared the following item of personal pecuniary interest: • Involved in a mathematical economic modelling project, funded by Novartis, on costing pathways. (From June 2009)
Ninth GDG Meeting **(13th November 2009)**	HM declared the following item of **personal pecuniary interest:** Received expenses from the Heart Failure Association of the European Society of Cardiology to attend and contribute to a meeting on heart failure with preserved ejection fraction (August 2009)
Future commitments	HM declared the following future commitments with **personal pecuniary interest:** • Member of Advisory Board for Takeda (Hypertension: Ivabradine – angina) (Nov 2009) • Member of Advisory Board for Sanofi (Dabigatron – prelicence anticoagulant (Dec 09) • Member of Advisory Board for MSD (Atrial fibrillation) (Dec09) • Member of Advisory Board for MSD (Sitagliptin – Diabetes) (Jan 2010)
Tenth GDG Meeting (9th April 2010)	No change to declaration
Eleventh GDG meeting (June 2010)	No change in declaration

Professor Jonathan Mant

GDG meeting	Declaration of Interests
GDG Application	JM declared the following items of **personal pecuniary interest:** • Consultancy for Expert-24, which advises on the Norwich Union HealthCare Site • Consultancy for PharmaSwiss, a drug company that markets drugs to parts of Southern and Eastern Europe. • Member of Regional Advisory Board for Boehringer Ingelheim (one meeting 10/11/2009). JM declared the following item of **personal family interest:** • Brother, Professor Tim Mant, is employed by Quintiles, which is a bioctech company involved in drug development. JM declared the following item of **personal non-pecuniary interest:** • Associate Director, Stroke Research Network JM did not declare any items of **non-personal pecuniary interest**
GDG Induction meeting **(30th January 2009)**	No change in declaration
First GDG meeting (27th February 2009)	No change in declaration
Second GDG Meeting **(27th March 2009)**	No change in declaration
Third GDG Meeting **(1st May 2009)**	No change in declaration
Fourth GDG Meeting **(5th June 2009)**	No change in declaration
Fifth GDG Meeting **(3rd July 2009)**	No change in declaration
Sixth GDG Meeting **(31st July 2009)**	No change in declaration
Seventh GDG Meeting **(18th September 2009)**	As above plus JM declared the following item of **personal pecuniary interest:** • Travel grant from Boehringer Ingelheim to attend European Society of Cardiology meeting at end of August 2009.
Eighth GDG Meeting **(16th October 2009)**	No change to declaration
Ninth GDG Meeting **(13th November 2009)**	No change to declaration
Tenth GDG Meeting (9th April 2010)	No change in declaration
Eleventh GDG meeting (June 2010)	No change in declaration

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

Mr Richard Mindham

GDG meeting	Declaration of Interests
GDG Application 11/11/08	RM did not declare any items of **personal pecuniary interest, personal family interest, non-personal pecuniary interest, personal non-pecuniary interest**
GDG Induction meeting **(30th January 2009)**	No change in declaration
First GDG meeting (27th February 2009)	No change in declaration
Second GDG Meeting **(27th March 2009)**	No change in declaration
Third GDG Meeting **(1st May 2009)**	No change in declaration
Fourth GDG Meeting **(5th June 2009)**	No change in declaration
Fifth GDG Meeting **(3rd July 2009)**	No change in declaration
Sixth GDG Meeting **(31st July 2009)**	No change in declaration
Seventh GDG Meeting **(18th September 2009)**	No change in declaration
Eighth GDG Meeting **(16th October 2009)**	No change in declaration
Ninth GDG Meeting **(13th November 2009)**	No change to declaration
Tenth GDG Meeting (9th April 2010)	No change to declaration
Eleventh GDG meeting (June 2010)	No change in declaration

Mr Adrian Price

GDG meeting	Declaration of Interests
GDG Application 30/1/09	AP did not declare any items of **personal pecuniary interest, personal family interest, non-personal pecuniary interest, personal non-pecuniary interest**
GDG Induction meeting **(30th January 2009)**	No change to declaration
First GDG meeting (27th February 2009)	No change to declaration
Second GDG Meeting **(27th March 2009)**	No change to declaration
Third GDG Meeting **(1st May 2009)**	No change to declaration
Fourth GDG Meeting **(5th June 2009)**	No change to declaration
Fifth GDG Meeting **(3rd July 2009)**	No change to declaration
Sixth GDG Meeting **(31st July 2009)**	No change to declaration
Seventh GDG Meeting **(18th September 2009)**	No change to declaration
Eighth GDG Meeting **(16th October 2009)**	No change to declaration
Ninth GDG Meeting **(13th November 2009)**	No change to declaration
Tenth GDG Meeting (9th April 2010)	No change to declaration
Eleventh GDG meeting (June 2010)	No change in declaration

Dr Paul Collinson (Expert Advisor)

GDG meeting	Declaration of Interests
GDG Application	Not applicable
GDG Induction meeting **(30th January 2009)**	DNA
First GDG meeting (27th February 2009)	PC declared no items of **personal pecuniary interest, personal family interest, non-personal pecuniary interest or personal non-pecuniary interest**
Second GDG Meeting **(27th March 2009)**	No changes to declaration
Third GDG Meeting **(1st May 2009)**	DNA
Fourth GDG Meeting **(5th June 2009)**	DNA
Fifth GDG Meeting **(3rd July 2009)**	DNA
Sixth GDG Meeting **(31st July 2009)**	No changes to declaration
Seventh GDG Meeting **(18th September 2009)**	DNA
Eighth GDG Meeting **(16th October 2009)**	DNA
Ninth GDG Meeting **(13th November 2009)**	DNA
Tenth GDG Meeting (9th April 2010)	DNA
Eleventh GDG meeting (June 2010)	DNA

Ms Aynsley Cowie (Expert Advisor)

GDG meeting	Declaration of Interests
GDG Application	Not applicable
GDG Induction meeting **(30th January 2009)**	DNA
First GDG meeting (27th February 2009)	DNA
Second GDG Meeting **(27th March 2009)**	DNA
Third GDG Meeting **(1st May 2009)**	DNA
Fourth GDG Meeting **(5th June 2009)**	DNA
Fifth GDG Meeting **(3rd July 2009)**	AC declared no items of **personal pecuniary interest, personal family interest, non-personal pecuniary interest or personal non-pecuniary interest**
Sixth GDG Meeting **(31st July 2009)**	DNA
Seventh GDG Meeting **(18th September 2009)**	DNA
Eighth GDG Meeting **(16th October 2009)**	DNA
Ninth GDG Meeting **(13th November 2009)**	DNA
Tenth GDG Meeting (9th April 2010)	DNA
Eleventh GDG meeting (June 2010)	DNA

Appendix M – 2003 Guideline

See separate file

Appendix N – 2003 deleted recommendations

Diagnosis

R2 Healthcare professionals should seek to exclude a diagnosis of heart failure through the following investigations:

- 12lead ECG
- And or natriuretic peptides (BNP or NT-proBNP) – where available

If one or both are abnormal a diagnosis of heart failure cannot be excluded and transthoracic Doppler 2D echocardiography should be performed because it consolidates the diagnosis and provides information on the underlying functional abnormality of the heart

R9 If the diagnosis is unclear or if a diagnosis of diastolic heart failure is being considered refer the patient for more specialist assessment

Treatment - Lifestyle

R12 Patients with heart failure should be encouraged to adopt regular aerobic and/or resistive exercise. This may be more effective when part of an exercise programme or a programme of rehabilitation.

Treatment – Pharmacological treatment

R22 All patients with heart failure due to left ventricular systolic dysfunction should be considered for treatment with an ACE inhibitor.

R23 ACE inhibitor therapy should be instituted in patients with heart failure due to left ventricular systolic dysfunction before beta-blockade is introduced.

R26 Beta-blockers licensed for use in heart failure should be initiated in patients with heart failure due to LV systolic dysfunction after diuretic and ACE inhibitor therapy (regardless of whether or not symptoms persist).

R32 At the time of issue of this guideline, angiotensin-II receptor antagonists (see Table 8) are not licensed in the UK for heart failure and studies are ongoing. However, angiotensin-II receptor antagonists may provide an alternative to ACE inhibitors for patients intolerant of ACE inhibitors (for example, because of cough

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

R 37 Anticoagulation is indicated for patients with the combination of heart failure and atrial fibrillation.

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

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

R52 For patients with heart failure and atrial fibrillation, specialist advice should be sought as to whether the aim is improvement of heart rate control or cardioversion (return to sinus rhythm).

R59 The principles of pharmacological management should be the same for all patients with heart

failure, regardless of ethnicity.

Treatment - Cardiac resynchronisation therapy

R47 Resynchronisation therapy should be considered in selected patients with left ventricular systolic dysfunction (LVEF <= 35%), drug refractory symptoms, and a QRS duration > 120 ms. The result of ongoing trials will help guide appropriate patient selection. [2003, R47]

Treatment - Implantable cardioverter-defibrillators (ICDs)

R48 Recommendation from NICE Technology Appraisal Guidance No. 11 Guidance on the use of implantable cardioverter defibrillators for arrhythmias (www.nice.org.uk/Docref.asp?d=10239):

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

"Secondary prevention" ie for patients who present, in the absence of a treatable cause, with:

- Cardiac arrest due to either ventricular tachycardia (VT) or ventricular fibrillation (VF).
- Spontaneous sustained VT causing syncope or significant haemodynamic compromise.
- Sustained VT without syncope/cardiac arrest, and who have an associated reduction in ejection fraction (less than 35%) but are no worse than class 3 of the New York Heart Association functional classification of heart failure.

"Primary prevention" for patients (see paragraph 2.5 for definition) with:

- a history of previous myocardial infarction (MI) and all of the following:
- i) non sustained VT on Holter (24 hour ECG) monitoring;
- ii) inducible VT on electrophysiological testing;
- iii) left ventricular dysfunction with an ejection fraction (EF) less than 35% and no worse than class III of the New York Heart Association functional classification of heart failure.
- A familial cardiac condition with a high risk of sudden death, including long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome, arrhythmogenic right ventricular dysplasia (ARVD) and following repair of Tetralogy of Fallot.[2003, R48]