Chronic heart failure: Evidence Update November 2011

Evidence Updates provide a regular, often annual, summary of selected new evidence published since the literature search was last conducted for the accredited guidance they update. They reduce the need for individuals, managers and commissioners to search for new evidence and inform guidance developers of new evidence in their field. In particular, Evidence Updates highlight any new evidence that might generate future change to the practice described in the most recent, accredited guidance, and provide a commentary on the potential impact. Any new evidence that may impact current guidance will be notified to the appropriate NICE teams. For contextual information, Evidence Updates should be read in conjunction with the relevant clinical guideline, available from the NHS Evidence topic page (www.evidence.nhs.uk/topic/chronic-heart-failure). NHS Evidence is a service provided by NICE to improve use of, and access to, evidence-based information about health and social care.

Evidence Updates do not replace current accredited guidance and do not provide formal practice recommendations.

National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
London WC1V 6NA
www.nice.org.uk

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Introduction

This Evidence Update identifies new evidence that might generate future change to the practice laid out in the following reference guidance:


Just over 2000 pieces of evidence were identified and assessed of which 35 were selected for the Evidence Update. An Evidence Update Advisory Group, comprised of subject experts, has reviewed the prioritised evidence and provided a commentary.

Other relevant NICE guidance

The focus of the Evidence Update is on the guidance stated above. However, overlap with other NICE guidance has been outlined as part of the Evidence Update process. Where relevant, this Evidence Update therefore makes reference to the following guidance:


Other relevant guidance

The following guidance, endorsed by the British Cardiovascular Society, is also of relevance to UK heart failure practice, however the Evidence Update does not discuss any potential effect the new evidence may have upon their recommendations:


1 NHS Evidence-accredited guidance is denoted by the accreditation symbol
2 Guidance published prior to NHS Evidence accreditation
Quality standards

- Chronic heart failure. NICE quality standard. Available from [www.nice.org.uk/guidance/qualitystandards/chronicheartfailure/home.jsp](http://www.nice.org.uk/guidance/qualitystandards/chronicheartfailure/home.jsp)

Other relevant information


- Cardiac rehabilitation service. NICE guide for commissioners. Available from [www.nice.org.uk/usingguidance/commissioningguides/cardiacrehabilitation/cardiacrehabilitation.jsp](http://www.nice.org.uk/usingguidance/commissioningguides/cardiacrehabilitation/cardiacrehabilitation.jsp)

- NHS Improvement – Heart failure. Available at [www.improvement.nhs.uk/heart/heartfailure](http://www.improvement.nhs.uk/heart/heartfailure)

Audit

The ongoing National Heart Failure Audit aims to provide national comparative data to help clinicians and managers improve the quality and outcomes of their services.


Feedback

If you have any comments you would like to make on this Evidence Update, please email contactus@evidence.nhs.uk
## Key messages

The following table summarises what the Evidence Update Advisory Group (EUAG) decided were the key messages from the Evidence Update. It also indicates the EUAG’s opinion on whether new evidence identified by the Evidence Update has potential to generate future change to the current guidance listed in the introduction.

The relevant NICE teams have been made aware of this evidence which will be considered when guidance is reviewed. For further details of the evidence behind these key messages and the specific guidance which may be affected, please see the full commentaries.

<table>
<thead>
<tr>
<th>Key message</th>
<th>Effect on guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>• B-type natriuretic peptide adds value in the diagnosis of patients clinically suspected of slow onset heart failure in primary care but cut-off values remain problematic.</td>
<td>✓</td>
</tr>
<tr>
<td>• Osteoprotegerin predicts worsening heart failure events. More data are needed on its mechanism of release and clinical utility.</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Non-pharmacological management</strong></td>
<td>✓</td>
</tr>
<tr>
<td>• Tai chi exercise may improve health-related quality of life although a larger study of its clinical and cost effectiveness is required.</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Pharmacological management</strong></td>
<td>✓</td>
</tr>
<tr>
<td>• Trimetazidine may be useful in the treatment of heart failure. Larger studies are warranted. However, the drug is not licensed in the UK.</td>
<td>✓</td>
</tr>
<tr>
<td>• Evidence is emerging on the potential benefit of active management of iron deficiency, anaemia and chronic kidney disease in patients with heart failure.</td>
<td>✓</td>
</tr>
<tr>
<td>• Ivabradine is not licensed in the UK for heart failure, and a NICE technology appraisal is due to begin in 2012 which should be referred to upon publication. Evidence suggests that ivabradine may be a useful adjunct to beta-blockers in heart failure management for those with a resting heart rate above 70 beats per minute intolerant of, or on maximum tolerated doses of, beta-blockers.</td>
<td>✓</td>
</tr>
<tr>
<td>• Evidence suggests that aldosterone antagonists may be of benefit in patients with moderate or severe left ventricular systolic dysfunction (left ventricular ejection fraction &lt; 35%) whether symptoms are mild, moderate or severe.</td>
<td>✓</td>
</tr>
<tr>
<td>• Novel potassium binding agents may offer a potential solution for patients with hyperkalaemia accompanying aldosterone antagonist use but more research is needed.</td>
<td>✓</td>
</tr>
<tr>
<td>• Evidence suggests that statins are ineffective in patients with moderate or severe heart failure and use should be confined to those with coronary disease and in accordance with existing NICE guidance.</td>
<td>✓</td>
</tr>
</tbody>
</table>
### Invasive procedures

- Cardiac resynchronization therapy (CRT) may reduce exacerbations of heart failure and may prolong life in patients with heart failure, left ventricular systolic dysfunction (LVSD) and a broad QRS width on the electrocardiogram even when symptoms are mild.
- Whether CRT with an implantable cardioverter-defibrillator leads to better outcomes than CRT alone is not yet clear.
- Skeletal myoblast implantation in an attempt to treat LVSD is an interesting area of research.
- Functional electrostimulation may be of benefit in those unable to take part in physical exercise but more evidence is needed.

### Monitoring

- Monitoring of pulmonary artery pressures using wireless implants shows promise. Longer, more robust studies are now required.
- There is a need for well-designed, definitive studies of telemonitoring to provide firm evidence of benefit and cost-effectiveness.
- Good heart rate control can reduce morbidity and mortality.
- The validity of N-terminal pro-B-type natriuretic peptide monitoring is questioned by current evidence and more evidence is needed in this area.
- Management of heart failure by sufficient numbers of well-trained staff and strict adherence to evidence-based prescribing may have similar benefits to home telemonitoring.
1 Commentary on new evidence

These commentaries analyse the key references identified specifically for the Evidence Update, which are identified in bold text. Supporting references are also provided.

1.1 Diagnosis

B-type natriuretic peptide

A meta analysis by Kelder et al. (2011) investigated the value of B-type natriuretic peptide (BNP) level as a diagnostic parameter in addition to typical clinical signs and symptoms in the identification of suspected slow-onset heart failure (HF) patients in primary care. The study dataset was a clinical cohort of 276 patients made up by combining existing datasets from two previous studies in Hillingdon, West London (1997) and Rotterdam (2000), where patients with suspected HF were referred to rapid access diagnostic clinics for diagnosis using European Society of Cardiology (ESC) criteria. A multivariate diagnostic model was developed and validated against the 2005 UK Natriuretic Peptide study of 306 patients. In the derivation dataset, 30.8% of patients were diagnosed with HF compared with 34% in the validation dataset.

BNP was found to be a robust biomarker for HF when added to clinical features. In contrast, the incorporation of any electrocardiogram abnormality or cardio-thoracic ratio > 0.55 added little diagnostic yield on top of clinical features alone. A comparison of BNP levels using the ESC guideline (and additionally the Dutch multidisciplinary guideline) cut-off points of < 100 pg/ml (or < 35 pg/ml) to 'rule out' or > 400 pg/ml (or > 100 pg/ml) to 'rule in' the diagnosis of HF also performed poorly. A significant number of this primary care population would still require echocardiographic assessment. The study found the use of BNP adds value in the diagnosis of those clinically suspected of slow onset HF in primary care but cut-off values remain problematic. This evidence is unlikely to affect NICE clinical guideline (CG) 108.

Key reference
Abstract: www.heart.bmj.com/content/97/12/959.abstract

Osteoprotegerin

In a sub-study of 1464 patients from the previously reported randomised Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA; patients ≥ 60 years; 10 mg rosuvastatin daily vs placebo), Ueland et al. (2011) found that osteoprotegerin (OPG) did not predict a primary end point of combined cardiovascular (CV) death, nonfatal myocardial infarction or nonfatal stroke, but did predict frequency of hospitalisation for worsening HF (hazard ratio [HR] = 1.10; 95% confidence interval [CI] 1.04 to 1.16) which remained significant following adjustment for N-terminal pro-B-type natriuretic peptide (NT-proBNP). OPG was also found to be strong predictor for non-CV death.

The study looked at a relatively large population and provides preliminary but potentially promising results for OPG as a predictor of worsening HF, however it is unclear if the higher levels of OPG are of vascular or myocardial origin. Until more conclusive data including cost-effectiveness analyses are available this evidence is unlikely to affect NICE CG108.
1.2 Non-pharmacological management

Physical fitness, exercise and tai chi

In a randomised controlled trial (RCT) of 69 patients (mean age ~60 years), Beckers et al. (2010) compared usual care with regimens of usual care plus either home training (with home exercise equipment), supervised training (in a rehab centre), or preferred training (PT; patients’ own choice of exercise). PT offered continued benefits over other programmes in terms of maintained or increased exercise capacity measured by workload at the respiratory compensation point (p = 0.045) and submaximal workload efficiency (p < 0.0001). The small size and relatively young age of the study population mean that results may need to be interpreted with caution; a larger trial more representative of the general HF population is required to fully understand how best to tailor interventions and support physical function and improvement in outcomes. Lack of detail regarding nature and intensity of exercise undertaken by those in the PT group also limited the learning potential of this evidence. This study tends to reinforce recommendations in NICE CG108 on exercise-based rehabilitation, however the question remains whether exercise actually affects the natural history of disease progression or whether benefits are due to improved patient wellbeing.

Kitzman et al. (2010) reported an RCT of exercise training (ET) in 53 patients (mean age 70 years) with HF and preserved left ventricular ejection fraction. Patients in the ET group had a significant increase in peak exercise VO2 power output and exercise time at follow-up compared with the control group (all p < 0.001). However there were no associated overall improvements in health-related quality of life (HRQOL) as measured by the Short Form-36 Item Health Survey, or the overall Minnesota Living with Heart Failure Questionnaire (MLHFQ) score (although a significant improvement [p < 0.03] in the physical functioning aspect of this score was observed).

Although the results seem to suggest that ET may have a place in HF management, the small sample size and age of the data (collected in the 1990s) mean it is difficult to extrapolate findings to the modern HF population and therefore this evidence is unlikely to affect NICE CG108.

An RCT by Yeh et al. (2011) of 100 patients (mean age ~67 years) with systolic HF and left ventricular ejection fraction (LVEF) of < 40% found that a 12-week course of weekly tai chi taught by trained instructors made no significant difference to the change in 6-minute walk distance and peak oxygen uptake between intervention and control groups. However improvements were seen in HRQOL (measured by MLHFQ; p = 0.02), exercise self-efficacy (p < 0.001) and mood (p = 0.01). Tai chi may be of benefit to physical and mental function, providing a novel addition to the range of more traditional exercises used during HF management. However this form of exercise may not suit all patients, and a larger study looking at clinical and cost effectiveness is required. Therefore currently this evidence is unlikely to affect NICE CG108.
Key references
Abstract: www.cpr.sagepub.com/content/17/6/660

Full text: www.circheartfailure.ahajournals.org/content/3/6/659.full.pdf+html

Abstract: www.archinte.ama-assn.org/cgi/content/abstract/171/8/750

Self management
Ditewig et al. (2010) conducted a systematic review of 19 RCTs (~4000 patients) comparing the effect of self-management with standard care on mortality, all-cause hospital readmission, HF hospitalisation rate and HRQOL. Due to considerable clinical and methodological heterogeneity between the included studies, no definitive conclusions on the effectiveness of self-management on the outcomes under investigation could be drawn, and therefore this evidence is unlikely to contribute substantially to current knowledge or affect NICE CG108.

In an RCT of 317 patients (mean age ~67 years) with HF comparing the effect of a moderately intensive nurse-led self-management programme with usual care, Smeulders et al. (2010) found that despite significant improvements immediately after the programme in each of cognitive symptom management, self-care behaviour and cardiac-specific HRQOL, no sustained effects were seen for these outcomes at 6- and 12-month follow-up. It is not clear if the relatively resource-intensive self-management support provided in the study (6 x weekly group sessions of 2.5 hours) would offer a cost-effective management strategy in the wider population. This evidence is unlikely to affect NICE CG108. As Jaarsma et al. (2008) recently reported in the COACH study, a high intensity intervention does not guarantee health benefits.

Two recent papers providing self-care management guidance (McDonagh et al. 2011 and Lainscak et al. 2011) may also be a useful further resource within this therapeutic area. A NICE cardiac rehabilitation service guide for commissioners is also available which provides support for the local implementation of NICE clinical guidelines through commissioning, and is a resource to help health professionals in England to commission an effective cardiac rehabilitation service.

Key references

1.3 Pharmacological management

Trimetazidine

The use of trimetazidine, which is not currently licensed in the UK, has been examined in HF in a meta-analysis of 17 RCTs (955 patients) by Gao et al. (2011). It was found that trimetazidine may significantly improve LVEF, New York Heart Association (NYHA) classification and exercise duration, and reduce left ventricular end-systolic volume (all p < 0.01). The data also suggest a beneficial effect on all-cause mortality, cardiovascular events and hospitalisation (all p < 0.00001). The analyses are based on small studies of variable quality and short follow-up periods, but trimetazidine shows potential in the treatment of HF, and a large, properly powered RCT with a long follow-up period may now be warranted. There are no current implications of the data for NICE CG108.

Key reference
Full text: www.heart.bmj.com/content/97/4/278.full

n-3 polyunsaturated fatty acids

In a sub-study of 1027 patients (mean age ~65 years) from the previously reported GISSI-HF trial, Ghio et al. (2010) investigated the effects of n-3 polyunsaturated fatty acids (n-3 PUFA) and rosuvastatin on left ventricular (LV) function. No significant effects were observed for rosuvastatin, but in the n-3 PUFA group LVEF increased by 11.5% at 3 years vs 9.9% in the placebo group (p = 0.005).

The evidence may potentially be limited by the reliance on interpretation of echocardiography, with its inherent subjectivity, to measure LVEF. The 3-year analysis also appears to have compared those surviving to 3 years with all the patients at baseline. This may need to be considered when interpreting findings, as a substantial number of participants had died by 3-year follow-up. The biological plausibility of the effect of n-3 PUFA may also be debatable, along with the question of whether the small, if significant, increase in LVEF reported in this study is of clinical relevance. The improvement in LVEF in both the treatment and placebo arms suggests that other therapies (such as beta-blockers) may have been responsible for some of the observed effects. This evidence is therefore unlikely to affect NICE CG108.

Key reference
Abstract: www.eurjhf.oxfordjournals.org/content/12/12/1345.abstract
**Erythropoiesis-stimulating agents**

A systematic review of 11 RCTs (794 patients) by Kotecha et al. (2011) found that treatment of anaemia in HF with erythropoiesis-stimulating agents (ESA) can improve exercise duration by 96.8 seconds ($p = 0.04$), and 6-minute walk distance by 69.3 metres ($p = 0.009$). Improvements were also noted for peak oxygen consumption ($p = 0.007$), NYHA class, ejection fraction and B-type natriuretic peptide (all $p < 0.001$). Anaemia was defined differently across the studies (haemoglobin levels ranging from 9 to < 12.5 g/dL), and a mean increase in haemoglobin of 2 g/dL ($p < 0.00001$) was observed.

The review used the Cochrane methodology, but the data are taken from small, heterogeneous studies with varying endpoints and short-term follow-up. A large trial of darbopoetin alfa (RED-HF) is underway which may help to provide further insight. In particular, there have been some concerns about the safety profile of ESAs in other trials (see FDA Drug Safety Communication: Modified dosing recommendations to improve the safe use of ESAs in chronic kidney disease for more information).

The current evidence is unlikely to affect NICE CG108, however the general area of iron deficiency, anaemia and chronic kidney disease in HF may now warrant greater attention. For example, iron therapy in the form of ferric carboxymaltose has recently been shown in an RCT to benefit HF patients with iron deficiency (Anker et al. 2009). ‘Anaemia management in people with chronic kidney disease’ (NICE CG114) should be the current point of reference for the use of ESAs in anaemia management in patients with HF with chronic kidney disease.

**Key reference**

**Supporting references**

RED-HF Trial - Reduction of Events With Darbepoetin Alfa in Heart Failure Trial.
[www.ukctg.nihr.ac.uk/trialdetails/NCT00358215](http://www.ukctg.nihr.ac.uk/trialdetails/NCT00358215)

**Ivabradine**

Ivabradine is not currently licensed in the UK for HF, and a NICE technology appraisal is due to begin in February 2012 ([www.guidance.nice.org.uk/TA/Wave26/10](http://www.guidance.nice.org.uk/TA/Wave26/10)). This guidance should be referred to as soon as it is published.

A recent study has investigated ivabradine for the treatment of HF. In an RCT of 6558 patients (the SHIFT trial; mean age ~60 years) with HF, Swedberg et al. (2010) reported that ivabradine led to a significant reduction in the number of primary endpoint events (cardiovascular death or hospital admission for worsening HF) compared with placebo (24% vs 29%; $p < 0.0001$). This primary end point was driven by a reduction in admissions for worsening heart failure (15% in the ivabradine patients vs 21% for placebo; $p < 0.0001$), but CV death was not significantly different (14% vs 15%; $p = 0.128$).

Despite the relatively young study population, the data suggest a potential role for ivabradine as an adjunct to beta-blockers in HF management. However it must be stressed that beta-blockers remain the primary therapy with a direct effect on heart rate proven to prolong life (ivabradine had no significant effect on overall mortality in the SHIFT study) and ivabradine may be introduced only in patients intolerant of beta-blockers or those whose heart rate remains above 70 beats per minute (bpm) despite a maximally tolerated beta-blocker dose.
Further information from the National Prescribing Centre on ivabradine in HF can be found at www.nww.npc.nhs.uk/secure/new_medicines/cardio/heart/oth_ivabradine.php

(See ‘Heart rate as a risk factor’ in section 1.5 ‘Monitoring’ for further research stemming from the SHIFT study).

**Key reference**
Abstract: www.thelancet.com/journals/lancet/article/PIIS0140-6736(10)61198-1/abstract

**Aldosterone antagonists**
Currently NICE CG108 recommends second-line treatment with aldosterone antagonists (AA) in patients with NYHA class III-IV or those who have had a myocardial infarction complicated by HF in the last month. Two recent papers have examined the effect of AAs in patients with milder HF.

In an RCT of 168 patients (NYHA class I–II; LVEF ≤ 40%; mean age 58 years in placebo arm, 61 years in treatment arm) Vizzardi et al. (2010) investigated the effect of spironolactone on LV remodeling. In the spironolactone group, LVEF increased from 35.2% to 39.1% (p < 0.001), LV end-diastolic and end-systolic volumes and myocardial mass all decreased, and LV diastolic filling pattern also improved. However the small study size, relatively short follow-up and the fact that the remodeling data go against findings in a larger RCT (Boccanelli et al. 2008) mean that the results may need to be interpreted cautiously.

Looking at an alternative AA, Zannad et al. (2011) conducted an RCT of eplerenone in 2737 patients with mild HF (NYHA class II; LVEF ≤ 35%; mean age ~69 years) and found that a primary event (death from cardiovascular causes or hospitalisation for HF) occurred in 18.3% of patients receiving eplerenone and 25.9% of patients in the placebo arm (p < 0.001).

Although the trial was stopped early due to prespecified rules (which may have resulted in overestimation of effects), the results suggest that eplerenone may be of benefit for patients with HF of all severities and LV systolic dysfunction. These findings may need to be considered in future reviews of NICE CG108. Further information from the National Prescribing Centre on eplerenone in mild HF can be found at www.npc.nhs.uk/rapidreview/?p=2359

Hyperkalaemia can be a potential problem associated with AA use, and Pitt et al. (2011) have examined whether inhibiting potassium absorption in the gut via a binding polymer (RLY5016) can prevent a rise in serum potassium in people with HF failure on AAs. In an RCT of 105 patients (mean age 68 years) with a history of hyperkalaemia with AA use, RLY5016 led to a lower incidence of hyperkalaemia (7.3% vs 24.5%; p = 0.015) and a greater tolerance of AAs (91% vs 74% titrated to spironolactone 50 mg/day; p = 0.019) than placebo.

Due to the small sample size and short follow-up of this study, the evidence is currently unlikely to affect NICE CG108, but shows some potential benefits of anti-hyperkalaemics. It is not clear whether preventing hyperkalaemia might interfere with the mechanism through which AAs mediate their beneficial effect, which may be precisely because AAs increase potassium. The hypokalaemic effect of RLY5016 might thus have a negative impact.

**Key references**
Full text: www.eurheartj.oxfordjournals.org/content/32/7/820.full.pdf+html
Abstract: [link]

Full text: [link]

Supporting reference
Full text: [link]

Statins

Three meta-analyses by Xu et al. (2010) (7 trials; 540 patients), Zhang et al. (2010) (11 trials; 590 patients) and Zhang et al. (2011) (10 trials; 6052 patients) have looked again at the use of statins in HF patients. All three studies are based predominantly on trials of atorvastatin involving small numbers of patients, with considerable heterogeneity between trials, and make no apparent attempt to examine publication bias. Despite results suggesting some beneficial effects, the shortcomings of the studies mean that the evidence adds little to the case for statins in HF.

In fact two RCTs (Kjekshus et al. 2007 and GISSI-HF investigators 2008) have already established that rosuvastatin, at least, is unlikely to be of benefit in people with HF. Statin use should therefore remain confined to those with coronary disease, which will in any case include a large proportion of the HF population. Statins should be used in accordance with ‘Lipid modification’ (NICE CG67).

Key references
Abstract: [link]

Abstract: [link]

Full text: [link]

Supporting references
Full text: [link]

Abstract: [link]

Complementary and alternative medicine

Two systematic reviews by Fu et al. 2011 (62 RCTs and ‘quasi’ RCTs; 5548 patients) and Zheng 2011 (6 RCTs; 440 patients) have evaluated two different Chinese herbal medicines (Huangqi – an extract of Radix astragali; and Shengmai – components include Panax ginseng, Ophiopogon japonicas and Schisandra chinensis) as complementary therapies in people with HF. These reviews found some limited evidence of NYHA class improvement, but otherwise do not appear to offer convincing proof of the effect of these interventions and
therefore are unlikely to affect NICE CG108. Longer term, higher quality studies would be required to make a definitive statement of effects within this therapeutic area.

Key references
Full text: www.ukpmc.ac.uk/articles/PMC3089614/
Full text: www.onlinelibrary.wiley.com/o/cochrane/clsysrev/articles/CD005052/frame.html

1.4 Invasive procedures

Cardiac resynchronisation therapy in less severe heart failure

The issue of whether cardiac resynchronisation therapy (CRT) should be used in patients with less severe HF has been investigated in three studies.

An RCT of 1798 patients (NYHA class II or III; mean age 66 years) by Tang et al. (2010) demonstrated a reduction in primary events (hospitalisation and mortality) in patients with less severe HF who had CRT as well as an implantable cardioverter–defibrillator (ICD) compared to those with an ICD alone (33.2% vs 40.3%; p < 0.001). Current NICE guidance in this area, ‘Cardiac resynchronisation therapy for the treatment of heart failure’ (NICE TA120), states that CRT should be used for NYHA class III–IV symptoms. This study suggests that CRT is of benefit in patients with cardiac dysfunction but mild symptoms (the NYHA class II subgroup saw a significant reduction alone) and may be a potential consideration in future reviews of NICE TA120.

Some important issues were also raised by the subgroup analysis. Patients with atrial fibrillation (AF) and QRS < 150 ms seemed to benefit less, and there was no benefit in patients with an existing pacemaker and broad QRS (> 200 ms). Data for other types of conduction delay from this study are inconsistent. There are no randomised data to suggest that ‘upgrading’ to CRT from standard pacemakers is of benefit.

A further issue arising from the Tang et al. (2010) study is the increased number of subsequent device-related complications: patients randomised to CRT experienced twice as many complications as those with an ICD alone.

In a meta-analysis of 25 trials (9082 patients), including the Tang et al. (2010) RCT discussed above, Al-Majed et al. (2011) found that in patients with NYHA class I and II symptoms, CRT reduced all-cause mortality (relative risk [RR] = 0.83; 95% CI 0.72 to 0.96) and HF hospitalisations (RR = 0.71; 95% CI 0.57 to 0.87). These data add to the evidence that CRT may be of benefit in less severe HF which may potentially affect NICE TA120. However, questions remain regarding interventions for patients currently in hospital, those with AF, narrow QRS and less severe cardiac dysfunction.

A further meta-analysis by Wells et al. (2011) also looked at CRT in HF. In 12 studies (7538 patients), again including the Tang et al. (2010) trial, the benefit of CRT on mortality was examined in two comparisons: CRT vs medical therapy (split into more and less symptomatic groups) and CRT plus ICD vs ICD alone. Compared with optimal medical therapy alone, CRT plus optimal medical therapy significantly reduced mortality (RR = 0.73; 95% CI 0.62 to 0.85). Compared with an ICD alone, CRT plus ICD significantly reduced mortality (RR 0.83; 95% CI 0.72 to 0.96). This remained significant among patients with NYHA class I or II but not those with class III or IV. These findings extend to patients with QRS duration 120–150ms.
There were some limitations to the studies included in the Wells meta-analysis. For example, in many studies randomisation was performed only after successful implantation, and medical therapy was not well reported. Despite these shortcomings, there is now evidence suggesting that CRT may benefit patients with milder forms of HF which may be a potential consideration in future reviews of NICE TA120. Widening the population indicated for CRT would also need to consider cost-effectiveness analyses.

**Key references**

Full text: [www.annals.org/content/154/6/401.full.pdf+html](www.annals.org/content/154/6/401.full.pdf+html)


Full text: [www.cmaj.ca/content/183/4/421.long](www.cmaj.ca/content/183/4/421.long)

**Implantable cardioverter-defibrillators**

A meta-analysis by Huang et al. (2010) of seven trials (4531 patients) looked at the effect of CRT with and without ICD on all-cause mortality. Although the study found evidence that CRT plus ICD significantly reduces all-cause mortality, of the four trials on which this is based, only one was a true RCT. With these limitations of the evidence, it may not yet be possible to make definitive conclusions on whether CRT with an ICD leads to better outcomes than CRT alone, and further research, including cost-effectiveness analyses, is therefore needed. Current guidance on ICDs, ‘Implantable cardioverter defibrillators for arrhythmias’ (NICE TA95), is unlikely to be affected by this evidence.

**Key reference**


**Skeletal myoblast transplantation**

In an early-phase RCT of 40 patients (mean age 59 years in intervention arm, 62 years in control arm), Duckers et al. (2011) investigated intramyocardial injection of skeletal muscle cells into the scarred areas of the hearts of patients with HF compared to a control group. Randomisation was not blinded. The study suggests that this technique is feasible, and some symptomatic improvement was observed. However, the evidence is still at a preliminary stage and is unlikely to affect current guidance or practice.

**Key reference**

Duckers HJ, Houtgraaf J, Hehrlein C et al. (2011) Final results of a phase IIa, randomised, open-label trial to evaluate the percutaneous intramyocardial transplantation of autologous skeletal myoblasts in congestive heart failure patients: the SEISMIC trial. Eurointervention 6: 805–12

**Functional electrical stimulation**

Sbruzzi et al. (2010) performed a meta-analysis of 7 studies examining the effect of functional electrical stimulation (FES) compared with either conventional aerobic exercise or no intervention in patients with HF. FES was less effective than conventional exercise for gain in peak exercise capacity and no different in terms of muscle strength or 6-minute walk test.
However compared with no intervention, FES led to an increase in peak VO\textsubscript{2} of 2.78 ml/kg per min (95% CI 1.44 to 4.13). FES may therefore be useful for those with co-morbidities limiting exercise to improve physical functioning and perhaps mood and quality of life. However as with exercise training, it is unlikely that it would lead to reduced mortality. The data suggest a large RCT may now be warranted, but currently evidence is unlikely to affect advice given in NICE CG108 regarding exercise programmes.

**Key references**
Abstract: [www.cpr.sagepub.com/content/17/3/254.abstract](www.cpr.sagepub.com/content/17/3/254.abstract)

### 1.5 Monitoring

**Remote monitoring**

Remote monitoring potentially enables physicians to deliver treatment more effectively and to detect the first signs of deterioration in HF patients, facilitating early intervention. A recent Cochrane review (Inglis et al. 2010 – not included in the Evidence Update as it was outside of the prespecified search date parameters) suggests that telemonitoring programmes may reduce mortality in patients with chronic HF, although the same may not be true for structured telephone support that provides only verbal contact but no direct physiological monitoring of heart rate, blood pressure, or weight. The overall findings of this review are unlikely to be affected by the studies considered below

Abraham et al. (2011) conducted a single-blind RCT of 550 patients (NYHA class III; mean age 61 years in the treatment arm, 62 years in the control arm) investigating the effect of information from an implanted wireless pulmonary artery haemodynamic monitoring system compared to standard care on rates of hospitalisation. They found a substantial reduction in the number of hospitalisations in patients with the implant vs standard care alone (83 vs 120; p < 0.001) which may have been due to the use of more nitrates and hydralazine. The overall rates of hospitalisation and mortality were lower than expected suggesting that the patients in this study were relatively stable. The implant may have shown greater effects in less stable patients, for instance those recently hospitalised for worsening HF. The system involves a different strategy to most previous remote monitoring trials as it aims at health improvement and maintenance rather than just crisis prediction.

This is currently a novel technology. Replication of these results in longer studies with harder outcomes such as mortality will help to inform the development of these technologies. As the trial was US-based, studies conducted in the UK will help ensure relevance to the NHS.

In a follow-up of the previously reported Randomised Trial of Phone Intervention in Chronic Heart Failure (DIAL study) in 1518 patients, which showed death or admission to hospital for worsening HF was less likely in those receiving telephone intervention than in those receiving usual care, Ferrante et al. (2010) have now found that this effect is sustained at both 1 year (relative risk reduction [RRR] = 19%; p = 0.013) and 3 years (RRR = 12%; p = 0.05) post-intervention. The effect at both time points was primarily due to reduced HF-related admissions.

The exact nature of the telephone intervention was not described, potentially limiting impact on implementation and on NICE CG108. It should also be noted that at the end of the initial follow-up for the original DIAL study, there was a difference in the proportion of patients in the intervention arm taking evidence-based medication which may have affected the continued benefit seen in this follow-up study.

In an RCT of 710 patients (NYHA class II or III; mean age 67 years) Koehler et al. (2011) looked at the effect of remote telemonitoring compared with usual care in out-patients with
HF. Telemonitoring had no effect on mortality, cardiovascular death or HF hospitalisation and results are unlikely to affect NICE CG108.

**Tompkins and Orwat (2010)** performed an RCT in 390 stable patients (mean age 76 years) with HF to investigate the effect of telemonitoring on outcomes compared with standard care. The primary outcome was not clear, but the intervention tended to increase rates of urgent care visits, but reduced the number of days in hospital. The follow-up was short at only 6 months, the trial was underpowered and the management of the control group was not described (which is important to help assess whether the care was standard, or if it was high-intensity expert care). Mortality data were not reported. Issues with reporting and underpowering may limit any conclusions, and reinforce the need for a well-designed, definitive study of telemonitoring to provide robust evidence of benefit and cost-effectiveness.

**Chaudhry et al. (2010)** conducted an RCT to evaluate whether a voice interactive system could reduce the incidence of all-cause mortality and all-cause hospital readmission in a cohort of 1653 patients (median age 61 years; 71% with an LVEF fraction < 40%) with an HF hospitalisation within the previous month. Patients were randomised to telephone support or usual care and those assigned to the automated voice interactive system were required to make daily reports on symptoms and weight. Over a 6-month period, there was no difference between patients assigned to the voice interactive system and usual care in the incidence of the primary composite endpoint of all-cause mortality and all-cause hospital readmission within 180 days after enrolment (52% vs 52%), all-cause readmissions (49% vs 47%), or all-cause mortality (11% vs 11%).

Poor compliance may have had an impact on the findings, as 14% of patients never actually used the system at all, a further 10% were non-compliant by the end of the first week and only 55% of patients used the system at least three times a week by the end of the study. The study may perhaps reflect a dislike among patients for voice-interactive systems, and these findings suggest that there is no benefit provided by the telephone system used in this study.

**Key references**
Abstract: [www.thelancet.com/journals/lancet/article/PIIS0140-6736%2811%2960101-3/abstract](www.thelancet.com/journals/lancet/article/PIIS0140-6736%2811%2960101-3/abstract)


Full text: [www.content.onlinejacc.org/cgi/reprint/56/5/372.pdf](www.content.onlinejacc.org/cgi/reprint/56/5/372.pdf)

Full text: [www.circ.ahajournals.org/content/123/17/1873.full](www.circ.ahajournals.org/content/123/17/1873.full)

Full text: [www.thefreelibrary.com/A+randomized+trial+of+telemonitoring+heart+failure+patients.-a0239529715](www.thefreelibrary.com/A+randomized+trial+of+telemonitoring+heart+failure+patients.-a0239529715)

**Supporting reference**
Inglis SC, Clark RA, McAlister FA et al. (2010) Structured telephone support or telemonitoring programmes for patients with chronic heart failure. Cochrane Database of Systematic Reviews issue 8: CD007228
Full text: [www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD007228.pub2/abstract;jsessionid=8C52DA193759A7EEE2D1C368964060B5.d01t04](www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD007228.pub2/abstract;jsessionid=8C52DA193759A7EEE2D1C368964060B5.d01t04)
Heart rate as a risk factor

In further work stemming from the SHIFT trial (see ‘Ivabradine’ in section 1.3 ‘Pharmacological management’ for further details) Bohm et al. (2010) examined the effect of resting heart rate on a primary composite endpoint of cardiovascular death or hospital admission for worsening HF. Patients in the placebo group with the highest heart rates (≥ 87 bpm) were at more than twice the risk of a primary endpoint event than those with the lowest heart rates (70–72 bpm) (HR = 2.34; 95% CI 1.84 to 2.98; p < 0.0001). In the ivabradine group, after 28 days on treatment, patients with heart rates < 60 bpm had fewest primary endpoint events (event rate 17.4%; 95% CI 15.3 to 19.6). When adjustment for heart rate change at 28 days was made, ivabradine’s treatment effect was no longer evident, suggesting that its effect is due to heart rate reduction.

These results demonstrate the potential benefits of good heart rate control in HF management. Titration of beta blockers is likely the best way to achieve heart rate control, however ivabradine may be a useful addition to existing heart rate control strategies. It should be noted that these results are in patients with sinus rhythm; in patients with AF the picture is less clear. Ivabradine is not currently licensed in the UK for heart failure.

Key reference
Abstract: [link](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(10)61198-1/abstract)

NT-proBNP monitoring

Eurlings et al. (2010) conducted an RCT in 345 patients (mean age ~72 years) hospitalised for HF with elevated NT-proBNP at admission to examine whether management of HF guided by an NT-proBNP target improves outcomes. Compared with standard HF management, the use of an NT-proBNP target did not affect the primary outcome of the number of days alive and out of hospital. However, there was a slightly greater decrease in NT-proBNP in those not managed according to a target.

The study was under-powered, and setting an NT-proBNP target based on the lowest level at discharge or at 2 weeks follow-up after admission (when levels are still elevated as a result of acute decompensation) meant that the target was too easily achievable. Diuretics were the predominant means of correcting raised NT-proBNP but these drugs are not known to alter the natural history of the disease, and could lead to worsening of any existing renal dysfunction that may increase NT-proBNP levels. Based on this evidence, NT-proBNP monitoring does not appear to affect health outcomes. Further research may help to increase understanding within this field.

In an RCT of 252 patients (NYHA class II-IV; mean age ~78 years) with HF and grossly elevated NT-proBNP levels (> 800 pg/ml for men, > 1000 pg/ml for women), Persson et al. (2010) have also investigated whether NT-proBNP-guided therapy (in addition to structured treatment according to guidelines) can improve clinical outcomes. No difference was observed in the primary endpoint (a composite of days alive and out of hospital and symptom score) between those who had NT-proBNP guided care and those who did not (p = 0.28). This evidence further suggests a lack of benefit with NT-proBNP monitoring and may need to be considered in future reviews of NICE CG108.
Key references
Abstract: www.content.onlinejacc.org/cgi/content/short/56/25/2090

Abstract: www.eurjhf.oxfordjournals.org/content/12/12/1300.abstract

Performance measures
Maeda et al. (2010) conducted a systematic review looking at the effect of performance measures on outcomes in patients with HF. From a mixture of studies (only two were prospective cohort studies and only one was an RCT), improved outcomes were observed with the use of angiotensin-converting enzyme inhibitors and beta-blockers at discharge, with some improvement also seen following issue of written discharge instructions, whereas measuring LV function and counselling about smoking had no impact.

For a UK audience, additional useful, contemporary and relevant NHS data may be obtained from the National Heart Failure Audit. The NICE chronic heart failure quality standard and the related heart failure section of NHS Improvement may also be referred to.

Key reference

Case management
In an RCT of 199 patients (mean age ~70 years), Peters-Klimm et al. (2010) examined the effect of case management, by doctors’ assistants, of HF in primary care, and found that outcomes in terms of generic and disease-specific HRQOL were no different between those who were case managed and those receiving usual care only.

This result may be explained by the possibility that a higher level of care was received by both groups of patients, which may also account for the 5% mortality rate at 1 year observed with or without case management (compared with, for example an annual mortality of 50% in the UK for those who experience an episode of worsening HF requiring hospitalisation). The potentially higher quality of care observed in the trial may in part be explained by the limited number of GPs agreeing to participate in the study (31 out of 252 approached), who may have been those already delivering a higher quality of care. A message to emerge from the study may be that well-trained staff and high levels of adherence to treatment guidelines can potentially achieve excellent results without more complex and costly interventions.

Key reference
Full text: www.trialsjournal.com/content/pdf/1745-6215-11-56.pdf
New evidence uncertainties

During the development of the Evidence Update, the following evidence uncertainties were identified that have not previously been listed on the NHS Evidence UK Database of Uncertainties about the Effects of Treatments (DUETs).

- **Trimetazidine for adult chronic heart failure patients**
  www.library.nhs.uk/DUETs/viewResource.aspx?resid=411114

- **Chronic heart failure self-management for patients with severe physical and mental co-morbidities**
  www.library.nhs.uk/DUETs/viewResource.aspx?resid=411109

- **Statins for chronic heart failure**
  www.library.nhs.uk/DUETs/viewResource.aspx?resid=411113

- **Huangqi injection for patients with chronic heart failure**
  www.library.nhs.uk/DUETs/viewResource.aspx?resid=411111

- **Cardiac resynchronisation therapy in patients with atrial fibrillation, compared with those with sinus rhythm**
  www.library.nhs.uk/DUETs/viewResource.aspx?resid=411107

- **Cardiac resynchronisation therapy versus optimal medical therapy in chronic heart failure patients with symptoms refractory to optimal medical therapy**
  www.library.nhs.uk/DUETs/viewResource.aspx?resid=411108

- **Cardiac resynchronisation therapy with implantable defibrillator (CRT-D) versus implantable cardioverter defibrillator (ICD) to reduce all-cause mortality in chronic heart failure patients**
  www.library.nhs.uk/DUETs/viewResource.aspx?resid=411441

- **Functional electrical stimulation versus conventional aerobic exercise in chronic heart failure patients**
  www.library.nhs.uk/DUETs/viewResource.aspx?resid=411110

- **Performance measures and outcome in chronic heart failure**
  www.library.nhs.uk/DUETs/viewResource.aspx?resid=411112

Further evidence uncertainties for chronic heart failure can be found at
www.library.nhs.uk/duets/ and in the NICE research recommendations database at

DUETs has been established in the UK to publish uncertainties about the effects of treatment which cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.
Appendix A: Methodology

Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:


No evidence was identified for palliative or end-of-life care, although it was within the scope.

Searches

The literature was searched to identify studies and reviews relevant to the scope. Searches were conducted of the following databases, covering the dates 30 June 2010 (the end of the search period of the most recent Annual Evidence Update) to 22 June 2011:

- CINAHL
- Cochrane Database of Systematic Reviews – Cochrane Library
- Embase
- MEDLINE

Table 1 provides details of the search strategy used. Given the breadth of the topic, it was necessary to adapt the search strategy used in the reference guidance and the previous chronic heart failure Annual Evidence Update. A highly specific search strategy was developed to provide a focused set of results, which was thoroughly tested to ensure that the comprehensiveness of the results was not compromised. The search strategy was used in conjunction with validated Scottish Intercollegiate Guidelines Network search filters for RCTs and systematic reviews (www.sign.ac.uk/methodology/filters.html).

Four other studies (Chaudhry et al. 2010, Kelder et al. 2011, Tang et al. 2010 and Wells et al. 2011) were also identified outside of the literature search. Figure 1 provides details of the evidence selection process.

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<tr>
<th>Table 1 MEDLINE search strategy (adapted for individual databases)</th>
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Figure 1 Flow chart of the evidence selection process

- 2023 records identified through search
- 1459 records after duplicates removed
- 528 records included after first sift
- 196 records included after second sift
- 36 records included after review
- 36 records included after critical appraisal
- 35 records included by EUAG in published update

564 duplicates from searching
931 records excluded after first sift
332 records excluded after second sift
160 records excluded after review by Update Advisor
0 records excluded after critical appraisal
5 records excluded by EUAG
4 additional records identified by EUAG
Appendix B: The Evidence Update Advisory Group and NHS Evidence project team

Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of subject experts who review the prioritised evidence obtained from the literature search and provide the commentary for the Evidence Update.

Professor Tom Quinn – Chair
Professor of Clinical Practice, Faculty of Health and Medical Sciences, University of Surrey and Clinical Lead, NHS Evidence

Dr James Beattie
Consultant Cardiologist, Birmingham Heartlands Hospital, and Clinical Lead, NHS Improvement

Professor Andrew L Clark
Consultant Cardiologist, Castle Hill Hospital, Cottingham, East Yorkshire

Professor John G F Cleland
Head, The Academic Unit of Cardiology, University of Hull

Professor Jonathan Mant
Professor of Primary Care Research, General Practice and Primary Care Research Unit, University of Cambridge

Dr Jillian Riley
Head of Postgraduate Education (Nursing), Royal Brompton and Harefield NHS Foundation Trust, London

Dr Klaus Witte
Senior Lecturer and Honorary Consultant Cardiologist, University of Leeds and Leeds General Infirmary

NHS Evidence project team

Alan Lovell
Evidence Hub Manager

Elly O’Brien
Information Specialist

Patrick Langford
Editor