

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Clinical Practice – Surveillance Programme

Recommendation for Guidance Executive

Clinical guideline

CG108: Chronic heart Failure

Publication date

August 2010

Surveillance report for GE

November 2014

Surveillance recommendation

GE is asked to consider the proposal to update the guideline as a standard update.

GE are asked to note that this 'yes to update' proposal will not be consulted on.

Key findings

			Potential impact on guidance	
			Yes	No
Evidence identified from Evidence Update			✓	
Evidence identified from literature search			✓	
Feedback from Guideline Development Group			✓	
Anti-discrimination and equalities considerations				✓
No update	CGUT update	Standard update	Transfer to static list	Change review cycle
			✓	

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Centre for Clinical Practice – Surveillance Programme

Surveillance review of CG108: Chronic Heart Failure

Recommendation for Guidance Executive

Background information

Guideline issue date: 2010 (partial update of CG5)
4 year review: 2014

NCC: National Clinical Guidelines Centre

Current four year surveillance review

1. The [Evidence Update](#) on CG108: Chronic heart failure (published November 2011) was used as a source of evidence for this surveillance review and considered new evidence since the guideline was published. The Evidence Update indicated that there was new evidence to generate future change in the guideline in 7 areas:
 - The potential benefit of active management of iron deficiency, anaemia and chronic kidney disease in patients with heart failure.
 - 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. Ivabradine has since been evaluated by Technical Appraisals ([TA267](#)) and is now part of the pathway for chronic heart failure (CHF).
 - Aldosterone antagonists may be of benefit in patients with moderate or severe left ventricular systolic dysfunction (left ventricular ejection fraction < 35%) whether symptoms are mild, moderate or severe.

- 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. CG108 already has a recommendation that states that statin therapy in chronic heart failure should only be for those with coronary artery disease hence there is no impact from the Evidence update.
 - Cardiac resynchronisation 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. This area of guidance has been reviewed and incorporated into a Technology Appraisal ([TA314](#)) so there is no impact on the guideline as indicated by the Evidence update.
 - Good heart rate control can reduce morbidity and mortality was stated as an area for update by the Evidence update. This area is extensively covered by CG108.
 - The validity of N-terminal pro-B-type natriuretic peptide monitoring is questioned by current evidence and more evidence is needed in this area.
2. For the 4 year Surveillance Review, a search to identify new evidence was carried out for systematic reviews and RCTs published between 22nd June 2011 (the end of the search period for the Evidence Update) and 23rd June 2014 and relevant abstracts were assessed. Clinical feedback on the guideline was obtained from 7 members of the GDG through a questionnaire. The GDG were split in the decision over whether to update CG108 with 3 members indicating that it may be better to wait for the results from trials on LCZ 696 and trials on ivabradine in heart failure with preserved ejection fraction to publish. However, this evidence may potentially impact on either new or current Technology Appraisals (Ivabradine for treating chronic heart failure ([TA267](#))) before it is considered for clinical guidelines. The GDG members who felt the guideline should be updated indicated that, as the previous update was only a partial update, there are a number of areas that have not been assessed which may now require a review. These included the use of aspirin with ischemic heart disease and heart failure, the continuing use of statins in patients who have developed heart failure and the diagnosis of heart failure with preserved ejection fraction. It was also noted that there was new evidence on treatments (including aldosterone antagonists), procedures and diagnosis.
 3. CG108 chronic heart failure was partially updated in 2010. The original guidance (CG5 published in 2003, included in the appendices of CG108) utilised methodology that has since been superseded by various versions of the guidelines manual. The guideline makes numerous cross referrals to other guidelines, which have since been updated, and covers areas that since have become guidance in their own right.
 4. New evidence that may impact on recommendations was identified relating to the following areas within the guideline:

Clinical area 1: Referral and approach to care		
Q: Is there evidence that support and education for carers and relatives of heart failure (HF) improves patient quality of life and clinical outcomes?		
Evidence summary	GDG/clinical perspective	Impact
<p><u>Evidence identified from Evidence update (2011)</u> None identified</p> <p><u>Evidence identified from surveillance review(2014)</u> Seven RCTs were identified that have looked at either carer or patient education. Compared to standard care; HF nurse education (1hr 1-to-1 session), patient activation, DVD decision aids and telephone reinforcement were all more effective in improving health behaviours and outcomes. Whereas, family member education, targeted cognitive training and an intensive multisession intervention did not improve health outcomes.</p> <ul style="list-style-type: none"> • A RCT comparing the effects of a 1h, one-on-one teaching session with a nurse educator to the standard discharge process in patients with systolic heart failure showed that HF nurse education at the time of hospital discharge resulted in improved patient knowledge and reduced risk of readmission¹. • A RCT in HF patients (n=84) indicated that a patient activation intervention compared with usual care increased patient activation and adherence and decreased hospitalisations². • A RCT in individuals with HF (n=480) indicated that a DVD decision aid increased levels of daily weight monitoring, monitoring of fluid intake and following a low-sodium diet compared to standard care³. • A RCT in patients with HF (n=605) indicated that telephone reinforcement (5 to 8 telephone counselling sessions over 1 month) of learning goals and self-care behaviours improved knowledge, health behaviours, and HF-related QoL compared 	<p>No GDG feedback was provided by the GDG questionnaire</p>	<p>Potential impact on the guideline. The new evidence from this surveillance time point indicates that education and support improves patient's outcomes. However, providing education to carers and relatives may have a limited impact.</p> <p>This review question is from CG5 and this section of the guideline has not been updated since 2003. The appendix M (CG5) indicates a systematic review was conducted but the evidence (if any was identified) is not presented within the original 2003 guideline or the update. There are a number of recommendations that could potentially be considered as 'education and support based' and it would appear that those from 2003 were consensus based:</p> <p>R80 Guidelines for good communication:</p> <ul style="list-style-type: none"> • Listen to patients and respect their views and beliefs • Give patients the information they ask for or need about their condition, its treatment and prognosis, in a way they can understand including information about any serious side effects of drugs to be prescribed

<p>to a single education session⁴.</p> <ul style="list-style-type: none"> • A RCT which investigated a group-based multi-professional education programme to increase family members' knowledge about CHF found that this intervention did not affect the patient's health care utilisation⁵. • A RCT in patients with HF (n=605) found that an intensive multisession intervention did not change clinical outcomes compared with a single-session intervention⁶. • A RCT in patients (n=125) with HF and mild cognitive impairment (MCI) indicated that a targeted self-care teaching intervention using principles of cognitive training increased heart failure knowledge at 30 days post-discharge; however, this did not impact readmission rates compared to standard care⁷. 		<ul style="list-style-type: none"> • Provide the most important information first • Explain how each item will affect patients personally • Present information in separate categories • Make advice specific, detailed and concrete • Use words the patients will understand; confirm understanding by questions; define unfamiliar words; write down key words; draw diagrams and keep a copy in the medical notes • Repeat the information using the same words each time • Prepare material, written or taped, to back up handwritten notes • Share information with patients' partners, close relatives or carers if they ask you to do so. When patients cannot indicate their consent for such sharing of information, it is advisable to share the information that those close to the patient need or want to know, except where you have reason to believe that the patient would object if able to do so. <p>R81 The content, style and timing of information provision should be tailored to the needs of the individual patient.</p>
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		<p>R82 Healthcare professionals should assess cognitive ability when sharing information.</p> <p>R83 Carers and relatives of patients who are cognitively impaired should be made aware of treatment regimens for the patients they care for and be encouraged to identify any need for clinical support.</p> <p>R82 is a strongly worded recommendation. How the clinician should assess the cognitive ability is not clear and there is no guidance on what clinicians should do with this information.</p> <p>In addition, an educational component is recommended as part of any exercise programme (2010). However, as not all patients with CHF are recommended to have this aspect of care there is therefore the potential for them to not receive the same education and support. This is potentially an equality issue for those that qualify for physical exercise programmes and those that don't.</p>
Clinical area 2: Measurement of circulating natriuretic peptide concentration		
Q: What is the accuracy of natriuretic peptides vs gold standard in the diagnosis of heart failure?		
Evidence summary	GDG/clinical perspective	Impact
<u>Evidence identified from Evidence update (2011)</u> A meta-analysis investigated the value of B-type natriuretic	GDG feedback indicated that the current guideline	Potential impact on the guideline.

<p>peptide (BNP) level as a diagnostic parameter in addition to typical clinical signs and symptoms in the identification of suspected slow-onset HF patients (n=276) in primary care⁸. 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.</p> <p>A comparison of BNP levels using the European Society of Cardiology (ESC) cut-off points of < 100pg/ml (or < 35pg/ml) to 'rule out' or > 400pg/ml (or > 100pg/ml) to 'rule in' the diagnosis of HF also performed poorly.</p> <p><u>Evidence identified from literature search (2014)</u> A focus search (which has an expanded inclusion criteria for of observational studies) was conducted for this question that identified 4 studies.</p> <p>A cohort study of patients (n=999, >60yrs) with coronary artery disease (CAD) with and without chronic kidney disease (CKD) indicated that higher cut off levels of BNP better detected CHF in CKD patients (4376pg/mL) than in non-CKD patients (298pg/mL)⁹.</p> <p>A retrospective medical records analysis of patients (n=57) hospitalised with a diagnosis of acute exacerbation of chronic obstructive pulmonary disease (COPD) assessed the performance of BNP in detecting left ventricular systolic dysfunction in patients with no history of HF. Mean BNP values in patients with systolic dysfunction (689pg/ml) were higher than those without (340pg/ml). For the detection of systolic dysfunction, a BNP level inferior to 100pg/ml yielded a sensitivity of 92% and a</p>	<p>recommendations on the whole were consistent with any new evidence. However, it was noted that the new ESC guidance (2012) had changed the natriuretic cut off points and it was felt that a discussion around whether NICE wished to be aligned with this was needed as original cut off points used in CG108 were consensus based.</p> <p>A cross-sectional study by Kelder <i>et al</i> 2011 which investigated the diagnostic value of physical examination and additional testing in primary care patients (n=721) with suspected HF was highlighted as relevant by the GDG¹². The study compared determination by an outcome panel to physical and history tests along with biomarkers. The combination of 3 items from history plus 6 from physical examination showed independent diagnostic value with NT-proBNP the most powerful supplementary diagnostic test.</p> <p>For daily practice, a diagnostic</p>	<p>The evidence identified in the EU supported the utility of using BNP in the diagnosis of HF but concluded at that time unlikely to affect NICE CG108.</p> <p>Further new evidence supports the use of BNP and adds value in the diagnosis of those clinically suspected of HF (including slow onset) in primary care. However a number of studies indicate that cut-off values remain problematic as these need to factor in co-morbidities as NT-proBNP /BNP values tend to be higher in patients with impaired renal function or COPD.</p> <p>As the cut off values used in CG108 were consensus derived and clinical feedback indicates that there is a wish to examine these due to newer levels within the ESC guidance, then this area may potentially require updating.</p>
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<p>negative predictive value of 91%, whereas BNP higher than 500 yielded a sensitivity of 80% and a positive predictive value of 47%¹⁰. A cross sectional study investigated NT-proBNP levels for the diagnosis of left ventricular dysfunction in patients (n=120) with severe acute exacerbations of COPD and renal dysfunction. Median NT-proBNP levels were significantly higher in these patients, irrespective of whether their renal function was normal or impaired. The threshold NT-proBNP value with the highest diagnostic accuracy was greater in the setting of renal dysfunction (2000pg/mL; sensitivity 71%, specificity 82%, compared with 1000pg/mL in patients with normal renal function; sensitivity 94%, specificity 82%¹¹).</p>	<p>rule was derived that may be useful to quantify the probability of heart failure in patients with new symptoms suggestive of heart failure. The GDG feedback stated that this new risk score may indicate that the diagnostic pathway would need changing.</p>	
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Clinical area 3: Treating Chronic Heart failure

Q: Are there sub groups of HF patients that should be treated differently?

- Congenital heart defect
- Angina pectoris
- Diastole
- Atrial fibrillation
- Heart transplantation
- Sleep apnoea syndrome
- Anaemia
- Diabetes mellitus
- Cognition disorder
- Older people
- Ethnic groups

Evidence summary	GDG/clinical perspective	Impact
<p><u>Evidence identified from Evidence update (2011)</u></p> <p>Anaemia treatment A systematic review of 11 RCTs found that treatment of anaemia</p>	<p>No GDG feedback was provided by the GDG questionnaire.</p>	<p>Potential impact on the guideline recommendations.</p> <p>The review identified in the Evidence Update</p>

<p>in HF with erythropoiesis-stimulating agents (ESA) improved exercise duration, 6-minute walk distance, peak oxygen, NYHA class, ejection fraction and B-type natriuretic peptide¹³.</p> <p><u>Evidence identified from literature search (2014)</u></p> <p>Anaemia treatment</p> <p>Numerous studies looking at the treatment of anaemia in patients with HF were identified (2 systematic reviews, 3 RCTs, 1 post-hoc analysis and an economic evaluation).</p> <p>A systematic review and meta-analysis (including 4 trials) indicated that iron supplementation for the treatment of CHF and iron deficiency improved QoL and iron indices without a change in haemoglobin levels¹⁴. A second meta-analysis (including 5 trials) of patients with CHF and iron deficiency treated with intravenous iron indicated that patients treated with intravenous iron had significant reductions in hospitalisations and adverse events with improvements in NYHA class and LVEF¹⁵.</p> <p>A RCT in iron-deficient CHF patients (n=459) with or without anaemia indicated that intravenous iron substitution using ferric carboxymaltose over a 24-week period improved health related QoL (HRQoL) and exercise tolerance compared to placebo¹⁶. A model-based cost-effectiveness analysis of this study from the UK payers' perspective indicates that the base case ICER was clearly below the threshold of £22 200-33 300/QALY gained and proved to be robust in sensitivity analysis¹⁷.</p> <p>A 24 week RCT in anaemic patients with HFPEF (n=56) indicated that subcutaneous epoetin alfa treatment resulted in increases in haemoglobin but did not changes end-diastolic volume, left</p>		<p>used the Cochrane methodology, but the data was from small heterogeneous studies with varying endpoints and short-term follow-up. As such, it was concluded that the evidence up to 2011 was unlikely to affect NICE CG108, however the general area of iron deficiency, anaemia or chronic kidney disease in HF potentially warranted greater attention and cited iron therapy in the form of ferric carboxymaltose as recently to have been shown in an RCT to benefit HF patients with iron deficiency³⁰. Since the completion of the Evidence Update numerous other trials relating to anaemia treatment have been identified that indicate treatment is beneficial for those with CHF and anaemia.</p> <p>The large multivariate analysis in patients with AF and HF on aldosterone antagonists should be considered when reviewing these agents for use in CHF (see below) as there are associated with an increased incidence of cardiovascular deaths in this sub group.</p> <p>In addition a number of small RCTs have looked at various treatment options in patients with CHF and a number of other co-morbidities such as growth hormone deficiency, diabetics/insulin sensitivity, CKD Chagas cardiomyopathy, COPD and low testosterone. On the whole the evidence base is still limited and these areas should continue</p>
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<p>ventricular mass, 6-minute walk distance nor QoL compared to placebo¹⁸.</p> <p>A post hoc analysis of the HF-ACTION trial (a RCT comparing exercise therapy vs usual care in 2331 patients with HF) indicates that anaemia is associated with increased rates of death, hospitalisation, and HF exacerbation in patients with CHF¹⁹.</p> <p>A RCT in patients with systolic HF and anaemia (n=2278) found that treatment with darbepoetin alfa did not improve clinical outcomes in patients compared to placebo²⁰.</p> <p>Growth hormone deficiency A long term 4 year RCT in patients with CHF deficient in growth hormone (n=56) indicates that growth hormone (GH) replacement therapy in addition to standard CHF therapy increase LVEF and peak VO₂²¹.</p> <p>Diabetics/insulin sensitivity A RCT in non-diabetic patients with stable ischemic CHF (n=36) indicated that irbesartan on top of standard CHF therapy improved insulin sensitivity compared to standard therapy alone²².</p> <p>A small 16 week RCT in patients (n=16) with CHF indicated that spironolactone improved insulin resistance in comparison to furosemide²³.</p> <p>Atrial Fibrillation A multivariate analysis based on a RCT in patients (n=1376) with atrial fibrillation (AF) and HF indicates that aldosterone antagonists are associated with an increased incidence of cardiovascular deaths²⁴.</p>		<p>to be surveyed until sufficient evidence to enable recommendations is available.</p>
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Kidney disease

A 6 month RCT in patients (n=18) with congestive HF (NYHA class III-IV, LVEF <45%) on continuous ambulatory peritoneal dialysis indicated that spironolactone increased ejection volume compared to placebo but did not increase serum potassium levels. This result indicates that spironolactone could be used in CHF patients on continuous ambulatory peritoneal dialysis²⁵.

A phase II RCT in patients (n=392) with HF and reduced ejection fraction associated with mild or moderate chronic kidney disease (CKD) found that unlicensed oral BAY 94-8862 was as effective as spironolactone in decreasing biomarkers of haemodynamic stress, but it was associated with lower incidences of hyperkalaemia and worsening renal function²⁶.

Chagas cardiomyopathy

A Cochrane systematic review to assess the benefits and harms of current pharmacological interventions for treating HF in patients with Chagas cardiomyopathy identified 2 studies both comparing carvedilol against placebo. However, carvedilol did not affect all-cause mortality²⁷.

COPD

A head to head trial which compared bisoprolol to carvedilol in patients (n=63) with CHF (NYHA class II) and moderate to severe COPD found that whilst betablockers frequently caused adverse events in this population bisoprolol induced demonstrably more improvement in pulmonary function and caused fewer adverse events²⁸.

Low Testosterone

<p>A 12 week RCT of a programme of exercise, with and without intramuscular testosterone supplementation, in male patients (n=41) with CHF and low testosterone indicates that this approach is both feasible and improves peak oxygen uptake, depression scores, leg strength and several aspects of QoL compared to placebo²⁹.</p>		
<p>Q: What is the evidence for recommending rehabilitation and/or a period of exercise training for patients with chronic HF?</p>		
Evidence summary	GDG/clinical perspective	Impact
<p><u>Evidence identified from Evidence update (2011)</u> Physical fitness and exercise A RCT of patients with HF (n=69) indicated that preferred training (PT; patients' own choice of exercise) offered continued benefits over other programmes (usual care and usual care plus either home training or supervised training in a rehab centre) in terms of maintained or increased exercise capacity measured by workload at the respiratory compensation point³¹.</p> <p>A second RCT in patients with HF and preserved left ventricular ejection fraction (HFPEF) (n=53) reported that exercise training increased peak exercise VO_2, power output and exercise time compared with the control group³². However there were no associated overall improvements in health-related quality of life (HRQoL).</p> <p>An RCT in patients (n=100) with systolic HF and reduced left ventricular ejection fraction (LVSD) 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 compared to control³³. However improvements were seen in HRQoL, exercise self-efficacy and mood.</p>	<p>No GDG feedback was provided by the GDG questionnaire.</p>	<p>Potential impact on guideline recommendations.</p> <p>The guideline currently recommends offering a supervised group exercise-based rehabilitation programme designed for patients with heart failure which includes a psychological and educational component in the programme. The guideline also states that the programme may be incorporated within an existing cardiac rehabilitation programme</p> <p>The updated secondary prevention of MI (CG172) and public health guidance PH52 make numerous recommendations for those that require exercise rehabilitation. As the population of CG108 is specifically excluded from CG172 it may be worth reconsidering the exercise recommendations to align them with other guidance. In addition there is new evidence that numerous approaches to exercise are beneficial, not just supervised exercise as considered and recommended in</p>

<p>Functional electrical stimulation</p> <p>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 CHF³⁴. 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 a not significant increase in peak VO₂.</p> <p><u>Evidence identified from literature search (2014)</u></p> <p>Thirty three studies were identified (4 systematic reviews, 28 RCT, 1 post hoc analysis) that have compared exercise programmes with either active controls (other exercise interventions) or controls (usual care or no exercise) in a range of CHF populations. Pooling of these studies is difficult due to the range of interventions, including; supervised, interval, inspiratory muscle training, cycling, Tai chi, Pilates, Nordic walking, aerobic, duration and comparators. In addition there are numerous outcomes reported ranging from QoL, exercise capacity to hospitalisation admissions and mortality.</p> <p>An update of a Cochrane systematic review which determined the effectiveness of exercise-based rehabilitation on the mortality, hospitalisation admissions, morbidity and health-related quality of life for people with HF included 33 trials (14 new trials) in people with HF predominantly with HFREF and NYHA classes II and III was identified³⁵. Overall compared with no exercise control, exercise-based rehabilitation did not increase or decrease the risk of all-cause mortality in the short term (up to 12-months' follow-up) but did reduce the risk of hospital admissions and confers important improvements in health-related QoL.</p>		<p>the original guidance. For those who are unable to actively exercise there is a growing evidence base that functional electrical stimulation benefits patient outcomes.</p>
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<p>A systematic review which included 7 studies indicated that inspiratory muscle training (IMT) in patients with HF increased the distance walked in the six-minute walk test and maximal static inspiratory pressure compared to control groups³⁶. However, IMT provides a significant improvement in peak oxygen consumption only in the studies that performed IMT for 12 weeks against no inspiratory load in patients with inspiratory muscle weakness. A second systematic review and meta-analysis which included 11 studies found IMT in patients with CHF improves cardio-respiratory fitness and QoL to a similar magnitude to conventional exercise training³⁷. In addition 3 RCTs on IMT were identified:</p> <ul style="list-style-type: none"> • A RCT of patients with CHF (n=43) found combined aerobic/IMT was more effective than a 12-week aerobic training programme³⁸. • A RCT in patients with CHF (n=22) found that a 4-week high-IMT improved both strength and endurance compared to sham IMT³⁹. • A RCT in patients (n=27, NYHA II/III and LVEF 29 + 7%) indicated that a 12 week combined aerobic training and resistance training with IMT resulted in incremental benefits in both peripheral and respiratory muscle weakness, cardiopulmonary function and QoL compared to that of aerobic training only⁴⁰. <p>Five RCTs looked at 'supervised' exercise programmes</p> <ul style="list-style-type: none"> • A RCT in patients with CHF (n=66) indicated that a 16 weeks of supervised exercise training improves heart rate variability in older patients with HF compared to attention-control⁴¹. • A RCT in patients with HFPEF (n=64) suggested that structured exercise training improves maximal exercise capacity, left ventricular diastolic function and QoL compared to usual care⁴². • A RCT of patients with CHF (n= 123) indicated that twice weekly 		
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<p>10-year exercise training maintains functional capacity of more than 60% of maximum VO₂ and confers a sustained improvement in QoL compared with a non-trained group who did not exercise formally⁴³.</p> <ul style="list-style-type: none"> • A post hoc analysis of the HF-ACTION RCT on stable outpatients with LVEF and HF randomised to either supervised exercise training plus usual care or to usual care alone indicated that there was no interaction between etiology and treatment for the primary outcome, cardiovascular mortality or hospitalisation⁴⁴. It was concluded that consideration of inclusion of HF patients in an exercise training program should be made independent of the cause of HF or the severity of the symptoms. • A RCT in patients (n=107) with symptomatic heart failure and LVEF determined that 24 weeks of exercise training did not improve exercise capacity, QoL or carer strain and was not cost saving to the National Health Service compared to usual care⁴⁵. <p>Seven RCTs investigated interval training:</p> <ul style="list-style-type: none"> • A RCT indicated that interval cycle training combined with strength training (3 times weekly training sessions for 3 months) induces a greater beneficial effect on vascular reactivity rather than interval exercise training alone in CHF patients (n=28 LVEF <37%)⁴⁶. • A RCT of patients with CHF (n=100, NYHA classes II-IV, ejection fraction < 50%) found that high intensity, interval exercise over 12 weeks improves QoL compared to no exercise advice⁴⁷. • A RCT in patients (n=26) with CHF indicated that an 8-week, high-intensity interval training was more effective than continuous training aerobic exercise in improving indices of sub-maximal exercise capacity⁴⁸. • A RCT in CHF patients (n=18) which compared high-intensity 		
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interval exercise (HIIE) to an isocaloric moderate-intensity continuous exercise found that that a single session of HIIE improves autonomic profile of CHF patients, leading to significant reductions of HR and arrhythmic events in a 24-h post-training period⁴⁹.

- A RCT in patients with post-infarction CHF under optimal medical treatment (n=20) found that aerobic continuous training and aerobic interval training provided the same level of benefit to this group of patients⁵⁰.
- A RCT in patients with signs of CHF and ejection fraction <45%, (n=17) found that 6 months of exercise using continuous aerobic cycling exercise training or low-volume high-intensity interval training were equally effective⁵¹.
- A RCT in patients with CHF (n=23) found no difference in functional improvements by either 16 weeks of continuous or intermittent exercise training⁵².

Four RCTs investigated aerobic training:

- A RCT in patients with CHF (n=30) found that light-to-moderate-aerobic exercise training (AET) for 3 months lead to a near normalisation of peak VO₂ compared to controls⁵³.
- A RCT in patients with HF (n=27) found that machine-assisted cycling was equivalent in improving exercise capacity as conventional exercise training⁵⁴.
- A RCT of patients with CHF and sleep apnoea (n=50) found that home based 3 month exercise programmes (aerobic training and aerobic with strength training) were equally effective and improved exercise related outcomes compared to an untrained control population⁵⁵.
- A RCT of patients with CHF (n=50) found that a 3 month aerobic exercise programme did not improve cardiac output and related parameters during exercise compared to the control group⁵⁶.

Two RCTs in patients with left ventricular assist device (LVAD) were identified: 1 RCT in patients with a left ventricular assist device (LVAD) (n=14) found no difference in exercise improvement between 8 weeks of exercise training with a progressive mobilisation program and mobilisation alone⁵⁷. However a second RCT of patients (n=15) with a LVAD or biventricular assist device indicated that moderate-intensity aerobic exercise using a bike or treadmill for 45min, three to five times a week improved peak oxygen consumption, VO₂ at ventilatory threshold, 6-min walk test distance and QoL⁵⁸.

In addition the following 7 RCTs and 1 systematic review investigating the efficacy of Nordic walking, high intensity, Tai chi, cycling and endurance training were found;

- A RCT in patients with (n=54) with moderate to severe HF found Nordic walking was superior to standard cardiac rehabilitation care in improving functional capacity⁵⁹.
- A RCT in patients with HF (n=50) found that high-intensity training for 2 months resulted in marked improvements in exercise capacity compared to control⁶⁰.
- A systematic review which included 9 trials (3 trials in CHF) found that the existing evidence suggests that Tai chi exercise is a good option for heart patients with very limited exercise tolerance and can be an adjunct to rehabilitation programs for patients with cardiac disease or CHF⁶¹.
- A RCT in patients with HFPEF (n=16) found that 12 weeks Tai chi and aerobic exercise both improved QoL and exercise capacity³³.
- A RCT (n=30) indicated that eccentric cycle training protocol personalised by the rate of perceived exertion induces functional improvement similar to conventional training with

<p>lower demand on the cardiovascular system during exercise⁶².</p> <ul style="list-style-type: none"> • A RCT in patients with CHF (n=61, NYHAII-III) found that both neuromuscular electrical stimulation of leg muscles or exercise training group with 12 weeks of cycling improved arterial stiffness⁶³. • A RCT in elderly HFPEF patients (n=63) found that 16 weeks of endurance exercise training improved peak VO₂ without altering endothelial function or arterial stiffness compared to attention control⁶⁴. • A RCT of patients with HF (n=16 NYHA class I-II) indicated that a 16 week Pilates intervention was more effective than conventional cardiac rehabilitation program in increasing peak VO₂⁶⁵. <p>Functional electrical stimulation (FES)</p> <p>A systematic review and meta-analysis of FES for CHF found that active cycling or other aerobic/resistance activity is more effective in patients able to exercise than FES^{37,66}. However in patients with HF unable to actively exercise FES is the preferred modality. The RCT indicated that a 6 week FES of peripheral muscles improves exercise capacity, QoL, emotional status and endothelial function in patients with HF and HFPEF (n=30, NYAH class II or III) compared with placebo group⁶⁷.</p>		
<p>Q: Should patients with HF be given advice on nutrition to improve morbidity and mortality?</p>		
Evidence summary	GDG/clinical perspective	Impact
<p><u>Evidence identified from Evidence update (2011)</u> None identified.</p>	<p>No GDG feedback was provided by the GDG questionnaire.</p>	<p>Potential impact on the guideline recommendations.</p>
<p><u>Evidence identified from literature search (2014)</u> Two RCTs indicated that nutritional advice benefited patients with CHF and 1 RCT indicated that micronutrient supplement was not</p>		<p>This section of the guidance has not been updated since 2003. The evidence base for diet and nutrition for patients with HF was</p>

<p>advantageous in patients with CHF.</p> <ul style="list-style-type: none"> • A RCT (n=46) evaluated usual care with medical and nursing staff against additional nutritional guidance about diet plus usual care and found that this educational intervention was effective in modifying nutritional knowledge and the quality of the diet of the patients⁶⁸. • A RCT indicated that a 12 month intervention of a multiple micronutrient supplement had no effect compared to placebo on LVEF in patients with CHF (n=74)⁶⁹. • A RCT of patients with stable CHF (n=97, NYHA class II-IV, on optimal medication, with previous signs of fluid retention) compared individualised salt and fluid restriction or information given by the nurse-led heart failure clinics compared to control⁷⁰. After 12 weeks, significantly more patients in the intervention than in the control group improved on the composite endpoint with improved NYHA class and leg oedema. No negative effects were seen on thirst, appetite, or QoL. 		<p>noted as being limited in 2003 and there was no reference made to education relating to nutrition. Hence no specific recommendations were made in this area. However in the 2010 update as detailed earlier (question 6) 'education' is now recommended as part of an exercise programme. What education this refers to is unclear.</p> <p>The new evidence indicates that education around nutritional factors specific to the patients' conditions may improve clinical outcomes.</p>
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Q: What is the best sequence for pharmacological therapy, and how should it be initiated?

Evidence summary	GDG/clinical perspective	Impact
<p><u>Evidence identified from Evidence update (2011)</u> Fatty acid oxidation inhibition</p> <p>Trimetazidine A meta-analysis of 17 RCTs which examined the use of trimetazidine reported significantly improved LVEF, NYHA classification and exercise duration, and reduce left ventricular end-systolic volume following treatment⁷¹. The data also suggest a beneficial effect on all-cause mortality, cardiovascular events and hospitalisation.</p> <p>Ivabradine</p>	<p>Clinical feedback highlighted the PARADIGM HF study which is an RCT investigating LCZ696 in comparison to enalapril in patients (n=8442) with class II - IV heart failure and an ejection fraction < 40%¹³¹. The results indicate that LCZ696 was superior to enalapril in reducing the risks of death and of hospitalisation for heart failure.</p>	<p>Potential impact on the guideline recommendations.</p> <p>Trimetazidine As trimetazidine, was not licensed in the UK at time of the Evidence Update it was considered that there were no implications of the data for NICE CG108 in 2011. Trimetazidine is now licensed and is indicated for adults as add-on therapy for the</p>

<p>The SHIFT RCT of patients with HF (n=6558) 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 placebo⁷². Despite the relatively young study population, the data suggests a potential role for ivabradine as an adjunct to beta-blockers in HF management.</p> <p>Statins Three meta-analyses were identified that have looked at the use of statins in HF patients⁷³⁻⁷⁵. All 3 studies are based predominantly on trials of atorvastatin involving small numbers of patients, with considerable heterogeneity between trials. The results indicate some beneficial effects; the shortcomings of the studies resulted in the Evidence Update concluding that the new evidence adds little to the case for statins in HF.</p> <p>n-3 polyunsaturated fatty acids (n-3 PUFA) In a sub-study of the GISSI-HF study the effects of (n-3 PUFA and rosuvastatin on left ventricular (LV) function were investigated⁷⁶. No significant effects were observed for rosuvastatin, but n-3 PUFA increased LVEF compared to placebo.</p> <p>Complementary and alternative medicine Two systematic reviews have evaluated two different Chinese herbal medicines (Huangqi – an extract of <i>Radix astragali</i>; and Shengmai – components include <i>Panax ginseng</i>, <i>Ophiopogon japonicas</i> and <i>Schisandra chinensis</i>) as complementary therapies in people with HF^{77,78}. 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.</p>	<p>Clinical feedback also indicated that there was a body of growing evidence that the use of aspirin for patients with ischaemic heart disease and HF may be associated with worse outcomes and mitigate against the benefits of ACEi.</p> <p>Similarly GDG Feedback suggested that that there had been specific trials investigating the use of statins and that it may be useful to address their continued use for patients who have developed HF as there is no evidence of benefit.</p>	<p>symptomatic treatment of patients with stable angina pectoris who are inadequately controlled by or intolerant to first-line anti-anginal therapies. This agent may now potentially be considered as a therapy for inclusion in CG108.</p> <p>Ivabradine Ivabradine was not currently licensed in the UK for HF when the Evidence Update was published in 2011. However, since then NICE TA267 has published. A number of studies supporting TA267 were identified through this surveillance review. TA267 currently recommends ivabradine as an option for treating CHF for people with NYHA class II - IV with systolic dysfunction in sinus rhythm (heart rate >75 bpm), LVEF (<35%) with ivabradine given in combination with standard therapy including BB therapy, ACEi and aldosterone antagonists.</p> <p>One RCT indicated that ivabradine may be effective for patients with HFPEF. Currently ivabradine is not recommended for this group. However, this is a small study and it may be premature to recommend this form of treatment based on this study and outcomes alone.</p> <p>Statins Statins were considered to be outside the</p>
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<p><u>Evidence identified from literature search (2014)</u></p> <p>Fatty acid oxidation inhibition A meta-analysis of the effects of trimetazidine in patients (n=994) with CHF which included 19 RCTs found an improvement in LVEF and NYHA class, a decrease in left ventricular end-systolic and diastolic volumes and hospitalisation for cardiac causes. However, there were no differences in exercise duration and all-cause mortality from placebo⁷⁹.</p> <p>Ivabradine (Drug covered by TA267) Eight reports and 1 cost effectiveness analyses from the SHIFT study where identified⁸⁰⁻⁸⁸. This trial formed the basis of TA267, (Ivabradine for treating chronic heart failure) and as such these studies support current guideline recommendations. In addition one RCT of patients (n=121) with HF (not specified) indicated that ivabradine alone or in combination with carvedilol is more effective than carvedilol alone at improving exercise tolerance and quality of life in HF patients⁸⁹. This supports the current recommendations within TA267.</p> <p>A RCT in patients (n=61) with Heart failure with preserved ejection fraction (HFPEF) found that 7 day treatment with ivabradine increased exercise capacity, with a contribution from improved left ventricular filling pressure response to exercise as reflected by the ratio of peak early diastolic mitral flow velocity to peak early diastolic mitral annular velocity⁹⁰.</p> <p>Statins Two post-hoc sub-group analyses from the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) which randomised patients with ischaemic systolic HF to rosuvastatin or</p>		<p>scope of the 2010 partial update, however due to evidence the GDG felt that the recommendations within CG5 should be deleted. The guideline then stated that for statins, the reader should refer to the guideline on lipid modification CG67 (recently replaced by CG181) and the Technology Appraisal 94 (recently replace by CG181) Statins for the prevention of cardiovascular events.</p> <p>From an assessment of the abstracts identified through this surveillance review it is difficult to ascertain how the evidence based impacts on the use of statins in patients with CHF as it is not clear if the patients have coronary artery disease (CAD) and the results from both the meta-analysis and RCTs are variable. In light of the GDG feedback indicating that the continuing use of statins in patients may have limited benefit it may now be worthwhile to update this area.</p> <p>n-3 PUFA There is evidence that n-3 PUFA may be beneficial for patients with CHF. However the GDG did discuss the GISSI-HF trial at that time of the 2010 guideline update but did not make recommendations as the area was considered to be outside the scope of the partial update. The evidence from the GISSI-</p>
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<p>placebo were identified. One indicates that for patients with galectin-3 values <19ng/mL may benefit from rosuvastatin treatment⁹¹. However, the data from this post hoc analysis should be interpreted with caution since the overall results of the CORONA study did not show a significant effect on the primary endpoint. The second analysis indicated that if including repeat events rosuvastatin reduces the risk of heart failure hospitalisations⁹².</p> <p>A RCT in patients with non-ischemic systolic HF (n=26, LVEF<35%) found that 3 month treatment with atorvastatin did not affect muscle sympathetic nerve activity compared to placebo⁹³.</p> <p>A meta-analysis of 15 studies for the long-term clinical outcomes of additional statin use in CHF indicated that statins persistently decreased all-cause mortality and the incidence of rehospitalisation for HF in patients with CHF, and the benefits might be partially associated with use of a specific statin, atorvastatin⁹⁴.</p> <p>A systematic review and meta-analysis which utilised data from 13 RCTs indicates that statin treatment does not reduce the risk of all-cause death, death for cardiovascular cause or pump failure and rehospitalisation for HF. When restricted to various statins and patients' age, the analysis demonstrated that atorvastatin was associated with reduced all-cause mortality and readmission rate for heart failure, and the superiority of statin therapy was significant in patients with CHF less than 65 yrs of age⁹⁵.</p> <p>n-3 polyunsaturated acids A post-hoc analysis of GISSI-HF trial an RCT with patients</p>		<p>HF trial and its subsequent post-hoc analyses may now be considered in an update of CG108 as the results of these studies indicate that these agents may be beneficial for patients with HF.</p> <p>Angiotensin receptor neprilysin inhibitor</p> <p>LCZ696 is a new agent which is currently going through the topic selection process as a potential technology appraisal topic.</p> <p>Diuretics The guideline currently recommends the routine use of diuretics for the relief of congestive symptoms and fluid retention in patients with HF and for those with HFPEF should usually be treated with a low to medium dose of loop diuretics. The new evidence supports these recommendations.</p> <p>New evidence relating to the direct renin inhibitor aliskiren does not impact the guideline recommendations. The new evidence on the use of vasopressin receptor 2 antagonists is still at an early stage and as such does not impact guideline recommendations.</p> <p>Inotropic treatment- The guideline currently has recommendations</p>
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<p>(n=6975) with chronic HF found no evidence that treatment with n-3 polyunsaturated acids (PUFAs) reduced the incidence of atrial fibrillation compared to placebo⁹⁶.</p> <p>A meta-analysis of 7 trials indicates that fish oil supplementation decreases anti-inflammatory markers in patients with CHF⁹⁷.</p> <p>Angiotensin receptor neprilysin inhibitor A 12 week phase II RCT evaluating the new agent LCZ696 against valsartan in patients (n=301) with HFPEF (NYHA class II-III heart failure) and NT-proBNP greater than 400pg/mL indicated that LCZ696 was more effective at lowering NT-proBNP⁹⁸.</p> <p>Diuretics An update of a Cochrane systematic review to assess the harms and benefits of diuretics for patients with CHF did not identify any new studies for inclusion. The available data from several small trials show that in patients with CHF, conventional diuretics appear to reduce the risk of death and worsening heart failure compared to placebo. Compared to active control, diuretics appear to improve exercise capacity⁹⁹.</p> <p>A systematic review (9 studies included) found data that supported the idea that flexible and individualised diuretic dosing is potentially associated with reduced emergency room visits, reduced rehospitalisation, and improved QoL in CHF patients with reduced ejection fraction¹⁰⁰.</p> <p>Loop Diuretics Two RCTs compared the therapeutic effects of azosemide, a long-acting loop diuretic with a short-acting one. The first study indicated that azosemide was more effective in improving</p>		<p>that date back to 2003 for the use of these agents. The recommendations state that intravenous inotropic agents (such as dobutamine, milrinone or enoximone) should only be considered for the short-term treatment of acute decompensation of chronic heart failure.</p> <p>Levosimendan was reviewed in 2003 but was not recommended as at that time it did not have a license in the UK. This agent is now licensed and evidence indicates that it may provide some benefit to patients with CHF. However the evidence base is still limited in terms of mid-long term outcomes so it may be better to evaluate this drug again during the next surveillance review of this guideline.</p> <p>Calcium channel blockers New evidence on the use of amlodipine in addition to conventional therapy indicates that it does not impact on mortality. This is line with the evidence found in 2003. As such it is unlikely that the new evidence will impact on the recommendation to consider amlodipine for the treatment of comorbid hypertension and/or angina in patients with HF.</p> <p>Selective phosphodiesterase-5 inhibitor Evidence indicates that sildenafil can be safely added to standard HF therapy and may be beneficial for the subgroup who have</p>
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<p>neurohumoral factors in outpatients (n=98) with CHF receiving an ACEi¹⁰¹ and the second longer term study indicated that azosemide reduced the risk of cardiovascular death or unplanned admission to hospital for patients (n=320) with CHF^{102,103}.</p> <p>Direct renin inhibitors (hypertension) A post hoc analysis of a 12 week RCT in patients (n=302) with stable NYHA class II-IV HF, BNP concentration >100pg/mL, and treated with an ACEi or ARB and BB randomised to aliskiren or placebo in patients who received (aldosterone antagonist + n=101) and did not receive (aldosterone antagonist -) was identified. Aliskiren did not affect any of the outcomes measured compared to placebo (BNP, N-terminal proBNP, plasma renin activity, and urinary aldosterone¹⁰⁴).</p> <p>Vasopressin receptor 2 antagonists A 7 day phase III RCT evaluated the efficacy and safety of tolvaptan, in treating HF patients (n=110) with volume overload despite the use of conventional diuretics. Compared with placebo, tolvaptan administered for 7 days significantly reduced body weight and improved symptoms associated with volume overload¹⁰⁵. These results were mirrored by a 7 day phase II RCT which utilised tolvaptan as an add-on therapy in treating HF patients with volume overload on stable doses of furosemide (n=117)¹⁰⁶. A third RCT compared tolvaptan to furosemide and the combination of tolvaptan and furosemide to placebo in patients (n=83) with HF and systolic dysfunction. All active treatments resulted in decreases in bodyweight with tolvaptan monotherapy resulting in the largest increase in urine volume¹⁰⁷.</p> <p>A phase II 8 week trial in outpatients (n=170) with HF and volume overload showed that daily lixivaptan, (not licensed in UK) when</p>		<p>exercise oscillatory breathing.</p> <p>Digoxin No new evidence on the use of digoxin that would impact guideline recommendations was identified.</p> <p>A number of agents were found to have some efficacy in patients with CHF: testosterone, L-citrulline, Flavanol-rich chocolate, and Interleukin-1 (IL-1) receptor antagonist. However, the majority of these studies were placebo comparisons and were small. Hence, as these RCTs are likely to not be adequately powered to assess the risk of these treatments in this high-risk population with regard to quality of life, clinical events, and safety, further evidence is required before they would impact guidance.</p> <p>The following agents were not effective in patients with CHF and hence do not impact current guidance: ascorbic acid, creatine, colchicine and opioids.</p> <p>Antithrombotic therapy CG108 currently recommends the use of aspirin (75–150 mg once daily) for patients with the combination of heart failure and atherosclerotic arterial disease (including coronary heart disease). The new evidence found gives contradictory results based on which trials were selected for the meta-</p>
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<p>added to standard therapy, reduced body weight compared to placebo¹⁰⁸.</p> <p>Inotropic treatment- Calcium sensitisers</p> <p>A meta-analysis of 6 trials on the intermittent levosimendan intravenous administration in patients (n=326) with CHF indicated that there was an improvement in mid-term survival associated with levosimendan but BNP values, ejection fraction and number of patients with NYHA >III status were not different to control¹⁰⁹.</p> <p>A RCT in patients (n=33) with CHF which evaluated monthly infusions of levosimendan indicated that levosimendan improved systolic and diastolic function, ventricular volumes, severity of mitral regurgitation, and BNP levels compared to furosemide¹¹⁰.</p> <p>Calcium Channel blockers</p> <p>A RCT which combined results with a previous study in patients (n=1654) with severe HF due to a nonischemic cardiomyopathy (ejection fraction <30%) indicated that the addition of amlodipine to conventional therapy did not impact mortality. The authors concluded amlodipine does not exert favourable effects on the clinical course of patients with HF, regardless of the presence or absence of underlying coronary artery disease¹¹¹.</p> <p>Selective phosphodiesterase-5 inhibitor</p> <p>A 12 week RCT in patients (n=106) with left systolic heart failure indicated that sildenafil did not decrease blood pressure and was well tolerated compared to placebo¹¹². A second RCT in stable outpatients with HFPEF (n=216) found that sildenafil for 24 weeks, compared with placebo, did not result in significant improvement in exercise capacity or clinical status¹¹³. However in</p>		<p>analysis. However overall the data supports current recommendations.</p> <p>Complementary and alternative medicine</p> <p>The Evidence Update indicated that the results of the included review should be interpreted with caution due to the high risk of bias of the included studies (particularly regarding allocation concealment and blinding), the small sample size of these studies, and the significant heterogeneity in outcomes such as ejection function, cardiac output and stroke volume^{77,78}. There was no evidence available concerning the effect of Shengmai on mortality, and more high quality studies with long-term follow-up are warranted. This would still be the case for the later review identified in 2014.</p>
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patients with HF and exercise oscillatory breathing (n=32) sildenafil therapy for 12 months, as an adjuvant to normal therapy, improved functional capacity (peak VO₂, exercise ventilation efficiency, pulmonary capillary wedge pressure, mean pulmonary artery pressure, pulmonary vascular resistance) and modulation of exercise oscillatory breathing compared to placebo¹¹⁴.

Digoxin

An update Cochrane systematic review which examined the effectiveness of digitalis glycosides in treating HF in patients with normal sinus rhythm found no new evidence with there been no difference in mortality between treatment and control groups, but digitalis therapy is associated with lower rates of both hospitalisation and clinical deterioration¹¹⁵.

Two sub group post hoc analyses from the Digitalis Investigation Group (DIG) trial were identified. The first indicated that in older patients with chronic diastolic heart failure, digoxin increased the risk of 30-day all-cause hospital admission, but not during longer follow-up¹¹⁶. Whereas the second indicated that in high risk sub groups (chronic HF patients with NYHA class III-IV, LVEF <25%, or CTR >55%) digoxin reduced the risk of the 2-year composite endpoint of HF mortality or HF hospitalisation compared to placebo¹¹⁷.

Testosterone

A meta-analysis which included 4 trials indicates that testosterone therapy was associated with a significant improvement in exercise capacity compared with placebo in male patients with stable CHF¹¹⁸.

L-citrulline

<p>A RCT in outpatients with systolic HF (n=35) indicated that L-citrulline supplementation increases LVEF compared to placebo¹¹⁹</p> <p>Creatine A RCT in male patients with functional class II to IV HF (n=33) found that 6 months of creatine supplementation did not improve functional capacity compared to placebo¹²⁰.</p> <p>Colchicine A 6-month course of anti-inflammatory treatment with colchicine in patients with stable CHF (n=267) did not affect patient functional status (NYHA class and objective treadmill exercise tolerance) or the likelihood of death or hospital stay compared to placebo¹²¹.</p> <p>Antithrombotic therapy A Cochrane systematic review which assessed anticoagulation versus placebo for HF in sinus rhythm only identified 2 RCTs (that were classed as up to date with modern practice). The WASH 2004 and HELAS 2006, found no differences in the incidence of myocardial infarction, non-fatal stroke and death between patients taking oral anticoagulation and those taking placebo. The review concluded that the available data does not support the routine use of anticoagulation in HF patients who remain in sinus rhythm¹²².</p> <p>Whereas, an updated meta-analysis on antithrombotic therapy (aspirin, antiplatelet agents, or anticoagulants) in patients with HF and sinus rhythm included trials suggesting that warfarin compared with aspirin reduces stroke risk but there is no mortality benefit¹²³. The study also indicated that aspirin use did not increase HF hospitalisation as has been previously suggested.</p> <p>Flavanol-rich chocolate</p>		
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<p>A RCT in patients (n=20) with CHF found that commercially available flavanol-rich chocolate improved vascular function (flow-mediated vasodilatation) compared to cocoa-liquor-free control chocolate¹²⁴.</p> <p>Ascorbic Acid A 3 day trial in patients with CHF (n=11) found no effect of ascorbic acid with regards to reversing the increased sympathetic activity as measured by microneurography and plasma norepinephrine levels¹²⁵.</p> <p>Opioids A RCT in patients (n=39) with CHF (NYHA class III-IV) on standard medical therapy found no benefit over placebo for the relief of breathlessness with short-term low-dose oral morphine, or oral oxycodone¹²⁶.</p> <p>Interleukin-1 (IL-1) receptor antagonist A small RCT of 12 patients with HFPEF indicated that interleukin-1 blockade with anakinra for 14 days increased aerobic exercise and reduced the systemic inflammatory response compared to placebo¹²⁷.</p> <p>Complementary and alternative medicine An update of a Cochrane systematic review which had found 4 new trials (14 in total) was identified¹²⁸. Eleven trials compared Shengmai (a selection of herbs) plus usual treatment with usual treatment alone, and 3 trials compared Shengmai with placebo. Improvement of NYHA class was more common in patients taking Shengmai plus usual treatment than in those receiving usual treatment alone. Beneficial effects of Shengmai in treating HF</p>		
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<p>were also observed in other outcomes, including exercise test, ejection fraction and cardiac output. The 3 RCTs comparing Shengmai with placebo reported improvement in NYHA class and in stroke volume.</p> <p>Unlicensed medications A systematic review (17 RCTs included) to assess the effectiveness and safety of meglumine adenosine cyclophosphate for the treatment of CHF found insufficient evidence due to study quality to determine the effectiveness of this agent¹²⁹.</p> <p>A RCT indicated that alagebrium did not improve exercise tolerance in patients with HF and systolic dysfunction¹³⁰.</p>		
<p>Q: 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?</p> <p>Research recommendation: What is the comparative effectiveness of aldosterone antagonists and angiotensin II receptor antagonists (ARBs) in symptomatic patients with heart failure due to left ventricular systolic dysfunction who are:</p> <p>A. on optimal therapy with a beta-blocker and an ACE Inhibitor, or B. on a beta-blocker but are intolerant of ACE inhibitors?</p>		
Evidence summary	GDG/clinical perspective	Impact
<p><u>Evidence identified from Evidence update (2011)</u> Two papers were identified that examined the effect of aldosterone antagonists in patients with milder HF.</p> <p>A RCT of patients (NYHA class I–II; LVEF ≤ 40% n=168) which compared the effect of spironolactone with placebo on LV remodelling was identified¹³². Spironolactone treatment increased LVEF, LV end-diastolic and end-systolic volumes and myocardial mass all decreased, and LV diastolic filling pattern also improved</p>	<p>Clinical feedback highlighted the EMPHASIS study: an RCT which investigated the use of eplerenone and indicated that this impacted on the guideline recommendations in that first line treatment for CHF should include BB, ACEi and aldosterone antagonist in</p>	<p>Potential impact on guideline recommendations.</p> <p>NICE CG108 recommends second-line treatment with aldosterone antagonists in patients with NYHA class III-IV or those who have had an acute myocardial infarction and who have symptoms and/or signs of HF and left ventricular systolic dysfunction,</p>

<p>compared to placebo.</p> <p>A RCT (EMPHASIS-HF) which utilised an alternative aldosterone antagonist, eplerenone in patients with mild HF (n=2737, NYHA class II; LVEF ≤ 35%) found that a death from cardiovascular causes or hospitalisation for HF were reduced in patients receiving eplerenone compared to placebo¹³³.</p> <p>Hyperkalaemia can be a potential problem associated with aldosterone antagonist use. A RCT which examined whether inhibiting potassium absorption in the gut via a binding polymer (RLY5016) could prevent a rise in serum potassium in people with HF (n=105) with a history of hyperkalaemia with AA use was identified¹⁰⁴. RLY5016 led to a lower incidence of hyperkalaemia and a greater tolerance of aldosterone antagonists than placebo.</p> <p><u>Evidence identified from literature search (2014)</u></p> <p>A systematic review and meta-analysis which identified 8 trials indicated that additional use of an aldosterone antagonist in patients with mild to moderate CHF (NYHA class I-II) reduced all-cause mortality and re-hospitalisation for cardiac causes, and improved cardiac function while simultaneously ameliorating LV reverse remodelling¹³⁴.</p> <p>Three post-hoc analyses of the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure), a study which found that eplerenone significantly reduced major cardiovascular events versus placebo in 2737 patients with mild symptoms of HF (LVEF <35%), in addition to recommended therapy was identified. The first analysis indicates that eplerenone provides substantial benefit on major events in this population even if patients are already receiving high doses of standard background therapies¹³⁵. A second analysis indicates that</p>	<p>patients with systolic heart failure and mild symptoms (NYHA class II). It was indicated that this would change the treatment algorithm as currently aldosterone antagonists are only recommended for post myocardial infarction or NYHA class III. The EMPHASIS study was also identified by the 4 year search.</p> <p>In addition the TOPCAT trial was also highlighted by the GDG. This RCT indicated that spironolactone reduced heart failure admissions in HFPEF (n=3445). However, spironolactone did not significantly reduce the incidence of the primary composite outcome of death from cardiovascular causes, aborted cardiac arrest, or hospitalisation for the management of HF.</p> <p>Feedback from the Acute heart failure guidance team indicated that wished the two guidelines to be aligned with regards to drug treatment (particularly</p>	<p>with treatment been initiated within 3-14 days of the MI, preferably after ACEi therapy. (This recommendation is from MI: secondary prevention NICE clinical guideline 48 (CG48 has been updated by CG172).)</p> <p>The Evidence Update noted that the data on spironolactone is from a small study with relatively short follow-up and the fact that the remodelling data goes against findings in a larger RCT mean that the results may need to be interpreted cautiously.</p> <p>The EMPHASIS-HF trial was stopped early due to pre-specified 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. The results support NICE guidance that an aldosterone antagonist should be considered in patients who are symptomatic despite optimal treatment with an ACEi and a BB licensed for HF. The Evidence Update indicated, as does clinical feedback and evidence from the 4 year surveillance review, that there is new evidence which impacts on NICE guidance and should be considered as a possible area for update.</p> <p>Due to the small sample size and short follow-up of the study on RLY5016, the evidence is</p>
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<p>eplerenone reduced the incidence of new onset atrial fibrillation or flutter¹³⁶. A third post-hoc sub group analysis in patients at high risk of hyperkalaemia and worsening renal function (including an eGFR >30 ml/min/1.73 m (2) and potassium <5.0 mmol/l,) indicates that eplerenone was both efficacious and safe when carefully monitored¹³⁷.</p> <p>Two post-hoc analysis of the Randomised Aldactone Evaluation Study (RALES), a RCT in patients NYHA class III-IV HF and LVEF) randomised to spironolactone or placebo were identified. The first analysis indicates that races influences the safety and efficacy of spironolactone in severe HF, with African Americans with HF exhibiting less hyperkalaemia and more hypokalaemia with spironolactone compared with non- African Americans and seemed they derived less clinical benefit¹³⁸. The second analysis indicates that the absolute benefit of spironolactone was greatest in patients with reduced eGFR¹³⁹.</p> <p>A RCT in patients (n=150) with or without metabolic syndrome HF (Class II NYHA, LVEF <45%) on optimal therapy found that canrenone (not licensed in UK) protects deterioration of myocardial mechano-energetic efficiency, improves diastolic dysfunction and maximises the decrease in BNP compared to placebo¹⁴⁰.</p> <p>A RCT in patients (n=44) with HFPEF treated for 6 months with either eplerenone or placebo found no improvement in exercise capacity. However, eplerenone was associated with a reduction in serum markers of collagen turnover and improvement in diastolic function¹⁴¹.</p> <p>The Aldo-DHF 12 month trial of ambulatory patients (n=422) with</p>	<p>aldosterone antagonists).</p>	<p>currently unlikely to affect NICE CG108, but shows some potential benefits of anti-hyperkalaemics.</p>
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CHF (NYHA class II-III, HFPEF) indicated that spironolactone improved left ventricular diastolic function but did not affect maximal exercise capacity, patient symptoms, or QoL compare to placebo ¹⁴² .		
Q: What drugs are to be avoided in patients with HF?		
Evidence summary	GDG/clinical perspective	Impact
<p><u>Evidence identified from Evidence update (2011)</u> None identified.</p> <p><u>Evidence identified from literature search (2014)</u> A multivariate analysis based on a RCT in patients (n=1376) with atrial fibrillation and HF indicates that aldosterone antagonists are associated with an increased incidence of cardiovascular deaths²⁴.</p>	No GDG feedback was provided by the GDG questionnaire.	<p>Potential impact on guideline recommendations.</p> <p>Aldosterone antagonists are currently recommended for patients with CHF as a second line therapy. The identified analysis indicates that for those patients with atrial fibrillation other options may need to be considered. There are currently no guideline recommendations specifically about aldosterone antagonist use in patients with CHF and atrial fibrillation.</p>
Q: What invasive procedures have a role in the treatment of HF including heart transplantation?		
Evidence summary	GDG/clinical perspective	Impact
<p><u>Evidence identified from Evidence update (2011)</u></p> <p>Cardiac resynchronisation therapy (CRT) Whether CRT should be used in patients with less severe HF has been investigated in 3 studies:</p> <ul style="list-style-type: none"> • A RCT of patients (n=1798) demonstrated a reduction in 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 alone¹⁴³. 	No GDG feedback was provided by the GDG questionnaire.	<p>Potential impact on guideline recommendations.</p> <p>CRT and ICDs The evidence identified by the Evidence Update in 2011 was stated as potentially impacting on TA120 ‘Cardiac resynchronisation therapy for the treatment of heart failure’ as it indicated that CRT could</p>

<p>However, there was an increased number of subsequent device-related complications in patients randomised to CRT. Subgroup analysis indicated that 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).</p> <ul style="list-style-type: none"> • A meta-analysis of 25 trials found that in patients with NYHA class I and II symptoms, CRT reduced all-cause mortality and HF hospitalisations¹⁴⁴. • A further meta-analysis of 12 studies investigated the benefit of CRT on mortality in 2 comparisons: CRT vs medical therapy (split into more and less symptomatic groups) and CRT plus ICD vs ICD alone¹⁴⁵. Compared with optimal medical therapy alone, CRT plus optimal medical therapy significantly reduced mortality. Compared with an ICD alone, CRT plus ICD significantly reduced mortality which remained significant among patients with NYHA class I or II but not those with class III or IV. <p>Implantable cardioverter-defibrillators (ICDs) A meta-analysis of 7 trials looked at the effect of CRT with and without ICD on all-cause mortality. The study found evidence that CRT plus ICD significantly reduces all-cause mortality¹⁴⁶.</p> <p>Cell transplantation Skeletal myoblast transplantation In an early-phase RCT of patients with HF (n=40) intramyocardial injection of skeletal muscle cells into the scarred areas of the heart was feasible in patients with HF and some symptomatic improvement was observed¹⁴⁷.</p> <p><u>Evidence identified from literature search (2014)</u></p>		<p>potentially be used in patients with cardiac dysfunction but mild symptoms (the NYHA class II subgroup saw a significant reduction alone). This TA has since been reviewed and updated in June 2014 to TA314.</p> <p>Additionally the evidence relating to CRT and ICDs has been reviewed and is now included within TA314.</p> <p>Cell transplantation Skeletal myoblast transplantation Evidence in this area is still at a preliminary stage and is unlikely to affect current guidance or practice.</p> <p>BMNC There is a growing evidence base related to the use of BMNC to treat IHD. Currently this area is not covered by recommendations within the guidance and no clinical feedback relating to the use of this treatment was provided.</p> <p>Respiratory devices No evidence that would impact on respiratory devices was identified.</p>
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CRT and ICD

Ten studies that were used as part of the evidence base for the recommendations within TA314 were identified¹⁴⁸⁻¹⁵⁷. In addition 8 RCTs that referred to methodological aspects of CRT were identified (lead placement)¹⁵⁸⁻¹⁶², sensor type¹⁶³, pacer position¹⁶⁴ pacer type^{165,166} and diaphragmatic stimulation¹⁶⁷.

Additionally 2 RCTs which evaluated the effect of CRT in patients with NYHA class III or IV with HF, a LVEF<35%, a QRS duration <130ms (or <120ms), and echocardiographic evidence of left ventricular dyssynchrony with CRT implant either on or off were identified^{168,169}. The RCTs were stopped early as CRT did not reduce clinical outcomes or left ventricular remodelling and was associated with potential harm as CRT in this sub group may increase mortality.

Furthermore, a RCT in patients with left ventricular assist device implantation found that inhaled nitric oxide did not improve right ventricular dysfunction compared to placebo¹⁷⁰.

Respiratory devices

A RCT patients with HF (n=72) found that a device-guided slow breathing had no impact on symptoms of CHF compared to placebo¹⁷¹.

Cell transplantation

A Cochrane systematic review which included 23 RCTs found that autologous bone marrow-derived mononuclear cell (BMNC) treatment reduced the incidence of mortality and rehospitalisation due to HF in the long term (>12 months) but not in the short term (< 12 months) in people with chronic ischaemic heart disease (IHD) and HF¹⁷². The treatment was also associated with a

<p>reduction in left ventricular end systolic volume (LVESV), stroke volume index, and an improvement LVEF, all at long-term follow-up. Overall, a reduction in functional class during short and long term follow-up was found.</p> <p>A second systematic review and meta-analysis of intramyocardial autologous cell engraftment in patients with ischaemic HF identified 5 studies (n=210 patients) and found that this treatment did not improve LVEF but did increase 6-min walk distance and lowered the incidence of NYHA functional class deterioration¹⁷³. However, the novel procedure did not result in a significant reduction in all-cause mortality.</p> <p>A RCT of cardiopoietic stem cell therapy (autologous bone marrow-derived and cardiogenically oriented mesenchymal stem cell) by endomyocardial injections in patients with HF of ischemic origin reported improved LVEF and the 6-min walk distance¹⁷⁴.</p> <p>A RCT of intracoronary injection autologous BMNCs injection in patients (n=234) with Chagas cardiomyopathy, NYHA class II to IV, LVEF <35% did not find any difference in left ventricular function or QoL following intervention compared to placebo¹⁷⁵.</p> <p>A RCT in patients (n=153) with chronic ischemic heart failure indicated that transendocardial injection of autologous BMCs compared with placebo did not improve left ventricular end-systolic volume, maximal oxygen consumption, or reversibility on single-photon emission tomography¹⁷⁶.</p> <p>A RCT in HF patients (n=23) with chronic post infarction cardiomyopathy, of image-guided, catheter-based intramyocardial injection myoblasts found no clinical benefits compared to</p>		
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<p>placebo¹⁷⁷.</p> <p>A RCT indicated that injections in 10 left ventricular sites with an infusion catheter in patients with ischemic cardiomyopathy (n=65) and LVEF <50 % of either transendocardial mesenchymal stem cells (MSCs), BMNCs or placebo was feasible with MSCs and BMNCs improving QoL¹⁷⁸.</p>		
<p>Q: Can domiciliary oxygen therapy be used to modify the outcome of HF in terms of quality of life, morbidity and mortality (including acute decompensation)?</p> <p>Q. Can CPAP be used to modify the outcome of HF in terms of quality of life, morbidity and mortality (including obstructive sleep apnoea acute decompensation)?</p>		
Evidence summary	GDG/clinical perspective	Impact
<p><u>Evidence identified from Evidence update (2011)</u> None identified.</p> <p><u>Evidence identified from surveillance review (2014)</u> Five RCTs were identified that have looked at the benefits of CPAP or adaptive servo-ventilation (ASV) in patients with CHF.</p> <p>A RCT on patients (n=10) with stable congestive HF and central sleep apnoea with Cheyne-Stokes respiration (CSA-CSR) oxygen through nasal prongs and concentrator or 8 weeks adaptive servo-ventilation (ASV) was identified¹⁷⁹. CSA-CSR was reduced to a greater extent by ASV than oxygen therapy over 8 weeks but was not accepted long term. Neither treatment improved prognostic indices of HF or symptoms in the short term.</p> <p>A RCT in patients (n=51) with severe CHF, despite optimal cardiac medication and/or LVEF <40% and Cheyne-Stokes breathing for >25% of sleeping time found that 3 months of ASV treatment improved LVEF and physical capacity compared to control¹⁸⁰.</p>	<p>No GDG feedback was provided by the GDG questionnaire</p>	<p>Potential impact on guideline recommendations.</p> <p>These areas were covered in CG5 (2003) and has not been updated since. At the time the GDG was unable to come to any recommendations on the use of domiciliary oxygen or CPAP therapy for patients with HF despite them improving patient outcomes.</p> <p>It is not possible based on the CG5 to determine the size of the evidence base previously but it was noted that the RCTs tended to be small with the the largest noted as having 66 participants. As such it is likely that the evidence base was similar to that presented in the 4 year update. A full systematic review and pooling of the trials from the last 11 years may enable recommendations to now be made.</p>

<p>A RCT in patients (n=22) with CHF and CSR-CSA after CRT defibrillator (CRTD) implantation, found that ASV treatment over 6 months improved indices for apnea-hypopnea, central apnea, oxyhemoglobin saturation, BNP levels, cardiac systolic and diastolic function compared to control¹⁸¹. Additionally the event-free rate was significantly higher in the ASV group than in the non-ASV group.</p> <p>A RCT which compared the efficacy of ASV and CPAP over a 12-month period in reducing breathing disturbances and improving cardiac parameters in patients with HF (n=70, NYHA classes II-III) and coexisting sleep-disordered breathing was identified¹⁸². Whilst both modes of therapy significantly improved respiratory disturbances, oxygen desaturations, and arousals over the study period, ASV reduced the central apnea hypopnea index and BNP levels more effectively as compared with CPAP.</p> <p>A RCT in patients (n=36) with HFPEF and sleep-disordered breathing randomised subjects to 6 months treatment with medications and ASV or medication only was identified¹⁸³. ASV therapy improved cardiac diastolic function and decreased cardio-ankle vascular index and BNP and increased the event-free rate.</p>		
Clinical area 4: Rehabilitation in chronic heart failure		
<p>Q: What is the efficacy and safety of patient (self monitoring) telemonitoring in comparison to outpatient monitoring for adults with chronic heart failure?</p> <p>Research recommendation: What is the effectiveness and cost effectiveness of home telemonitoring, monitoring of serum natriuretic peptides and formal follow-up by a heart failure team for patients with heart failure due to left ventricular systolic dysfunction?</p>		
Evidence summary	GDG/clinical perspective	Impact

<p><u>Evidence identified from Evidence update (2011)</u></p> <p>Telemonitoring (TM)</p> <p>In a follow-up of the previously reported Randomised Trial of Phone Intervention in Chronic Heart Failure (DIAL study n=1518) at 1 year and 3 years death or admission to hospital for worsening HF was less likely in those receiving telephone intervention than in those receiving usual care¹⁸⁴.</p> <p>Three RCTs comparing TM to usual care were also identified:</p> <ul style="list-style-type: none"> • A RCT of patients (n=710, NYHA class II or III) indicated telemonitoring had no effect on mortality, cardiovascular death or HF hospitalisation¹⁸⁵. • A RCT in stable HF patients (n=390) found the intervention tended to increase rates of urgent care visits, but reduced the number of days in hospital¹⁸⁶. • A RCT found that a voice interactive system made no difference to all-cause mortality and all-cause hospital readmission compared to usual care patients (n=1653, 71% with an LVEF fraction < 40%) with an HF hospitalisation within the previous month¹⁸⁷. <p>Remote monitoring</p> <p>A RCT of patients (n=550, NYHA class III) found that information from an implanted wireless pulmonary artery haemodynamic monitoring system led to a reduction in the number of hospitalisations compared to standard care¹⁸⁸.</p> <p><u>Evidence identified from surveillance review (2014)</u></p> <p>TM</p> <p>Eight studies (2 systematic reviews, 1 sub group analysis and 5 RCTs) were identified that have addressed TM in CHF patients.</p>	<p>The GDG highlighted the decision analysis modelling of cost-effectiveness study by Thokala <i>et al</i> 2013 as potentially impacting on the guidance¹⁹⁹.</p> <p>The study estimated the cost-effectiveness of various remote monitoring strategies versus usual care for adults recently discharged after a HF exacerbation in Acute hospitals in the UK. TM was the most cost-effective strategy in the scenario using these base case costs but there is considerable uncertainty in relation to clear descriptions of the interventions and robust estimation of costs.</p>	<p>Potential impact on guideline recommendations</p> <p>Given the difficulties of interpretation of the evidence (8 studies in 2010) with regard to cost-effectiveness and the impact of TM per se (such as increased access compared to TM) the GDG did not make specific recommendations for home telemonitoring but agreed that a research recommendation should be made. Since then the evidence base has expanded with 2 systematic reviews indicating that overall this approach improves patients' outcomes. Some RCTs still indicate no difference in TM compared to usual care which may indicate different requirements by differing patient populations. As such it may now be appropriate to review this section of guidance and determine the cost effectiveness of this approach in UK settings.</p> <p>Remote monitoring</p> <p>Implantable wireless pulmonary artery haemodynamic monitoring systems are a novel technology. Overall 2 studies have been identified. Whilst this technology appears to reduce hospitalisations its impact on other clinical outcomes such as mortality and QoL would ideally be required.</p>
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<p>A systematic review of TM and structured telephone support identified 30 RCTs and found that telemonitoring reduced all-cause mortality¹⁸⁹. Both TM and structured telephone support reduced CHF-related hospitalisations and improved QoL, reduced costs, and were acceptable to patients. In addition, a second systematic review with 14 studies included suggests that TM resulted in significant improvement of HF self-care behaviours of daily weighing, medication management, exercise adherence, fluid and alcohol restriction, salt restriction, or stress reduction in the telehealth intervention group in 5 studies¹⁹⁰. However, 5 other studies found no difference between the intervention and control groups.</p> <ul style="list-style-type: none"> • A RCT which compared 6 months of intense follow-up facilitated by TM or usual care in CHF patients (n=160 LVEF <35%) was identified¹⁹¹. All-cause mortality was lower and number of days lost to hospitalisation, death, or dialysis was significantly lower in the TM group compared with usual care. • A RCT indicated that a telephone support intervention did not affect the Packer score (a clinical composite consisting of mortality, overnight hospitalisation for worsened HF and NYHA class global self-assessment) in patients with a general practice diagnosis of HF (n=405) compared to usual care¹⁹². However, the telephone support intervention reduced hospitalisation for any cause among a rural and remote cohort. • A RCT in patients (n=100) which compared mobile phone TM and control groups found that there was an improvement in QoL through improved self-care and clinical management from the intervention but there was no difference in BNP levels, self-care management, and LVEF between the groups¹⁹³. • A RCT of patients recently hospitalised with HF (n=344, 57% 		
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had a (LVEF) <30%). found that daily electronic transmission of body weight to a HF did not impact on cardiac re-hospitalisation, all-cause hospitalisation, death from any cause or the composite endpoint of cardiac hospitalisation and death from any cause compared to control¹⁹⁴.

- A RCT of TM versus usual care in patients with HF (n=382, mean LVEF <38%) found no difference in time to first heart failure-related hospitalisation, total hospitalisations, heart failure admission and all-cause mortality between the groups¹⁹⁵.
- A subgroup analyses for the TIME-HF trial, an RCT in stable chronic HF patients (n=710, NYHA class II or III with a history of HF decompensation within 2 years previously or a LVEF < 25%) randomly assigned to TM or usual care indicates that TM management may not be appropriate for all HF patients¹⁹⁶.

Remote monitoring

A RCT involving patients with HF and ICDs (n=200) compared remote monitoring (internet-based remote interrogation systems) with standard patient management consisting of scheduled visits and patient response to audible ICD alerts¹⁹⁷. Remote monitoring reduced emergency department utilisation and other health care visits. However, there was no difference in clinical outcomes between the intervention and control group. A cost-utility analysis of this study from the perspectives of the health care system and the patient showed that remote monitoring is a cost-effective and dominant solution¹⁹⁸.

Ongoing research

5. Ongoing trials on LCZ 696 in heart failure with preserved ejection fraction (due to complete in 2015/16) and of Ivabradine in heart failure with preserved ejection fraction (due to complete in 2016/17) were highlighted by the GDG as potentially important.

Anti-discrimination and equalities considerations

6. None identified.

Implications for other NICE programmes

7. This guideline relates to a Quality Standard on Chronic Heart Failure ([QS9 Chronic heart failure](#) published June 2011). The current surveillance review recommendation to update the guideline may potentially impact on the Quality Standard.
8. Three of the quality statements are likely to be affected by the proposed areas for update.
 - Statement 5. People with chronic heart failure are offered personalised information, education, support and opportunities for discussion throughout their care to help them understand their condition and be involved in its management, if they wish.
 - Statement 7. People with chronic heart failure due to left ventricular systolic dysfunction are offered angiotensin-converting enzyme inhibitors (or angiotensin II receptor antagonists licensed for heart failure if there are intolerable side effects with angiotensin-converting enzyme inhibitors) and beta-blockers licensed for heart failure, which are gradually increased up to the optimal tolerated or target dose with monitoring after each increase.
 - Statement 8. People with stable chronic heart failure and no precluding condition or device are offered a supervised group exercise-based cardiac rehabilitation programme that includes education and psychological support.

Conclusion

9. Through the surveillance review of CG108 new evidence which may potentially impact guideline recommendations was identified in the following areas:
 - a. Referral and approach to care
 - b. Measurement of circulating natriuretic peptide concentration
 - c. Treating chronic heart failure

d. Rehabilitation in chronic heart failure

10. For all other areas of the guideline no new evidence was identified which would impact on recommendations.

11. For the following reasons it was decided that this guideline should be fully updated through the standard development process:

- There are potentially 11 clinical questions that require updating and many of these are linked to other questions within the guideline. Some of these areas may require more complex health economic modelling, one question relates to diagnosis and BNP cut off levels and is consensus based and would therefore not be suitable for discrete update through the standing committee.
- The majority of the guideline dates back to 2003 and the evidence base from those areas not previously updated uses older methodology, does not include GRADE and is not readily available for extraction.
- The guideline has complex links and cross refers to numerous related guidelines which have either been updated or are now covered by new guidance.

12. Given the complexity of the update it would be difficult to update CG108 in the context of a standing committee update and a full scoping exercise for the update of CG108 would be required. The update will be commissioned when capacity becomes available.

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Centre for Clinical Practice
December 2014

Appendix 1 Decision matrix

Surveillance and identification of triggers for updating CG108. The table below provides summaries of the evidence for key questions for which studies were identified.

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
Diagnosing Heart Failure			
Q1 What is the accepted definition of HF?			
None identified.	None identified.	No GDG feedback was provided by the GDG questionnaire.	None identified.
Q2 What is the current burden of HF in the UK, and trends in prevalence, and what do we know about prognosis and how is it being affected by current management?			
None identified.	None identified.	No GDG feedback was provided by the GDG questionnaire.	None identified.
Q3 What is the burden of HF for the patient?			
None identified.	None identified.	No GDG feedback was provided by the GDG questionnaire.	None identified.
Q4 What is best practice for communication at the initial diagnosis of HF, and in ongoing management to improve quality of life?			
None identified.	None identified.	No GDG feedback was provided by the GDG questionnaire.	None identified.
Q5 What are the aims of HF treatment for the patient and the healthcare professional, in terms of morbidity and mortality?			
Performance measures A systematic review looking at the	None identified.	No GDG feedback was provided by the GDG	None identified.

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
effect of performance measures on outcomes in patients with HF was identified ²⁰⁰ . From a mixture of studies (2 were prospective cohort studies and only one was an RCT), improved outcomes were observed with the use of angiotensin-converting enzyme inhibitors (ACEi) and beta-blockers (BB) at discharge, with some improvement also seen following issue of written discharge instructions, whereas measuring left ventricular (LV) function and counselling about smoking had no impact.		questionnaire.	The Evidence Update did not state that the study identified on performance measures had any impact on CG108.
Clinical area : Referral and approach to care			
Q6 Is there evidence that support and education for carers and relatives of HF improves patient quality of and clinical outcomes?			
None identified.	Seven RCTs were identified that have looked at either carer or patient education. Compared to standard care; HF nurse education (1hr 1-to-1 session), patient activation, DVD decision aids and telephone reinforcement were all more effective in improving health behaviours and	No GDG feedback was provided by the GDG questionnaire.	Potential impact on the guideline. The new evidence from this surveillance time point indicates that education and support improves patient's outcomes. However, providing education to carers and relatives may have a limited impact. This review question is from CG5 and this section of the guideline has not

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>outcomes. Whereas, family member education, targeted cognitive training and an intensive multisession intervention did not improve health outcomes.</p> <ul style="list-style-type: none"> • A RCT comparing the effects of a 1h, one-on-one teaching session with a nurse educator to the standard discharge process in patients with systolic heart failure showed that HF nurse education at the time of hospital discharge resulted in improved patient knowledge and reduced risk of readmission¹. • A RCT in HF patients (n=84) indicated that a patient activation intervention compared with usual care increased patient activation and adherence and decreased hospitalisations². • A RCT in individuals with HF (n=480) indicated that a 		<p>been updated since 2003. The appendix M (CG5) indicates a systematic review was conducted but the evidence (if any was identified) is not presented within the original 2003 guideline or the update. There are a number of recommendations that could potentially be considered as 'education and support based' and it would appear that those from 2003 were consensus based:</p> <p>R80 Guidelines for good communication:</p> <ul style="list-style-type: none"> • Listen to patients and respect their views and beliefs • Give patients the information they ask for or need about their condition, its treatment and prognosis, in a way they can understand including information about any serious side effects of drugs to be prescribed • Provide the most important information first • Explain how each item will

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>DVD decision aid increased levels of daily weight monitoring, monitoring of fluid intake and following a low-sodium diet compared to standard care³.</p> <ul style="list-style-type: none"> • A RCT in patients with HF (n=605) indicated that telephone reinforcement (5 to 8 telephone counselling sessions over 1 month) of learning goals and self-care behaviours improved knowledge, health behaviours, and HF-related QoL compared to a single education session⁴. • A RCT which investigated a group-based multi-professional education programme to increase family members' knowledge about CHF found that this intervention did not affect the patient's health care utilisation⁵. • A RCT in patients with HF 		<p>affect patients personally</p> <ul style="list-style-type: none"> • Present information in separate categories • Make advice specific, detailed and concrete • Use words the patients will understand; confirm understanding by questions; define unfamiliar words; write down key words; draw diagrams and keep a copy in the medical notes • Repeat the information using the same words each time • Prepare material, written or taped, to back up handwritten notes • Share information with patients' partners, close relatives or carers if they ask you to do so. When patients cannot indicate their consent for such sharing of information, it is advisable to share the information that those close to the patient need or want to know, except where you have

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>(n=605) found that an intensive multisession intervention did not change clinical outcomes compared with a single-session intervention⁶.</p> <ul style="list-style-type: none"> • A RCT in patients (n=125) with HF and mild cognitive impairment (MCI) indicated that a targeted self-care teaching intervention using principles of cognitive training increased heart failure knowledge at 30 days post-discharge; however, this did not impact readmission rates compared to standard care⁷. 		<p>reason to believe that the patient would object if able to do so.</p> <p>R81 The content, style and timing of information provision should be tailored to the needs of the individual patient.</p> <p>R82 Healthcare professionals should assess cognitive ability when sharing information.</p> <p>R83 Carers and relatives of patients who are cognitively impaired should be made aware of treatment regimens for the patients they care for and be encouraged to identify any need for clinical support.</p> <p>R82 is a strongly worded recommendation. How the clinician should assess the cognitive ability is not clear and there is no guidance on what clinicians should do with this information.</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
			In addition, an educational component is recommended as part of any exercise programme (2010). However, as not all patients with CHF are recommended to have this aspect of care there is therefore the potential for them to not receive the same education and support. This is potentially an equality issue for those that qualify for physical exercise programmes and those that don't.
Q7 In what circumstances should a previous diagnosis of HF be reassessed?			
None identified.	None identified.	No GDG feedback was provided by the GDG questionnaire.	None identified.
Symptoms, signs and investigation			
Q8 What is the diagnostic accuracy of a collection of symptoms and signs, including any scoring systems vs gold standard in the diagnosis of HF?			
None identified.	None identified.	No GDG feedback was provided by the GDG questionnaire.	None identified.
Measurement of circulating natriuretic peptide concentration			
Q9 What is the accuracy of natriuretic peptides vs gold standard in the diagnosis of heart failure?			
A meta-analysis investigated the value of B-type natriuretic peptide (BNP) level as a diagnostic	A focus search (which has an expanded inclusion criteria for of observational studies) was	GDG feedback indicated that the current guideline recommendations on the	Potential impact on the guideline. The evidence identified in the EU

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
<p>parameter in addition to typical clinical signs and symptoms in the identification of suspected slow-onset HF patients (n=276) in primary care⁸. 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.</p> <p>A comparison of BNP levels using the European Society of Cardiology (ESC) cut-off points of < 100pg/ml (or < 35pg/ml) to 'rule out' or > 400pg/ml (or > 100pg/ml) to 'rule in' the diagnosis of HF also performed poorly.</p>	<p>conducted for this question that identified 4 studies.</p> <p>A cohort study of patients (n=999, >60yrs) with coronary artery disease (CAD) with and without chronic kidney disease (CKD) indicated that higher cut off levels of BNP better detected CHF in CKD patients (4376pg/mL) than in non-CKD patients (298pg/mL)⁹.</p> <p>A retrospective medical records analysis of patients (n=57) hospitalised with a diagnosis of acute exacerbation of chronic obstructive pulmonary disease (COPD) assessed the performance of BNP in detecting left ventricular systolic dysfunction in patients with no history of HF. Mean BNP values in patients with systolic dysfunction (689pg/ml) were higher than those without (340pg/ml). For the detection of</p>	<p>whole were consistent with any new evidence. However, it was noted that the new ESC guidance (2012) had changed the natriuretic cut off points and it was felt that a discussion around whether NICE wished to be aligned with this was needed as original cut off points used in CG108 were consensus based.</p> <p>A cross-sectional study by Kelder <i>et al</i> 2011 which investigated the diagnostic value of physical examination and additional testing in primary care patients (n=721) with suspected HF was highlighted as relevant by the GDG¹². The study compared determination by an outcome panel to physical and history tests along with biomarkers. The combination of 3 items from history plus 6 from</p>	<p>supported the utility of using BNP in the diagnosis of HF but concluded at that the evidence identified at that time unlikely to affect NICE CG108.</p> <p>Further new evidence supports the use of BNP and adds value in the diagnosis of those clinically suspected of HF (including slow onset) in primary care. However a number of studies indicate that cut-off values remain problematic as these need to factor in co-morbidities as NT-proBNP /BNP values tend to be higher in patients with impaired renal function or COPD.</p> <p>As the cut off values used in CG108 were consensus derived and clinical feedback indicates that there is a wish to examine these due to newer levels within the ESC guidance, then this area may potentially require updating.</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>systolic dysfunction, a BNP level inferior to 100pg/ml yielded a sensitivity of 92% and a negative predictive value of 91%, whereas BNP higher than 500 yielded a sensitivity of 80% and a positive predictive value of 47%¹⁰. A cross sectional study investigated NT-proBNP levels for the diagnosis of left ventricular dysfunction in patients (n=120) with severe acute exacerbations of COPD and renal dysfunction. Median NT-proBNP levels were significantly higher in these patients, irrespective of whether their renal function was normal or impaired. The threshold NT-proBNP value with the highest diagnostic accuracy was greater in the setting of renal dysfunction (2000pg/mL; sensitivity 71%, specificity 82%, compared with 1000pg/mL in patients with normal renal function; sensitivity 94%,</p>	<p>physical examination showed independent diagnostic value with NT-proBNP the most powerful supplementary diagnostic test.</p> <p>For daily practice, a diagnostic rule was derived that may be useful to quantify the probability of heart failure in patients with new symptoms suggestive of heart failure. The GDG feedback stated that this new risk score may indicate that the diagnostic pathway would need changing.</p>	

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	specificity 82% ¹¹).		
Q10 What is the accuracy of echocardiography vs natriuretic peptides in the diagnosis of diastolic dysfunction?			
None identified.	None identified.	No GDG feedback was provided by the GDG questionnaire.	None identified.
Q11 Does serial BNP monitoring (guided therapy) improve outcome compared to standard care in adults with chronic heart failure?			
<p>A RCT in patients (n=345) hospitalised for HF with elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) at admission which examined whether management of HF guided by an NT-proBNP target improves outcomes was identified²⁰¹. 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.</p> <p>In an RCT of patients (n=252, NYHA class II-IV) with HF and</p>	<p>New evidence identified from systematic reviews (3), RCTs (2), a cost effectiveness analysis (1) and post-hoc analyses of RCTs (5) supports the hypothesis that natriuretic peptide (NP)-guided therapy is superior to symptom-guided therapy for improving quality of life (QoL) and numerous clinical outcomes in CHF outpatients. However, some RCTs failed to document significant clinical improvement in terms of overall mortality and morbidity using a BNP-guided strategy.</p> <p>A systematic review and meta-analysis of 11 RCTs found that compared with usual clinical</p>	<p>Clinical feedback stated that there was new evidence (not specified) that expanded the evidence base regarding the use of NT-proBNP in monitoring treatment. It was indicated that in general this new evidence supports the current guideline recommendations.</p>	<p>No impact on guideline recommendations.</p> <p>This section of the guideline was updated in 2010 and included 5 trials and a health economic analysis developed specifically for this guideline. The cost effectiveness data found that the optimisation of drug therapy in CHF using serial measurement in secondary care of BNP concentration was cost-effective compared to clinical assessment in secondary care and to usual care in the community. The preferred option for patients older than 75 years might be clinical assessment in secondary care. This led to the recommendation in CG108 that specialist monitoring of serum natriuretic peptides is</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
<p>grossly elevated NT-proBNP levels (> 800 pg/ml for men, > 1000 pg/ml for women), no difference was observed in days alive and out of hospital and symptom score between those who had NT-proBNP guided care and those who did not²⁰².</p>	<p>care, BNP guided therapy reduces all-cause mortality and HF rehospitalisation, especially in patients younger than 70 years or with higher baseline BNP²⁰³. A second systematic review of NP guided therapy in patients with CHF identified 12 RCTs²⁰⁴. This study found that NP-guided therapy and NT-proBNP guide therapy reduced all-cause mortality and HF-related hospitalisation, but not all-cause hospitalisation. Conversley, BNP-guided therapy did not reduce all-cause mortality, HF-related hospitalisation or all-cause hospitalisation. The third systematic review which included an individual patient meta-analysis for NP-guided treatment of HF on all-cause mortality utilised 11 studies (data from 2000 patients) and found all-cause mortality was reduced by NP-guided</p>		<p>considered in some patients (for example, those in whom up-titration is problematic or those who have been admitted to hospital).</p> <p>Based on the new evidence identified in the Evidence Update, this report concluded that NT-proBNP monitoring did not appear to affect health outcomes and may need to be considered for updating in future reviews of NICE CG108. However, 1 study was under-powered, and used setting an NT-proBNP target based on the lowest level at discharge or at 2 weeks when levels were still elevated as a result of acute decompensation²⁰¹. This means that the target was too easily achievable and would possibly lead to not clinically effective outcomes. The second study had participants with a mean age of 78 years and as such the evidence is in line with that found within the guidance.</p> <p>Finally, the new evidence found as</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>treatment with the survival benefit been seen in younger (<75 years) patients only. Hospitalisation due to HF or coronary artery disease (CAD) was also lower in NP-guided patients²⁰⁵.</p> <p>A report from the UPSTEP RCT of symptomatic patients with worsening HF (n=279, New York Heart Association (NYHA) class II-IV) comparing BNP-guided to conventional HF treatment was identified²⁰⁶. The study found that BNP-guided HF treatment did not improve morbidity and mortality or need for hospitalisation. A subgroup analysis comparing treatment responders versus non-responders found improved survival among responders.</p> <p>A RCT of patients hospitalised for HF (n=130) with LVEF<35% found that there was no difference in days alive and hospitalisation rates with either</p>		<p>part of the 4 year surveillance review and the clinical feedback in general supports the current guideline recommendations.</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>a BNP- guided outpatient diuretic management programme or by clinical assessment²⁰⁷ . However, BNP strategy patients received more ACEi, BB, and the combination of ACEi or ARB plus BB. Three post hoc reports from the ProBNP Outpatient Tailored Chronic Heart Failure Therapy (PROTECT) study in patients with left ventricular ejection fraction (LVEF) CHF (n=151) which compared amino-terminal pro-B type natriuretic peptide (NT-proBNP) guided therapy to standard-of-care (SOC) management over 10 months were identified²⁰⁸⁻²¹⁰ . Compared to SOC HF management, NT-proBNP guided care was well tolerated, associated with greater and more sustained improvement in QoL, reduced cardiovascular event rates and more favourable cardiac remodelling outcomes.</p>		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>Two post-hoc studies from the TIME-CHF RCT (patients with HF (n=499, LVEF<45%), NT-proBNP-guided versus standard treatment) were also identified. A safety analysis indicated no increase in adverse events with intensified NT-proBNP-guided treatment^{211,212}. The results of a 5 year follow up indicated that the intensified treatment did not improve overall hospital free or overall survival but did improve HF hospitalisation-free survival. However, within the subgroup of patients aged 60-74 years, it improved overall mortality.</p> <p>A cost-effectiveness analysis of three monitoring strategies (serial NP by a specialist, clinical assessment by a specialist, or usual care in the community) for optimising medical therapy in CHF based on 6 RCTs was identified²¹³.</p>		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	The analysis concluded that serial measurement of NP concentration by a specialist is the most cost-effective strategy for CHF due to left ventricular systolic dysfunction from any cause, except in the subgroup of patients >75yrs with CHF from any cause, where treatment guided by NP measurement may be harmful and not cost-effective.		
Q12 What are the most appropriate tests in a patient with suspected HF to confirm diagnosis?			
A sub-study of patients (n=1464) from the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA), 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 which remained significant following adjustment for NT-proBNP ²¹⁴ .	A systematic review and meta-analysis which included 7 studies (375 patients with CHF and 181 healthy control participants) indicated that a quantitative assessment of left ventricular function by 3-dimensional speckle-tracking echocardiography in patients with CHF was feasible. No clear comparator to other methodology or gold standard was indicated in the abstract ²¹⁵	No GDG feedback was provided by the GDG questionnaire.	No impact on guideline recommendations. The study on OPG 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.

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
Q13 What are the key elements for interpreting the results of cardiac imaging, to confirm a diagnosis of HF?			
None identified.	None identified.	No GDG feedback was provided by the GDG questionnaire.	None identified.
Q14 What is the best method for diagnosis of isolated diastolic dysfunction?			
None identified.	None identified.	No GDG feedback was provided by the GDG questionnaire.	None identified.
Treating Chronic Heart failure			
Q15 Are there sub groups of HF patients that should be treated differently? Angina pectoris Diastole Atrial fibrillation Heart transplantation Sleep apnoea syndrome Anaemia Diabetes mellitus Cognition disorder Older people Ethnic groups			
Anaemia treatment A systematic review of 11 RCTs found that treatment of anaemia in HF with erythropoiesis-stimulating agents (ESA) improved exercise duration, 6-minute walk distance, peak oxygen, NYHA class, ejection	Anaemia treatment Numerous studies looking at the treatment of anaemia in patients with HF were identified (2 systematic reviews, 3 RCTs, 1 post-hoc analysis and an economic evaluation).	No GDG feedback was provided by the GDG questionnaire.	Potential impact on the guideline recommendations. The review identified in the Evidence Update used the Cochrane methodology, but the data was from small heterogeneous studies with

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
fraction and B-type natriuretic peptide ¹³ .	<p>A systematic review and meta-analysis (including 4 trials) indicated that iron supplementation for the treatment of CHF and iron deficiency improved QoL and iron indices without a change in haemoglobin levels¹⁴. A second meta-analysis (including 5 trials) of patients with CHF and iron deficiency treated with intravenous iron indicated that patients treated with intravenous iron had significant reductions in hospitalisations and adverse events with improvements in NYHA class and LVEF¹⁵.</p> <p>A RCT in iron-deficient CHF patients (n=459) with or without anaemia indicated that intravenous iron substitution using ferric carboxymaltose over a 24-week period improved health related QoL (HRQoL)</p>		<p>varying endpoints and short-term follow-up. As such, it was concluded that the evidence up to 2011 was unlikely to affect NICE CG108, however the general area of iron deficiency, anaemia and chronic kidney disease in HF potentially warranted greater attention and cited iron therapy in the form of ferric carboxymaltose as recently to have been shown in an RCT to benefit HF patients with iron deficiency³⁰. Since the completion of the Evidence Update numerous other trials relating to anaemia treatment have been identified that indicate treatment is beneficial for those with CHF and anaemia.</p> <p>The large multivariate analysis in patients with AF and HF on aldosterone antagonists should be considered when reviewing these agents for use in CHF (see below) as there are associated with an increased incidence of cardiovascular deaths in this sub group.</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>and exercise tolerance compared to placebo ¹⁶. A model-based cost-effectiveness analysis of this study from the UK payers' perspective indicates that the base case ICER was clearly below the threshold of £22 200-33 300/QALY gained and proved to be robust in sensitivity analysis¹⁷.</p> <p>A 24 week RCT in anaemic patients with HFPEF (n=56) indicated that subcutaneous epoetin alfa treatment resulted in increases in haemoglobin but did not changes end-diastolic volume, left ventricular mass, 6-minute walk distance nor QoL compared to placebo¹⁸.</p> <p>A post hoc analysis of the HF-ACTION trial (a RCT comparing exercise therapy vs usual care in 2331 patients with HF) indicates that anaemia is</p>		<p>In addition a number of small RCTs have looked at various treatment options in patients with CHF and a number of other co-morbidities such as growth hormone deficiency, diabetics/insulin sensitivity, CKD Chagas cardiomyopathy, COPD and low testosterone. On the whole the evidence based is still limited and these areas should continue to be surveyed until sufficient evidence to enable recommendations is available.</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>associated with increased rates of death, hospitalisation, and HF exacerbation in patients with CHF¹⁹.</p> <p>A RCT in patients with systolic HF and anaemia (n=2278) found that treatment with darbepoetin alfa did not improve clinical outcomes in patients compared to placebo²⁰.</p> <p>Growth hormone deficiency A long term 4 year RCT in patients with CHF deficient in growth hormone (n=56) indicates that growth hormone (GH) replacement therapy in addition to standard CHF therapy increase LVEF and peak VO₂²¹.</p> <p>Diabetics/insulin sensitivity A RCT in non-diabetic patients with stable ischemic CHF (n=36) indicated that irbesartan on top of standard CHF therapy</p>		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>improved insulin sensitivity compared to standard therapy alone²².</p> <p>A small 16 week RCT in patients (n=16) with CHF indicated that spironolactone improved insulin resistance in comparison to furosemide²³.</p> <p>Atrial Fibrillation A multivariate analysis based on a RCT in patients (n=1376) with atrial fibrillation (AF) and HF indicates that aldosterone antagonists are associated with an increased incidence of cardiovascular deaths²⁴.</p> <p>Kidney disease A 6 month RCT in patients (n=18) with congestive HF (NYHA class III-IV, LVEF <45%) on continuous ambulatory peritoneal dialysis indicated that spironolactone increased ejection volume compared to</p>		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>placebo but did not increase serum potassium levels. This result indicates that spironolactone could be used in CHF patients on continuous ambulatory peritoneal dialysis²⁵.</p> <p>A phase II RCT in patients (n=392) with HF and reduced ejection fraction associated with mild or moderate chronic kidney disease (CKD) found that unlicensed oral BAY 94-8862 was as effective as spironolactone in decreasing biomarkers of haemodynamic stress, but it was associated with lower incidences of hyperkalaemia and worsening renal function²⁶.</p> <p>Chagas cardiomyopathy A Cochrane systematic review to assess the benefits and harms of current pharmacological interventions for treating HF in patients with</p>		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>Chagas cardiomyopathy identified 2 studies both comparing carvedilol against placebo. However, carvedilol did not affect all-cause mortality²⁷.</p> <p>COPD A head to head trial which compared bisoprolol to carvedilol in patients (n=63) with CHF (NYHA class II) and moderate to severe COPD found that whilst betablockers frequently caused adverse events in this population bisoprolol induced demonstrably more improvement in pulmonary function and caused fewer adverse events²⁸.</p> <p>Low Testosterone A 12 week RCT of a programme of exercise, with and without intramuscular testosterone supplementation, in male patients (n=41) with CHF and</p>		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	low testosterone indicates that this approach is both feasible and improves peak oxygen uptake, depression scores, leg strength and several aspects of QoL compared to placebo ²⁹ .		
Q16 What is the evidence of benefit of lifestyle advice and other therapies (homeopathy, reflexology, hydrotherapy, crystal therapy and acupuncture) in terms of morbidity, mortality, and quality of life?			
None identified.	<p>Three RCTs were identified:</p> <ul style="list-style-type: none"> •Reflexology; A RCT indicated that reflexology has no immediate haemodynamic effect in patients with CHF (n=12) compared to control²¹⁶. •Balneotherapy: A RCT investigating balneotherapy (hot baths 10min daily for 2 weeks) in patients with CHF (n=32, NYHA class II or III) found that this procedure improved clinical symptoms (both cardiac and inflammatory) compared to control²¹⁷. •Vaccination: A RCT that investigated double dose versus standard dose 	No GDG feedback was provided by the GDG questionnaire.	<p>No impact on guideline recommendations.</p> <p>This topic was not within the scope of the partial update of CG108 (2010). No recommendations were made regarding reflexology or balneotherapy. The new evidence found indicates reflexology is ineffective and there is only limited evidence for balneotherapy from a small short term study. At present it is unlikely that the guideline would need updating with regards to these areas.</p> <p>CG108 recommends that patients with heart failure should be offered an annual vaccination against influenza. The new evidence supports this</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	influenza vaccination in patients with HF (n=28) found that there were no differences in titres in any of the virus types between treatment groups ²¹⁸ .		recommendation.
Q17 What is the evidence for recommending rehabilitation and/or a period of exercise training for patients with chronic HF?			
<p>Physical fitness and exercise A RCT of patients with HF (n=69) indicated that preferred training (PT; patients' own choice of exercise) offered continued benefits over other programmes (usual care and usual care plus either home training or supervised training in a rehab centre) in terms of maintained or increased exercise capacity measured by workload at the respiratory compensation point³¹.</p> <p>A second RCT in patients with HF and preserved left ventricular ejection fraction (HFPEF) (n=53) reported that exercise training increased peak exercise $\dot{V}O_2$, power output and exercise time</p>	<p>Thirty three studies were identified (4 systematic reviews, 28 RCT, 1 post hoc analysis) that have compared exercise programmes with either active controls (other exercise interventions) or controls (usual care or no exercise) in a range of CHF populations. Pooling of these studies is difficult due to the range of interventions, including; supervised, interval, inspiratory muscle training, cycling, Tai chi, Pilates, Nordic walking, aerobic, duration and comparators. In addition there are numerous outcomes reported ranging from QoL, exercise capacity to hospitalisation admissions and</p>	<p>No GDG feedback was provided by the GDG questionnaire.</p>	<p>Potential impact on guideline recommendations.</p> <p>The guideline currently recommends offering a supervised group exercise-based rehabilitation programme designed for patients with heart failure which includes a psychological and educational component in the programme. The guideline also states that the programme may be incorporated within an existing cardiac rehabilitation programme</p> <p>The updated secondary prevention of MI (CG172) and public health guidance PH52 make numerous recommendations for those that require exercise rehabilitation. As the population of CG108 is specifically</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
<p>compared with the control group³². However there were no associated overall improvements in health-related quality of life (HRQoL).</p> <p>An RCT in patients (n=100) with systolic HF and reduced left ventricular ejection fraction (LVSD) 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 compared to control³³. However improvements were seen in HRQoL, exercise self-efficacy and mood.</p> <p>Functional electrical stimulation 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 CHF³⁴. FES was less effective than conventional exercise for gain in peak exercise</p>	<p>mortality.</p> <p>An update of a Cochrane systematic review which determined the effectiveness of exercise-based rehabilitation on the mortality, hospitalisation admissions, morbidity and health-related quality of life for people with HF included 33 trials (14 new trials) in people with HF predominantly with HFREF and NYHA classes II and III was identified³⁵. Overall compared with no exercise control, exercise-based rehabilitation did not increase or decrease the risk of all-cause mortality in the short term (up to 12-months' follow-up) but did reduce the risk of hospital admissions and confers important improvements in health-related QoL.</p> <p>A systematic review which included 7 studies indicated that</p>		<p>excluded from CG172 it may be worth reconsidering the exercise recommendations to align them with other guidance. In addition there is new evidence that numerous approaches to exercise are beneficial, not just supervised exercise as considered and recommended in the original guidance. For those who are unable to actively exercise there is a growing evidence base that functional electrical stimulation benefits patient outcomes.</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
<p>capacity and no different in terms of muscle strength or 6-minute walk test. However compared with no intervention, FES led to a not significant increase in peak VO_2.</p>	<p>inspiratory muscle training (IMT) in patients with HF increased the distance walked in the six-minute walk test and maximal static inspiratory pressure compared to control groups³⁶. However, IMT provides a significant improvement in peak oxygen consumption only in the studies that performed IMT for 12 weeks against no inspiratory load in patients with inspiratory muscle weakness. A second systematic review and meta-analysis which included 11 studies found IMT in patients with CHF improves cardio-respiratory fitness and QoL to a similar magnitude to conventional exercise training³⁷. In addition 3 RCTs on IMT were identified:</p> <ul style="list-style-type: none"> • A RCT of patients with CHF (n=43) found combined aerobic/IMT was more effective than a 12-week aerobic training programme³⁸. 		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<ul style="list-style-type: none"> • A RCT in patients with CHF (n=22) found that a 4-week high-IMT improved both strength and endurance compared to sham IMT³⁹. • A RCT in patients (n=27, NYHA II/III and LVEF 29 + 7%) indicated that a 12 week combined aerobic training and resistance training with IMT resulted in incremental benefits in both peripheral and respiratory muscle weakness, cardiopulmonary function and QoL compared to that of aerobic training only⁴⁰. <p>Five RCTs looked at 'supervised' exercise programmes</p> <ul style="list-style-type: none"> • A RCT in patients with CHF (n=66) indicated that a 16 weeks of supervised exercise training improves heart rate variability in older patients with HF compared to attention-control⁴¹. 		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<ul style="list-style-type: none"> • A RCT in patients with HFPEF (n=64) suggested that structured exercise training improves maximal exercise capacity, left ventricular diastolic function and QoL compared to usual care ⁴². • A RCT of patients with CHF (n= 123) indicated that twice weekly 10-year exercise training maintains functional capacity of more than 60% of maximum VO₂ and confers a sustained improvement in QoL compared with a non-trained group who did not exercise formally ⁴³. • A post hoc analysis of the HF-ACTION RCT on stable outpatients with LVEF and HF randomised to either supervised exercise training plus usual care or to usual care alone indicated that there was no interaction between etiology and treatment for the primary outcome, 		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>cardiovascular mortality or hospitalisation⁴⁴. It was concluded that consideration of inclusion of HF patients in an exercise training program should be made independent of the cause of HF or the severity of the symptoms.</p> <ul style="list-style-type: none"> • A RCT in patients (n=107) with symptomatic heart failure and LVEF determined that 24 weeks of exercise training did not improve exercise capacity, QoL or carer strain and was not cost saving to the National Health Service compared to usual care⁴⁵. <p>Seven RCTs investigated interval training:</p> <ul style="list-style-type: none"> • A RCT indicated that interval cycle training combined with strength training (3 times weekly training sessions for 3 months) induces a greater beneficial effect on vascular reactivity rather than interval 		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>exercise training alone in CHF patients (n=28 LVEF <37%)⁴⁶.</p> <ul style="list-style-type: none"> • A RCT of patients with CHF (n=100, NYHA classes II-IV, ejection fraction < 50%) found that high intensity, interval exercise over 12 weeks improves QoL compared to no exercise advice⁴⁷. • A RCT in patients (n=26) with CHF indicated that an 8-week, high-intensity interval training was more effective than continuous training aerobic exercise in improving indices of sub-maximal exercise capacity⁴⁸. • A RCT in CHF patients (n=18) which compared high-intensity interval exercise (HIIE) to an isocaloric moderate-intensity continuous exercise found that that a single session of HIIE improves autonomic profile of CHF patients, leading to significant reductions of HR and 		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>arrhythmic events in a 24-h post-training period⁴⁹.</p> <ul style="list-style-type: none"> • A RCT in patients with post-infarction CHF under optimal medical treatment (n=20) found that aerobic continuous training and aerobic interval training provided the same level of benefit to this group of patients⁵⁰. • A RCT in patients with signs of CHF and ejection fraction <45%, (n=17) found that 6 months of exercise using continuous aerobic cycling exercise training or low-volume high-intensity interval training were equally effective⁵¹. • A RCT in patients with CHF (n=23) found no difference in functional improvements by either 16 weeks of continuous or intermittent exercise training⁵². <p>Four RCTs investigated aerobic</p>		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>training:</p> <ul style="list-style-type: none"> • A RCT in patients with CHF (n=30) found that light-to-moderate- aerobic exercise training (AET) for 3 months lead to a near normalisation of peak VO₂ compared to controls⁵³. • A RCT in patients with HF (n=27) found that machine-assisted cycling was equivalent in improving exercise capacity as conventional exercise training⁵⁴. • A RCT of patients with CHF and sleep apnoea (n=50) found that home based 3 month exercise programmes (aerobic training and aerobic with strength training) were equally effective and improved exercise related outcomes compared to an untrained control population⁵⁵. • A RCT of patients with CHF (n=50) found that a 3 month 		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>aerobic exercise programme did not improve cardiac output and related parameters during exercise compared to the control group⁵⁶.</p> <p>Two RCTs in patients with left ventricular assist device (LVAD) were identified: 1 RCT in patients with a left ventricular assist device (LVAD) (n=14) found no difference in exercise improvement between 8 weeks of exercise training with a progressive mobilisation program and mobilisation alone⁵⁷. However a second RCT of patients (n=15) with a LVAD or biventricular assist device indicated that moderate-intensity aerobic exercise using a bike or treadmill for 45min, three to five times a week improved peak oxygen consumption, VO₂ at ventilatory threshold, 6-min walk test distance and QoL⁵⁸.</p>		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>In addition the following 7 RCTs and 1 systematic review investigating the efficacy of Nordic walking, high intensity, Tai chi, cycling and endurance training were found;</p> <ul style="list-style-type: none"> • A RCT in patients with (n=54) with moderate to severe HF found Nordic walking was superior to standard cardiac rehabilitation care in improving functional capacity⁵⁹. • A RCT in patients with HF (n=50) found that high-intensity training for 2 months resulted in marked improvements in exercise capacity compared to control⁶⁰. • A systematic review which included 9 trials (3 trials in CHF) found that the existing evidence suggests that Tai chi exercise is a good option for heart patients with very limited 		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>exercise tolerance and can be an adjunct to rehabilitation programs for patients with cardiac disease or CHF⁶¹.</p> <ul style="list-style-type: none"> • A RCT in patients with HFPEF (n=16) found that 12 weeks Tai chi and aerobic exercise both improved QoL and exercise capacity³³. • A RCT (n=30) indicated that eccentric cycle training protocol personalised by the rate of perceived exertion induces functional improvement similar to conventional training with lower demand on the cardiovascular system during exercise⁶². • A RCT in patients with CHF (n=61, NYHAI-III) found that both neuromuscular electrical stimulation of leg muscles or exercise training group with 12 weeks of cycling improved arterial stiffness⁶³. • A RCT in elderly HFPEF 		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>patients (n=63) found that 16 weeks of endurance exercise training improved peak VO₂ without altering endothelial function or arterial stiffness compared to attention control⁶⁴.</p> <ul style="list-style-type: none"> • A RCT of patients with HF (n=16 NYHA class I-II) indicated that a 16 week Pilates intervention was more effective than conventional cardiac rehabilitation program in increasing peak VO₂⁶⁵. <p>Functional electrical stimulation (FES) A systematic review and meta-analysis of FES for CHF found that active cycling or other aerobic/resistance activity is more effective in patients able to exercise than FES^{37,66}. However in patients with HF unable to actively exercise FES is the preferred modality. The RCT indicated that a 6 week</p>		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	FES of peripheral muscles improves exercise capacity, QoL, emotional status and endothelial function in patients with HF and HFPEF (n=30, NYAH class II or III) compared with placebo group ⁶⁷ .		
Q18 Should patients with HF be given advice on nutrition to improve morbidity and mortality?			
None identified.	<p>Two RCTs indicated that nutritional advice benefitted patients with CHF and 1 RCT indicated that micronutrient supplement was not advantageous in patients with CHF.</p> <ul style="list-style-type: none"> • A RCT (n=46) evaluated usual care with medical and nursing staff against additional nutritional guidance about diet plus usual care and found that this educational intervention was effective in modifying nutritional knowledge and the quality of the diet of the patients⁶⁸. • A RCT indicated that a 12 month intervention of a 	No GDG feedback was provided by the GDG questionnaire.	<p>Potential impact on the guideline recommendations.</p> <p>This section of the guidance has not been updated since 2003. The evidence base for diet and nutrition for patients with heart HF was noted as been limited in the 2003 and there was no reference made to education relating to nutrition. Hence no specific recommendations were made in this area.</p> <p>However in the 2010 update as detailed earlier (question 6) 'education' is now recommended as part of an exercise programme. What education this refers to is unclear.</p> <p>The new evidence indicates that</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>multiple micronutrient supplement had no effect compared to placebo on LVEF in patients with CHF (n=74)⁶⁹.</p> <ul style="list-style-type: none"> • A RCT of patients with stable CHF (n=97, NYHA class II-IV, on optimal medication, with previous signs of fluid retention) compared individualised salt and fluid restriction or information given by the nurse-led heart failure clinics compared to control⁷⁰. After 12 weeks, significantly more patients in the intervention than in the control group improved on the composite endpoint with improved NYHA class and leg oedema. No negative effects were seen on thirst, appetite, or QoL. 		<p>education around nutritional factors specific to the patients' conditions may improve clinical outcomes.</p>
<p>Q19 What is the best sequence for pharmacological therapy, and how should it be initiated? This question in CG5 covered all (pharmacological treatments).</p>			
<p>Fatty acid oxidation inhibition</p>	<p>Fatty acid oxidation inhibition A meta-analysis of the effects of</p>	<p>Clinical feedback highlighted the PARADIGM HF study</p>	<p>Potential impact on the guideline recommendations.</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
<p>Trimetazidine A meta-analysis of 17 RCTs which examined the use of trimetazidine reported significantly improved LVEF, NYHA classification and exercise duration, and reduce left ventricular end-systolic volume following treatment⁷¹. The data also suggest a beneficial effect on all-cause mortality, cardiovascular events and hospitalisation.</p> <p>Ivabradine The SHIFT RCT of patients with HF (n=6558) 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 placebo⁷². Despite the relatively young study population, the data suggests a potential role for ivabradine as an adjunct to beta-blockers in HF management.</p> <p>Statins</p>	<p>trimetazidine in patients (n=994) with CHF which included 19 RCTs found an improvement in LVEF and NYHA class, a decrease in left ventricular end-systolic and diastolic volumes and hospitalisation for cardiac causes. However, there were no differences in exercise duration and all-cause mortality from placebo⁷⁹.</p> <p>Ivabradine (Drug covered by TA267) Eight reports and 1 cost effectiveness analyses from the SHIFT study where identified⁸⁰⁻⁸⁸. This trial formed the basis of TA267, (Ivabradine for treating chronic heart failure) and as such these studies support current guideline recommendations. In addition one RCT of patients (n=121) with HF (not specified) indicated that ivabradine alone or in</p>	<p>which is an RCT which investigating LCZ696 in comparison to enalapril in patients (n=8442) with class II -IV heart failure and an ejection fraction < 40%¹³¹. The results indicate that LCZ696 was superior to enalapril in reducing the risks of death and of hospitalisation for heart failure.</p> <p>Clinical feedback also indicated that there was a body of growing evidence that the use of aspirin for patients with ischaemic heart disease and HF may be associated with worse outcomes and mitigate against the benefits of ACEi.</p> <p>Similarly GDG Feedback suggested that that there had been specific trials investigating the use of</p>	<p>Trimetazidine As trimetazidine, was not licensed in the UK at time of EU it was considered that there were no implications of the data for NICE CG108 in 2011. Trimetazidine is now licensed and is indicated for adults as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled by or intolerant to first-line anti-anginal therapies. This agent may now potentially be considered as a therapy for inclusion in CG108.</p> <p>Ivabradine Ivabradine was not currently licensed in the UK for HF when the EU was published in 2011. However, since then NICE TA267 has published. A number of studies supporting TA267 were identified through this surveillance review. TA267 currently recommends ivabradine as an option for treating CHF for people with NYHA</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
<p>Three meta-analyses were identified that have looked at the use of statins in HF patients⁷³⁻⁷⁵. All 3 studies are based predominantly on trials of atorvastatin involving small numbers of patients, with considerable heterogeneity between trials. The results indicate some beneficial effects; the shortcomings of the studies resulted in the Evidence Update concluding that the new evidence adds little to the case for statins in HF.</p> <p>n-3 polyunsaturated fatty acids (n-3 PUFA) In a sub-study of the GISSI-HF study the effects of (n-3 PUFA and rosuvastatin on left ventricular (LV) function were investigated⁷⁶. No significant effects were observed for rosuvastatin, but n-3 PUFA increased LVEF compared to placebo.</p>	<p>combination with carvedilol is more effective than carvedilol alone at improving exercise tolerance and quality of life in HF patients⁸⁹. This supports the current recommendations within TA267.</p> <p>A RCT in patients (n=61) with Heart failure with preserved ejection fraction (HFPEF) found that 7 day treatment with ivabradine increased exercise capacity, with a contribution from improved left ventricular filling pressure response to exercise as reflected by the ratio of peak early diastolic mitral flow velocity to peak early diastolic mitral annular velocity⁹⁰.</p> <p>Statins Two post-hoc sub-group analyses from the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA)</p>	<p>statins and that it may be useful to address their continued use for patients who have developed HF as there is no evidence of benefit.</p>	<p>class II - IV with systolic dysfunction in sinus rhythm (heart rate >75 bpm), LVEF (<35%) with ivabradine given in combination with standard therapy including BB therapy, ACEi and aldosterone antagonists.</p> <p>One RCT indicated that ivabradine may be effective for patients with HFPEF. Currently ivabradine is not recommended for this group. However, this is a small study and it may be premature to recommend this form of treatment based on this study and outcomes alone.</p> <p>Statins Statins were considered to be outside the scope of the 2010 partial update, however due to evidence the GDG felt that the recommendations within CG5 should be deleted. The guideline then stated that for statins, the reader should refer to the guideline on lipid modification CG67 (recently replaced by CG181) and the Technology Appraisal 94 (recently replaced by</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
<p>Complementary and alternative medicine</p> <p>Two systematic reviews have evaluated two different Chinese herbal medicines (Huangqi – an extract of <i>Radix astragali</i>; and Shengmai – components include <i>Panax ginseng</i>, <i>Ophiopogon japonicas</i> and <i>Schisandra chinensis</i>) as complementary therapies in people with HF^{77,78}. 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.</p>	<p>which randomised patients with ischaemic systolic HF to rosuvastatin or placebo were identified. One indicates that for patients with galectin-3 values <19ng/mL may benefit from rosuvastatin treatment⁹¹. However, the data from this post hoc analysis should be interpreted with caution since the overall results of the CORONA study did not show a significant effect on the primary endpoint. The second analysis indicated that if including repeat events rosuvastatin reduces the risk of heart failure hospitalisations⁹².</p> <p>A RCT in patients with non-ischemic systolic HF (n=26, LVEF<35%) found that 3 month treatment with atorvastatin did not affect muscle sympathetic nerve activity compared to placebo⁹³.</p>		<p>CG181) Statins for the prevention of cardiovascular events.</p> <p>From an assessment of the abstracts identified through this surveillance review it is difficult to ascertain how the evidence based impacts on the use of statins in patients with CHF as it is not clear if the patients have coronary artery disease (CAD) and the results from both the meta-analysis and RCTs are variable. In light of the GDG feedback indicating that the continuing use of statins in patients may have limited benefit it may now be worthwhile to update this area.</p> <p>n-3 PUFA</p> <p>There is evidence that n-3 PUFA may be beneficial for patients with CHF. However the GDG did discuss the GISSI-HF trial at that time of the 2010 guideline update but did not make recommendations as the area was considered to be outside the scope of the partial update. The evidence from</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>A meta-analysis of 15 studies for the long-term clinical outcomes of additional statin use in CHF indicated that statins persistently decreased all-cause mortality and the incidence of rehospitalisation for HF in patients with CHF, and the benefits might be partially associated with use of a specific statin, atorvastatin⁹⁴.</p> <p>A systematic review and meta-analysis which utilised data from 13 RCTs indicates that statin treatment does not reduce the risk of all-cause death, death for cardiovascular cause or pump failure and rehospitalisation for HF. When restricted to various statins and patients' age, the analysis demonstrated that atorvastatin was associated with reduced all-cause mortality and readmission rate for heart failure, and the superiority of statin therapy was significant in</p>		<p>the GISSI-HF trial and its subsequent post-hoc analyses may now wish to be considered in an update of CG108 as the results of these studies indicate that these agents may be beneficial for patients with HF.</p> <p>Angiotensin receptor neprilysin inhibitor</p> <p>LCZ696 is a new agent that potentially will be scheduled in the Technology Appraisals work programme in January. CONFIDENTIAL INFORMATION</p> <p>Diuretics</p> <p>The guideline currently recommends the routine use of diuretics for the relief of congestive symptoms and fluid retention in patients with HF and for those with HFPEF should usually be treated with a low to medium dose of loop diuretics. The new evidence supports these recommendations.</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>patients with CHF less than 65 yrs of age⁹⁵.</p> <p>n-3 polyunsaturated acids A post-hoc analysis of GISSI-HF trial an RCT with patients (n=6975) with chronic HF found no evidence that treatment with n-3 polyunsaturated acids (PUFAs) reduced the incidence of atrial fibrillation compared to placebo⁹⁶.</p> <p>A meta-analysis of 7 trials indicates that fish oil supplementation decreases anti-inflammatory markers in patients with CHF⁹⁷.</p> <p>Angiotensin receptor neprilysin inhibitor A 12 week phase II RCT evaluating the new agent LCZ696 against valsartan in patients (n=301) with HFPEF (NYHA class II-III heart failure) and NT-proBNP greater than</p>		<p>New evidence relating to the direct renin inhibitor aliskiren does not impact the guideline recommendations. The new evidence on the use of vasopressin receptor 2 antagonists is still at an early stage and as such does not impact guideline recommendations.</p> <p>Inotropic treatment- The guideline currently has recommendations that date back to 2003 for the use of these agents. The recommendations state that intravenous inotropic agents (such as dobutamine, milrinone or enoximone) should only be considered for the short-term treatment of acute decompensation of chronic heart failure.</p> <p>Levosimendan was reviewed in 2003 but was not recommended as at that time it did not have a license in the UK. This agent is now licensed and evidence indicates that it may provide</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>400pg/mL indicated that LCZ696 was more effective at lowering NT-proBNP⁹⁸.</p> <p>Diuretics An update of a Cochrane systematic review to assess the harms and benefits of diuretics for patients with CHF did not identify any new studies for inclusion. The available data from several small trials show that in patients with CHF, conventional diuretics appear to reduce the risk of death and worsening heart failure compared to placebo. Compared to active control, diuretics appear to improve exercise capacity⁹⁹.</p> <p>A systematic review (9 studies included) found data that supported the idea that flexible and individualised diuretic dosing is potentially associated with reduced emergency room</p>		<p>some benefit to patients with CHF. However the evidence base is still limited in terms of mid-long term outcomes so it may be better to evaluate this drug again during the next surveillance review of this guideline.</p> <p>Calcium channel blockers New evidence on the use of amlodipine in addition to conventional therapy indicates that it does not impact on mortality. This is line with the evidence found in 2003. As such it is unlikely that the new evidence will impact on the recommendation to consider amlodipine for the treatment of comorbid hypertension and/or angina in patients with HF.</p> <p>Selective phosphodiesterase-5 inhibitor Evidence indicates that sildenafil can be safely added to standard HF therapy and may be beneficial for the subgroup who have exercise oscillatory breathing.</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>visits, reduced rehospitalisation, and improved QoL in CHF patients with reduced ejection fraction¹⁰⁰.</p> <p>Loop Diuretics Two RCTs compared the therapeutic effects of azosemide, a long-acting loop diuretic with a short-acting one. The first study indicated that azosemide was more effective in improving neurohumoral factors in outpatients (n=98) with CHF receiving an ACEi¹⁰¹ and the second longer term study indicated that azosemide reduced the risk of cardiovascular death or unplanned admission to hospital for patients (n=320) with CHF^{102,103}.</p> <p>Direct renin inhibitors (hypertension) A post hoc analysis of a 12 week RCT in patients (n=302)</p>		<p>Digoxin No new evidence on the use of digoxin that would impact guideline recommendations was identified.</p> <p>A number of agents were found to have some efficacy in patients with CHF: testosterone, L-citrulline, Flavanol-rich chocolate, and Interleukin-1 (IL-1) receptor antagonist. However, the majority of these studies were placebo comparisons and were small. Hence, as these RCTs are likely to not be adequately powered to assess the risk of these treatments in this high-risk population with regard to quality of life, clinical events, and safety, further evidence is required before they would impact guidance.</p> <p>The following agents were not effective in patients with CHF and hence do not impact current guidance: ascorbic acid, creatine, colchicine and opioids.</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>with stable NYHA class II-IV HF, BNP concentration >100pg/mL, and treated with an ACEi or ARB and BB randomised to aliskiren or placebo in patients who received (aldosterone antagonist + n=101) and did not receive (aldosterone antagonist -) was identified. Aliskiren did not affect any of the outcomes measured compared to placebo (BNP, N-terminal proBNP, plasma renin activity, and urinary aldosterone¹⁰⁴).</p> <p>Vasopressin receptor 2 antagonists A 7 day phase III RCT evaluated the efficacy and safety of tolvaptan, in treating HF patients (n=110) with volume overload despite the use of conventional diuretics. Compared with placebo, tolvaptan administered for 7 days significantly reduced body weight and improved symptoms</p>		<p>Antithrombotic therapy CG108 currently recommends the use of aspirin (75–150 mg once daily) for patients with the combination of heart failure and atherosclerotic arterial disease (including coronary heart disease). The new evidence found gives contradictory results based on which trials were selected for the meta-analysis. However overall the data supports current recommendations.</p> <p>Complementary and alternative medicine The Evidence Update indicated that the results of the included review should be interpreted with caution due to the high risk of bias of the included studies (particularly regarding allocation concealment and blinding), the small sample size of these studies, and the significant heterogeneity in outcomes such as ejection function, cardiac output and stroke volume. There was no evidence available concerning the effect of Shengmai on</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>associated with volume overload¹⁰⁵. These results were mirrored by a 7 day phase II RCT which utilised tolvaptan as an add-on therapy in treating HF patients with volume overload on stable doses of furosemide (n=117)¹⁰⁶. A third RCT compared tolvaptan to furosemide and the combination of tolvaptan and furosemide to placebo in patients (n=83) with HF and systolic dysfunction. All active treatments resulted in decreases in bodyweight with tolvaptan monotherapy resulting in the largest increase in urine volume¹⁰⁷.</p> <p>A phase II 8 week trial in outpatients (n=170) with HF and volume overload showed that daily lixivaptan, (not licensed in UK) when added to standard therapy, reduced body weight compared to placebo¹⁰⁸.</p>		<p>mortality, and more high quality studies with long-term follow-up are warranted. This would still be the case for the later review identified in 2014.</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>Inotropic treatment- Calcium sensitisers A meta-analysis of 6 trials on the intermittent levosimendan intravenous administration in patients (n=326) with CHF indicated that there was an improvement in mid-term survival associated with levosimendan but BNP values, ejection fraction and number of patients with NYHA >III status were not different to control¹⁰⁹.</p> <p>A RCT in patients (n=33) with CHF which evaluated monthly infusions of levosimendan indicated that levosimendan improved systolic and diastolic function, ventricular volumes, severity of mitral regurgitation, and BNP levels compared to furosemide¹¹⁰.</p> <p>Calcium Channel blockers A RCT which combined results with a previous study in patients</p>		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>(n=1654) with severe HF due to a nonischemic cardiomyopathy (ejection fraction <30%) indicated that the addition of amlodipine to conventional therapy did not impact mortality. The authors concluded amlodipine does not exert favourable effects on the clinical course of patients with HF, regardless of the presence or absence of underlying coronary artery disease¹¹.</p> <p>Selective phosphodiesterase-5 inhibitor A 12 week RCT in patients (n=106) with left systolic heart failure indicated that sildenafil did not decrease blood pressure and was well tolerated compared to placebo¹¹². A second RCT in stable outpatients with HFPEF (n=216) found that sildenafil for 24 weeks, compared with placebo, did not result in significant</p>		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>improvement in exercise capacity or clinical status¹¹³. However in patients with HF and exercise oscillatory breathing (n=32) sildenafil therapy for 12 months, as an adjuvant to normal therapy, improved functional capacity (peak VO₂, exercise ventilation efficiency, pulmonary capillary wedge pressure, mean pulmonary artery pressure, pulmonary vascular resistance) and modulation of exercise oscillatory breathing compared to placebo¹¹⁴.</p> <p>Digoxin An update Cochrane systematic review which examined the effectiveness of digitalis glycosides in treating HF in patients with normal sinus rhythm found no new evidence with there been no difference in mortality between treatment and control groups, but digitalis</p>		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>therapy is associated with lower rates of both hospitalisation and clinical deterioration¹¹⁵.</p> <p>Two sub group post hoc analyses from the Digitalis Investigation Group (DIG) trial were identified. The first indicated that in older patients with chronic diastolic heart failure, digoxin increased the risk of 30-day all-cause hospital admission, but not during longer follow-up¹¹⁶. Whereas the second indicated that in high risk sub groups (chronic HF patients with NYHA class III-IV, LVEF <25%, or CTR >55%) digoxin reduced the risk of the 2-year composite endpoint of HF mortality or HF hospitalisation compared to placebo¹¹⁷.</p> <p>Testosterone A meta-analysis which included 4 trials indicates that</p>		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>testosterone therapy was associated with a significant improvement in exercise capacity compared with placebo in male patients with stable CHF¹¹⁸.</p> <p>L-citrulline A RCT in outpatients with systolic HF (n=35) indicated that L-citrulline supplementation increases LVEF compared to placebo¹¹⁹</p> <p>Creatine A RCT in male patients with functional class II to IV HF (n=33) found that 6 months of creatine supplementation did not improve functional capacity compared to placebo¹²⁰.</p> <p>Colchicine A 6-month course of anti-inflammatory treatment with colchicine in patients with stable CHF (n=267) did not affect</p>		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>patient functional status (NYHA class and objective treadmill exercise tolerance) or the likelihood of death or hospital stay compared to placebo¹²¹.</p> <p>Antithrombotic therapy A Cochrane systematic review which assessed anticoagulation versus placebo for HF in sinus rhythm only identified 2 RCTs (that were classed as up to date with modern practice). The WASH 2004 and HELAS 2006, found no differences in the incidence of myocardial infarction, non-fatal stroke and death between patients taking oral anticoagulation and those taking placebo. The review concluded that the available data does not support the routine use of anticoagulation in HF patients who remain in sinus rhythm¹²².</p> <p>Whereas, an updated meta-</p>		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>analysis on antithrombotic therapy (aspirin, antiplatelet agents, or anticoagulants) in patients with HF and sinus rhythm included trials suggesting that warfarin compared with aspirin reduces stroke risk but there is no mortality benefit¹²³. The study also indicated that aspirin use did not increase HF hospitalisation as has been previously suggested.</p> <p>Flavanol-rich chocolate A RCT in patients (n=20) with CHF found that commercially available flavanol-rich chocolate improved vascular function (flow-mediated vasodilatation) compared to cocoa-liquor-free control chocolate¹²⁴.</p> <p>Ascorbic Acid A 3 day trial in patients with CHF (n=11) found no effect of ascorbic acid with regards to</p>		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>reversing the increased sympathetic activity as measured by microneurography and plasma norepinephrine levels¹²⁵.</p> <p>Opioids A RCT in patients (n=39) with CHF (NYHA class III-IV) on standard medical therapy found no benefit over placebo for the relief of breathlessness with short-term low-dose oral morphine, or oral oxycodone¹²⁶.</p> <p>Interleukin-1 (IL-1) receptor antagonist A small RCT of 12 patients with HFPEF indicated that interleukin-1 blockade with anakinra for 14 days increased aerobic exercise and reduced the systemic inflammatory response compared to placebo¹²⁷.</p>		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>Complementary and alternative medicine An update of a Cochrane systematic review which had found 4 new trials (14 in total) was identified¹²⁸. Eleven trials compared Shengmai (a selection of herbs) plus usual treatment with usual treatment alone, and 3 trials compared Shengmai with placebo. Improvement of NYHA class was more common in patients taking Shengmai plus usual treatment than in those receiving usual treatment alone. Beneficial effects of Shengmai in treating HF were also observed in other outcomes, including exercise test, ejection fraction and cardiac output. The 3 RCTs comparing Shengmai with placebo reported improvement in NYHA class and in stroke volume.</p> <p>Unlicensed medications</p>		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>A systematic review (17 RCTs included) to assess the effectiveness and safety of meglumine adenosine cyclophosphate for the treatment of CHF found insufficient evidence due to study quality to determine the effectiveness of this agent¹²⁹.</p> <p>A RCT indicated that alagebrium did not improve exercise tolerance in patients with HF and systolic dysfunction¹³⁰.</p>		
<p>Q20 What is the efficacy and safety of ACEi in people with heart failure and preserved left ventricular ejection fraction?</p> <p>R1 What is the effectiveness of angiotensin-converting enzyme (ACE) inhibitors and betablockers (given either alone or in combination) compared with placebo in patients with heart failure and preserved left ventricular ejection fraction?</p>			
None identified.	A 6 month RCT in patients (n=200) with functional class (FC) I-II, HFPEF with hypertensive disease indicated that both metoprolol succinate or quinapril improved	No GDG feedback was provided by the GDG questionnaire.	<p>No impact on guideline recommendations</p> <p>Currently treatment with BB or ACEi in people with HFPEF is not recommended due to a lack of</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>parameters of LV diastolic function, but only quinapril effectively changed LV structural geometric parameters and systolic function. Only treatment with quinapril was associated with improvement of renin-angiotensin system, elevation of tolerance to physical effort, and increased $VO_2 \max$²¹⁹.</p> <p>A RCT with a median follow up of 3.2yrs of 245 patients (n=245) with HFPHF indicated that patients treated with carvedilol did not have an improved prognosis compared to non-carvedilol treatment²²⁰.</p>		<p>evidence within this population. The new evidence provides a heterogeneous profile of effectiveness for BB in this population and provides a limited evidence base for effectiveness on some outcomes for ACEi. As such the new evidence base is unlikely to be sufficient at present to enable recommends to be made.</p>
<p>Q21 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?</p> <p>R4 What is the comparative effectiveness of aldosterone antagonists and angiotensin II receptor antagonists (ARBs) in symptomatic patients with heart failure due to left ventricular systolic dysfunction who are: A. on optimal therapy with a beta-blocker and an ACE Inhibitor, or B. on a beta-blocker but are intolerant of ACE inhibitors?</p>			
Two papers were identified that	A systematic review and meta-	Clinical feedback highlighted	Potential impact on guideline

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
<p>examined the effect of aldosterone antagonists in patients with milder HF.</p> <p>A RCT of patients (NYHA class I–II; LVEF ≤ 40% n=168) which compared the effect of spironolactone with placebo on LV remodelling was identified¹³². Spironolactone treatment increased LVEF, LV end-diastolic and end-systolic volumes and myocardial mass all decreased, and LV diastolic filling pattern also improved compared to placebo.</p> <p>A RCT (EMPHASIS-HF) which utilised an alternative aldosterone antagonist, eplerenone in patients with mild HF (n=2737, NYHA class II; LVEF ≤ 35%) found that a death from cardiovascular causes or hospitalisation for HF were reduced in patients receiving eplerenone compared to placebo¹³³.</p> <p>Hyperkalaemia can be a potential</p>	<p>analysis which identified 8 trials indicated that additional use of a aldosterone antagonist in patients with mild to moderate CHF (NYHA class I-II) reduced all-cause mortality and re-hospitalisation for cardiac causes, and improved cardiac function while simultaneously ameliorating LV reverse remodelling¹³⁴.</p> <p>Three post-hoc analysis of the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure), a study which found that eplerenone significantly reduced major cardiovascular events versus placebo in 2737 patients with mild symptoms of HF (LVEF <35%), in addition to recommended therapy was identified. The first analysis indicates that eplerenone provides substantial benefit on major events in this population</p>	<p>the EMPHASIS study: an RCT which investigated the use of eplerenone and indicated that this impacted on the guideline recommendations in that first line treatment for CHF should include BB, ACEi and aldosterone antagonist in patients with systolic heart failure and mild symptoms (NYHA class II). It was indicated that this would change the treatment algorithm as currently aldosterone antagonists are only recommended for post myocardial infarction or NYHA class III. The EMPHASIS study was also identified by the 4 year search.</p> <p>In addition the TOPCAT trial was also highlighted by the GDG. This RCT indicated that spironolactone reduced</p>	<p>recommendations.</p> <p>NICE CG108 recommends second-line treatment with aldosterone antagonists in patients with NYHA class III-IV or those who have had an acute myocardial infarction and who have symptoms and/or signs of HF and left ventricular systolic dysfunction, with treatment been initiated within 3-14 days of the MI, preferably after ACEi therapy. (This recommendation is from MI: secondary prevention NICE clinical guideline 48.)</p> <p>The Evidence Update noted that the data on spironolactone is from a small study with relatively short follow-up and the fact that the remodelling data go against findings in a larger RCT mean that the results may need to be interpreted cautiously.</p> <p>The EMPHASIS-HF trial was stopped early due to pre-specified rules (which may have resulted in overestimation of</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
<p>problem associated with aldosterone antagonist use. A RCT which examined whether inhibiting potassium absorption in the gut via a binding polymer (RLY5016) could prevent a rise in serum potassium in people with HF (n=105) with a history of hyperkalaemia with AA use was identified¹⁰⁴. RLY5016 led to a lower incidence of hyperkalaemia and a greater tolerance of aldosterone antagonist s than placebo.</p>	<p>even if patients are already receiving high doses of standard background therapies¹³⁵. A second analysis indicates that eplerenone reduced the incidence of new onset atrial fibrillation or flutter¹³⁶. A third post-hoc sub group analysis in patients at high risk of hyperkalaemia and worsening renal function (including an eGFR >30 ml/min/1.73 m (2) and potassium <5.0 mmol/l,) indicates that eplerenone was both efficacious and safe when carefully monitored¹³⁷.</p> <p>Two post-hoc analysis of the Randomised Aldactone Evaluation Study (RALES), a RCT in patients NYHA class III-IV HF and LVEF) randomised to spironolactone or placebo were identified. The first analysis indicates that races influences the safety and efficacy of</p>	<p>heart failure admissions in HFPEF (n=3445). However, spironolactone did not significantly reduce the incidence of the primary composite outcome of death from cardiovascular causes, aborted cardiac arrest, or hospitalisation for the management of HF.</p> <p>Feedback from the Acute heart failure guidance team indicated that wished the two guidelines to be aligned with regards to drug treatment (particularly aldosterone antagonists).</p>	<p>effects). The results suggest that eplerenone may be of benefit for patients with HF of all severities and LV systolic dysfunction. The results support NICE guidance that an aldosterone antagonist should be considered in patients who are symptomatic despite optimal treatment with an ACEi and a BB licensed for HF. The Evidence Update indicated, as does clinical feedback and evidence from the 4 year surveillance review, that there is new evidence which impacts on NICE guidance and should be considered as a possible area for update.</p> <p>Due to the small sample size and short follow-up of the study on RLY5016, the evidence is currently unlikely to affect NICE CG108, but shows some potential benefits of anti-hyperkalaemics.</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>spironolactone in severe HF, with African Americans with HF exhibiting less hyperkalaemia and more hypokalaemia with spironolactone compared with non- African Americans and seemed they derived less clinical benefit¹³⁸. The second analysis indicates that the absolute benefit of spironolactone was greatest in patients with reduced eGFR¹³⁹.</p> <p>A RCT in patients (n=150) with or without metabolic syndrome HF (Class II NYHA, LVEF <45%) on optimal therapy found that canrenone (not licensed in UK) protects deterioration of myocardial mechano-energetic efficiency, improves diastolic dysfunction and maximises the decrease in BNP compared to placebo¹⁴⁰.</p> <p>A RCT in patients (n=44) with HFPEF treated for 6 months</p>		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>with either eplerenone or placebo found no improvement in exercise capacity. However, eplerenone was associated with a reduction in serum markers of collagen turnover and improvement in diastolic function ¹⁴¹.</p> <p>The Aldo-DHF 12 month trial of ambulatory patients (n=422) with CHF (NYHA class II-III, HFPEF) indicated that spironolactone improved left ventricular diastolic function but did not affect maximal exercise capacity, patient symptoms, or QoL compare to placebo ¹⁴².</p>		
<p>Q22 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?</p>			
None identified.	A 56 month long RCT (the I-PRESERVE trial) in patients with symptomatic HFPEF (n=3605) found that irbesartan did not substantially improve QoL scores during a long period	No GDG feedback was provided by the GDG questionnaire.	<p>No impact on guideline recommendations.</p> <p>ARBs are currently not recommended for the treatment of HFPEF. The new evidence supports current guidance</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>of follow-up compared to placebo²²¹.</p> <p>A post hoc analysis in Chinese adults (n = 545) with symptomatic heart failure (NYHA II-IV) and intolerant ACEi demonstrated at 4.8year follow-up that high dose losartan was more effective than low dose losartan in reducing the risk of all cause death or hospitalisation²²².</p>		<p>recommendations. In addition the guideline states that an ARB licensed for HF can be considered as an alternative to an ACEi for patients with heart failure due to left ventricular systolic dysfunction who have intolerable side effects with ACEi. The post hoc analysis identified through the 4 year surveillance review supports the use of ARBs in patients who have side effects to ACEi.</p>
<p>Q23 What is the efficacy and safety of:</p> <p>a) angiotensin-II receptor antagonists (ARBs) plus an Angiotensin Converting Enzyme Inhibitor (ACEI) in comparison to ACEI plus placebo</p> <p>b) ARB + ACEI + BB vs placebo + ACEI + BB</p> <p>in the medical management of adults with HF?</p>			
None identified.	<p>ARBs</p> <p>A Cochrane systematic review which identified 22 studies comparing ARBs with ACEIs or placebo found that ARBs did not reduce total mortality or total morbidity as measured by total hospitalisations compared with</p>	No GDG feedback was provided by the GDG questionnaire	<p>No impact on guideline recommendations.</p> <p>This area of guidance was updated in 2010. New evidence is in line with that stated in the guideline which resulted in the recommendation to consider an ARB licensed for HF as</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>placebo or ACEi²²³. Adding an ARB in combination with an ACEI does not reduce total mortality or total hospital admission but increases withdrawals due to adverse effects compared with ACEI alone.</p> <p>A RCT in patients (n=514) with stable symptomatic NYHA II-IV HF and any LVEF were randomised to candesartan as adjunctive to standard therapy (ACEi/BB) did not reduce circulating BNP more than standard therapy (primary endpoint), but it significantly improved LV function and produced a marked decrease in aldosterone levels at study end²²⁴. A second smaller 24 week RCT which also evaluated the add-on effect of candesartan to ACEi in patients (n=35) with CHF (NYHA class III-IV) found no difference in</p>		<p>an alternative to an ACE inhibitor for patients with HF due to left ventricular systolic dysfunction who have intolerable side effects with ACE inhibitors. Or to consider adding either an aldosterone antagonist or an ARB if a patient remains symptomatic despite optimal therapy with an ACEi and a BB.</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>aerobic capacity but an increase in exercise time and right atrial pressure and pulmonary capillary wedge pressure at rest²²⁵.</p> <p>ACEi A head-to-head 6 year RCT of the effect of ramipril and zofenopril (not licensed in the UK) on patients with CHF (n=224) indicates that ramipril and zofenopril are equivalent with regard to cardiovascular mortality²²⁶.</p>		
<p>Q24 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?</p>			
<p>In work stemming from the SHIFT trial the effect of resting heart rate on a primary composite endpoint of cardiovascular death or hospital admission for worsening HF was examined²²⁷. Patients in the placebo group with the highest heart rates were at more than twice the risk of a primary endpoint event</p>	<p>A sub-group analysis of outcomes in patients (n=125) with reduced right ventricular ejection fraction in the Beta-Blocker Evaluation of Survival Trial (BEST): a RCT in patients (n=2708) with CHF and LVEF< 35%, receiving standard background therapy (ARB,</p>	<p>No GDG feedback was provided by the GDG questionnaire.</p>	<p>No impact on guideline recommendations.</p> <p>CG108 currently recommends that both ACEi and BB licensed for HF are offered to all patients with HF due to left ventricular systolic dysfunction and clinical judgement be used to when decide which drug to start first. With</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
<p>than those with the lowest heart rates. In the ivabradine group, after 28 days on treatment, patients with heart rates < 60 bpm had fewest primary endpoint events. 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.</p>	<p>digoxin, and diuretics) receiving either bucindolol or placebo was identified²²⁸. In the sub-group a RVEF < 20% had no intrinsic association with mortality. However, in those receiving additional therapy with bucindolol, RVEF < 20% had a significant independent association with increased risk of mortality. A second post-hoc analysis of the Beta-Blocker Evaluation of Survival Trial (BEST) indicated that bucindolol reduced HF hospitalisation in systolic HF patients regardless of baseline systolic blood pressure but reduced mortality only in those with systolic blood pressure > 120 mm Hg²²⁹.</p> <p>A post-hoc analysis of the HF-ACTION trial of 2,331 ambulatory HF patients with systolic dysfunction (NYHA class II - IV, LEVF <35%) randomised to exercise training</p>		<p>regards to BBs these are introduced in a "start low, go slow" manner, and assess heart rate, blood pressure, and clinical status after each titration.</p> <p>The new evidence identified by the Evidence Update on heart rate as a risk factor was stated as an impact on CG108 due to the effectiveness of ivabradine. This agent has since been recommended in TA267.</p> <p>The new evidence identified at the 4 year surveillance point supports current guideline recommendations for the use of BBs in patients with CHF.</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>versus usual care, with median follow-up of 2.5 years was identified. The report indicated that there was an inverse relationship between BB dose and the endpoint of all-cause death or all-cause hospitalisation²³⁰.</p> <p>A 24 month head to head trial of nebivolol versus carvedilol in hypertensive patients (n=160) with CHF, (LVEF <40%, NYHA class I –III) found both drugs to be equally effective in increasing LVEF and 6 minute walk test or decreasing heart rate and NYHA functional class²³¹.</p> <p>A post hoc analysis of the CIBIS III trial was identified²³². Patients with stable CHF (n=1010) were randomised to up-titration of monotherapy with either bisoprolol or enalapril for 6 months, followed by their</p>		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	combination for 6-24 months. The analysis indicated that the order of drug administration plays an important role in whether CHF patients reach target doses of bisoprolol and enalapril and the dose level reached is associated with baseline characteristics and adverse events.		
Q25 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?			
None identified.	None stated.	No GDG feedback was provided by the GDG questionnaire	None identified.
Q26 What drugs are to be avoided in patients with HF?			
None identified.	A multivariate analysis based on a RCT in patients (n=1376) with atrial fibrillation and HF indicates that aldosterone antagonists are associated with an increased incidence of cardiovascular deaths ²⁴ .	No GDG feedback was provided by the GDG questionnaire.	Potential impact on guideline recommendations. Aldosterone antagonists are currently recommended for patients with CHF as a second line therapy. The identified analysis indicates that for those patients with atrial fibrillation other options may need to be considered. There are currently no guideline

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
			recommendations specifically about aldosterone antagonist use in patients with CHF and atrial fibrillation.
Q27 Does a fully informed patient impact on concordance with treatment and outcome?			
None identified.	None stated.	No GDG feedback was provided by the GDG questionnaire.	None identified.
Q28 What invasive procedures have a role in the treatment of HF including heart transplantation?			
<p>Cardiac resynchronisation therapy (CRT) Whether CRT should be used in patients with less severe HF has been investigated in 3 studies:</p> <ul style="list-style-type: none"> • A RCT of patients (n=1798) demonstrated a reduction in 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 alone¹⁴³. However, there was an increased number of subsequent device-related complications in patients 	<p>CRT and ICD Ten studies that were used as part of the evidence base for the recommendations within TA314 were identified ¹⁴⁸⁻¹⁵⁷. In addition 8 RCTs that referred to methodological aspects of CRT were identified (lead placement ¹⁵⁸⁻¹⁶², sensor type ¹⁶³, pacer position ¹⁶⁴ pacer type ^{165,166} and diaphragmatic stimulation ¹⁶⁷.</p> <p>Additionally 2 RCTs which evaluated the effect of CRT in patients with NYHA class III or IV with HF, a LVEF<35%, a QRS duration <130ms (or</p>	No GDG feedback was provided by the GDG questionnaire.	<p>Potential impact on guideline recommendations.</p> <p>CRT and ICDs The evidence identified by the Evidence Update in 2011 was stated as potentially impacting on TA120 'Cardiac resynchronisation therapy for the treatment of heart failure' as it indicated that CRT could potentially be used in patients with cardiac dysfunction but mild symptoms (the NYHA class II subgroup saw a significant reduction alone). This TA has since been reviewed and updated in June 2014 to TA314.</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
<p>randomised to CRT. Subgroup analysis indicated that 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).</p> <ul style="list-style-type: none"> • A meta-analysis of 25 trials found that in patients with NYHA class I and II symptoms, CRT reduced all-cause mortality and HF hospitalisations¹⁴⁴. • A further meta-analysis of 12 studies investigated the benefit of CRT on mortality in 2 comparisons: CRT vs medical therapy (split into more and less symptomatic groups) and CRT plus ICD vs ICD alone¹⁴⁵. Compared with optimal medical therapy alone, CRT plus optimal medical therapy significantly reduced mortality. Compared with an ICD alone, CRT plus ICD significantly reduced mortality which remained 	<p><120ms), and echocardiographic evidence of left ventricular dyssynchrony with CRT implant either on or off were identified^{168,169}. The RCTs were stopped early as CRT did not reduce clinical outcomes or left ventricular remodelling and was associated with potential harm as CRT in this sub group may increase mortality.</p> <p>Furthermore, a RCT in patients with left ventricular assist device implantation found that inhaled nitric oxide did not improve right ventricular dysfunction compared to placebo¹⁷⁰.</p> <p>Respiratory devices A RCT patients with HF (n=72) found that a device-guided slow breathing had no impact on symptoms of CHF compared to placebo¹⁷¹.</p>		<p>Additionally the evidence relating to CRT and ICDs has been reviewed and is now included within TA314.</p> <p>Cell transplantation Skeletal myoblast transplantation Evidence in this area is still at a preliminary stage and is unlikely to affect current guidance or practice.</p> <p>BMNC There is a growing evidence base related to the use of BMNC to treat IHD. Currently this area is not covered by recommendations within the guidance and no clinical feedback relating to the use of this treatment was provided.</p> <p>Respiratory devices No evidence that would impact on respiratory devices was identified.</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
<p>significant among patients with NYHA class I or II but not those with class III or IV.</p> <p>Implantable cardioverter-defibrillators (ICDs) A meta-analysis of 7 trials looked at the effect of CRT with and without ICD on all-cause mortality. The study found evidence that CRT plus ICD significantly reduces all-cause mortality¹⁴⁶.</p> <p>Cell transplantation Skeletal myoblast transplantation In an early-phase RCT of patients with HF (n=40) intramyocardial injection of skeletal muscle cells into the scarred areas of the heart was feasible in patients with HF and some symptomatic improvement was observed¹⁴⁷.</p>	<p>Cell transplantation A Cochrane systematic review which included 23 RCTs found that autologous bone marrow-derived mononuclear cell (BMNC) treatment reduced the incidence of mortality and rehospitalisation due to HF in the long term (>12 months) but not in the short term (< 12 months) in people with chronic ischaemic heart disease (IHD) and HF¹⁷². The treatment was also associated with a reduction in left ventricular end systolic volume (LVESV), stroke volume index, and an improvement LVEF, all at long-term follow-up. Overall, a reduction in functional class during short and long term follow-up was found.</p> <p>A second systematic review and meta-analysis of intramyocardial autologous cell engraftment in patients with ischaemic HF identified 5 studies (n=210</p>		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>patients) and found that this treatment did not improve LVEF but did increase 6-min walk distance and lowered the incidence of NYHA functional class deterioration¹⁷³. However, the novel procedure did not result in a significant reduction in all-cause mortality.</p> <p>A RCT of cardiopoietic stem cell therapy (autologous bone marrow-derived and cardiogenically oriented mesenchymal stem cell) by endomyocardial injections in patients with HF of ischemic origin reported improved LVEF and the 6-min walk distance¹⁷⁴.</p> <p>A RCT of intracoronary injection autologous BMNCs injection in patients (n=234) with Chagas cardiomyopathy, NYHA class II to IV, LVEF <35% did not find any difference in left ventricular function or QoL following</p>		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>intervention compared to placebo¹⁷⁵.</p> <p>A RCT in patients (n=153) with chronic ischemic heart failure indicated that transendocardial injection of autologous BMCs compared with placebo did not improve left ventricular end-systolic volume, maximal oxygen consumption, or reversibility on single-photon emission tomography¹⁷⁶.</p> <p>A RCT in HF patients (n=23) with chronic post infarction cardiomyopathy, of image-guided, catheter-based intramyocardial injection myoblasts found no clinical benefits compared to placebo¹⁷⁷.</p> <p>A RCT indicated that injections in 10 left ventricular sites with an infusion catheter in patients with ischemic cardiomyopathy</p>		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	(n=65) and LVEF <50 % of either transendocardial mesenchymal stem cells (MSCs), BMNCs or placebo was feasible with MSCs and BMNCs improving QoL ¹⁷⁸ .		
Q29 Can domiciliary oxygen therapy be used to modify the outcome of HF in terms of quality of life, morbidity and mortality (including acute decompensation)?			
Q30 Can CPAP be used to modify the outcome of HF in terms of quality of life, morbidity and mortality (including obstructive sleep apnoea acute decompensation)?			
None identified.	<p>5 RCTs were identified that have looked at the benefits of CPAP or adaptive servo-ventilation (ASV) in patients with CHF.</p> <p>A RCT on patients (n=10) with stable congestive HF and central sleep apnoea with Cheyne-Stokes respiration (CSA-CSR) oxygen through nasal prongs and concentrator or 8 weeks adaptive servo-ventilation (ASV)¹⁷⁹. CSA-CSR was reduced to a greater extent by ASV than oxygen therapy</p>	No GDG feedback was provided by the GDG questionnaire.	<p>Potential impact.</p> <p>These areas were covered in CG5 (2003) and has not been updated since. At the time the GDG was unable to come to any recommendations on the use of domiciliary oxygen or CPAP therapy for patients with HF despite them improving patient outcomes.</p> <p>It is not possible based on the CG5 to determine the size of the evidence base previously but it was noted that the RCTs tended to be small with the 1 of the largest noted as having 66</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>over 8 weeks but was not accepted long term. Neither treatment improved prognostic indices of HF or symptoms in the short term.</p> <p>A RCT in patients (n=51) with severe CHF, despite optimal cardiac medication and/or LVEF <40% and Cheyne-Stokes breathing for >25% of sleeping time found that 3 months of ASV treatment improved LVEF and physical capacity compared to control¹⁸⁰.</p> <p>A RCT in patients (n=22) with CHF and CSR-CSA after CRT defibrillator (CRTD) implantation, found that ASV treatment over 6 months improved indices for apnea-hypopnea, central apnea, oxyhemoglobin saturation, BNP levels, cardiac systolic and diastolic function compared to control¹⁸¹. Additionally the</p>		<p>participants. As such it is likely that the evidence base was similar to that presented in the 4 year update. A full systematic review and pooling of the trials from the last 11 years may enable recommendations to now be made.</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>event-free rate was significantly higher in the ASV group than in the non-ASV group.</p> <p>A RCT which compared the efficacy of ASV and CPAP over a 12-month period in reducing breathing disturbances and improving cardiac parameters in patients with HF (n=70, NYHA classes II-III) and coexisting sleep-disordered breathing was identified¹⁸². Whilst both modes of therapy significantly improved respiratory disturbances, oxygen desaturations, and arousals over the study period, ASV reduced the central apnea hypopnea index and BNP levels more effectively as compared with CPAP.</p> <p>A RCT in patients (n=36) with HFPEF and sleep-disordered breathing randomised subjects to 6 months treatment with medications and ASV or medication only was identified¹⁸³. ASV therapy</p>		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	improved cardiac diastolic function and decreased cardio-ankle vascular index and BNP and increased the event-free rate.		
Rehabilitation in chronic heart failure			
Q31 Can monitoring of digoxin levels facilitate improved therapeutic care for individuals with HF (including acute decompensation)?			
None identified.	None identified.	No GDG feedback was provided by the GDG questionnaire.	None identified.
Q32 What is the efficacy and safety of patient telemonitoring in comparison to outpatient monitoring for adults with chronic heart failure?			
R2 What is the effectiveness and cost effectiveness of home telemonitoring, monitoring of serum natriuretic peptides and formal follow-up by a heart failure team for patients with heart failure due to left ventricular systolic dysfunction?			
Telemonitoring (TM) In a follow-up of the previously reported Randomised Trial of Phone Intervention in Chronic Heart Failure (DIAL study n=1518) at 1 year and 3 years death or admission to hospital for worsening HF was less likely in those receiving telephone intervention than in those receiving usual care ¹⁸⁴ .	TM Eight studies (2 systematic reviews, 1 sub group analysis and 5 RCTs) were identified that have addressed TM in CHF patients. A systematic review of TM and structured telephone support identified 30 RCTs and found that telemonitoring reduced all-cause mortality ¹⁸⁹ . Both TM and	The GDG highlighted the decision analysis modelling of cost-effectiveness study by Thokala <i>et al</i> 2013 as potentially impacting on the guidance ¹⁹⁹ . The study estimated the cost-effectiveness of various remote monitoring strategies versus usual care for adults recently discharged after a	Potential impact on guideline recommendations Given the difficulties of interpretation of the evidence (8 studies in 2010) with regard to cost-effectiveness and the impact of TM per se (such as increased access compared to TM) the GDG did not make specific recommendations for home telemonitoring but agreed that a research recommendation should be

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
<p>Three RCTs comparing TM to usual care were also identified:</p> <ul style="list-style-type: none"> • A RCT of patients (n=710, NYHA class II or III) indicated telemonitoring had no effect on mortality, cardiovascular death or HF hospitalisation¹⁸⁵. • A RCT in stable HF patients (n=390) found the intervention tended to increase rates of urgent care visits, but reduced the number of days in hospital¹⁸⁶. • A RCT found that a voice interactive system made no difference to all-cause mortality and all-cause hospital readmission compared to usual care patients (n=1653, 71% with an LVEF fraction < 40%) with an HF hospitalisation within the previous month¹⁸⁷. <p>Remote monitoring A RCT of patients (n=550, NYHA class III) found that information from an implanted wireless</p>	<p>structured telephone support reduced CHF-related hospitalisations and improved QoL, reduced costs, and were acceptable to patients. In addition, a second systematic review with 14 studies included suggests that TM resulted in significant improvement of HF self-care behaviours of daily weighing, medication management, exercise adherence, fluid and alcohol restriction, salt restriction, or stress reduction in the telehealth intervention group in 5 studies¹⁹⁰. However, 5 other studies found no difference between the intervention and control groups.</p> <ul style="list-style-type: none"> • A RCT which compared 6 months of intense follow-up facilitated by TM or usual care in CHF patients (n=160 LVEF <35%) was identified¹⁹¹. All-cause mortality was lower and 	<p>HF exacerbation in Acute hospitals in the UK. TM was the most cost-effective strategy in the scenario using these base case costs but there is considerable uncertainty in relation to clear descriptions of the interventions and robust estimation of costs.</p>	<p>made. Since then the evidence base has expanded with 2 systematic reviews indicating that overall this approach improves patients' outcomes. Some RCTs still indicate no difference in TM compared to usual care which may indicate different requirements by differing patient populations. As such it may now be appropriate to review this section of guidance and determine the cost effectiveness of this approach in UK settings.</p> <p>Remote monitoring Implantable wireless pulmonary artery haemodynamic monitoring systems are a novel technology. Overall 2 studies have been identified. Whilst this technology appears to reduce hospitalisations its impact on other clinical outcomes such as mortality and QoL would ideally be required.</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
<p>pulmonary artery haemodynamic monitoring system led to a reduction in the number of hospitalisations compared to standard care¹⁸⁸.</p>	<p>number of days lost to hospitalisation, death, or dialysis was significantly lower in the TM group compared with usual care.</p> <ul style="list-style-type: none"> • A RCT indicated that a telephone support intervention did not affect the Packer score (a clinical composite consisting of mortality, overnight hospitalisation for worsened HF and NYHA class global self-assessment) in patients with a general practice diagnosis of HF (n=405) compared to usual care¹⁹². However, the telephone support intervention reduced hospitalisation for any cause among a rural and remote cohort. • A RCT in patients (n=100) which compared mobile phone TM and control groups found that there was an improvement in QoL through improved self-care and clinical 		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>management from the intervention but there was no difference in BNP levels, self-care management, and LVEF between the groups¹⁹³.</p> <ul style="list-style-type: none"> • A RCT of patients recently hospitalised with HF (n=344, 57% had a (LVEF) <30%). found that daily electronic transmission of body weight to a HF did not impact on cardiac re-hospitalisation, all-cause hospitalisation, death from any cause or the composite endpoint of cardiac hospitalisation and death from any cause compared to control¹⁹⁴. • A RCT of TM versus usual care in patients with HF (n=382, mean LVEF <38%) found no difference in time to first heart failure-related hospitalisation, total hospitalisations, heart failure admission and all-cause mortality between the 		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<p>groups¹⁹⁵.</p> <ul style="list-style-type: none"> • A subgroup analyses for the TIME-HF trial, an RCT in stable chronic HF patients (n=710, NYHA class II or III with a history of HF decompensation within 2 years previously or a LVEF < 25%) randomly assigned to TM or usual care indicates that TM management may not be appropriate for all HF patients¹⁹⁶. <p>Remote monitoring A RCT involving patients with HF and ICDs (n=200) compared remote monitoring (internet-based remote interrogation systems) with standard patient management consisting of scheduled visits and patient response to audible ICD alerts¹⁹⁷. Remote monitoring reduced emergency department utilisation and other health care visits. However, there was no</p>		

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	difference in clinical outcomes between the intervention and control group. A cost-utility analysis of this study from the perspectives of the health care system and the patient showed that remote monitoring is a cost-effective and dominant solution ¹⁹⁸ .		
Referral and approach to care			
Q33 In what circumstances should a patient with an established diagnosis of HF be referred back to primary care, referred to secondary care, including hospitalisation, to ensure best possible treatment?			
None identified.	A RCT in clinically stable systolic HF outpatients (n=921, 89% NYHA class I-II) on optimal medical therapy comparing extended follow-up in specialised HF clinics with referral back to their GP was identified ²³³ . No difference was found between the 2 strategies as far as the composite endpoint of death or a cardiovascular admission, mortality, HF admission, QoL, number of days admitted, and number of admissions.	No GDG feedback was provided by the GDG questionnaire.	No impact on guideline recommendations. Currently the guideline recommends that only the following diagnosed patients should be referred to specialist multidisciplinary HF team for management: <ul style="list-style-type: none"> • severe HF (NYHA class IV) • HF that does not respond to treatment • HF that can no longer be managed effectively in the home setting

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
			<p>The guideline also recommends that patients with HF should generally be discharged from hospital only when their clinical condition is stable and the management plan is optimised. However the guideline also recommends that HF care should be delivered by a multidisciplinary team with an integrated approach across the healthcare community. As such the new evidence is unlikely to impact guideline recommendations.</p>
<p>Q34 Under what circumstances should the optimal treatment of HF patients involve the work of non-NHS agencies?</p>			
None identified.	None identified.	No GDG feedback was provided by the GDG questionnaire.	None identified.
<p>Q35 What support groups help patients and families to cope with HF?</p>			
None identified.	<p>A RCT of reciprocal peer support (RPS) for patients compared to nurse care management found that patients failed to engage with the RPS and the program did not improve outcomes compared with usual HF nurse care management²³⁴.</p>	No GDG feedback was provided by the GDG questionnaire.	<p>No impact on guideline recommendations.</p> <p>Although the guideline states that healthcare professionals should be aware of local cardiac support networks and provide this information to patients and carers (CG5: 2003), peer support groups are not seen as</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
			an alternative to HF nurse management or multi-disciplinary team management. Hence it is unlikely that the finding from the new evidence that RPS is not as effective as HF nurse management will impact on the guidance.
Q36 How should the initial management plan be determined?			
<p>Self-management A systematic review of 19 RCTs which compared the effect of self-management with standard care on mortality, all-cause hospital readmission, HF hospitalisation rate and HRQoL was identified²³⁵. 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.</p> <p>A RCT of patients with HF (n=317) comparing the effect of a moderately intensive nurse-led</p>	None identified.	No GDG feedback was provided by the GDG questionnaire.	<p>No impact on guideline recommendations.</p> <p>Due to the limitations cited in the systematic review of self-management it is unlikely to contribute substantially to current knowledge or affect recommendations within NICE CG108.</p> <p>In addition, it is not clear if the relatively resource-intensive self-management support provided in the RCT evaluating a nurse-led programme would offer a cost-effective management strategy in the wider population. The Evidence Update concluded that the evidence is unlikely to affect NICE CG108.</p>

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
<p>self-management programme with usual care found that despite significant improvements immediately after the programme in cognitive symptom management, self-care behaviour and cardiac-specific HRQoL, no sustained effects were seen for these outcomes at 6- and 12-month follow-up²³⁶.</p> <p>Case management A RCT of patients of HF in primary care (n=199) examined the effect of case management, by doctors' assistants, 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 only²³⁷.</p>			
Q37 What evidence is there that palliative care improves the care of patients with HF? When should a patient be referred to such care?			
None identified.	None identified.	No GDG feedback was provided by the GDG questionnaire.	None identified.
Q38 At what stage is it appropriate to consider end of life issues for HF patients?			
None identified.	None identified.	No GDG feedback was	None identified.

Conclusions from Evidence Update (2011)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014)	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
		provided by the GDG questionnaire.	
Research Recommendations			
R1 What is the effectiveness of angiotensin-converting enzyme (ACE) inhibitors and betablockers (given either alone or in combination) compared with placebo in patients with heart failure and preserved left ventricular ejection fraction?			
None identified.	See question 20.	See question 20.	See question 20.
R2 What is the effectiveness and cost effectiveness of home telemonitoring, monitoring of serum natriuretic peptides and formal follow-up by a heart failure team for patients with heart failure due to left ventricular systolic dysfunction?			
None identified.	See question 32.	See question 32.	See question 32.
R3 What is the optimal use of natriuretic peptides in the management and prognostic stratification of patients with heart failure?			
None identified.	None identified.	No GDG feedback was provided by the GDG questionnaire.	None identified.
R4 What is the comparative effectiveness of aldosterone antagonists and angiotensin II receptor antagonists (ARBs) in symptomatic patients with heart failure due to left ventricular systolic dysfunction who are: A. on optimal therapy with a beta-blocker and an ACE Inhibitor, or B. on a beta-blocker but are intolerant of ACE inhibitors?			
None identified.	See question 21.	See question 21.	See question 21.
R5 What is the comparative effectiveness of vasodilator therapy with nitrates and hydralazine in patients with heart failure and preserved ventricular ejection fraction?			
None identified.	None identified.	No GDG feedback was provided by the GDG questionnaire.	None identified.

References

1. Kommuri NV, Johnson ML, and Koelling TM. (2012) Relationship between improvements in heart failure patient disease specific knowledge and clinical events as part of a randomized controlled trial. SO: Patient Education and Counseling 86:233-238.
2. Shively MJ, Gardetto NJ, Kodiath MF et al. (2013) Effect of patient activation on self-management in patients with heart failure. Journal of Cardiovascular Nursing 28:20-34.
3. Veroff DR, Sullivan LA, Shoptaw EJ et al. (2012) Improving self-care for heart failure for seniors: the impact of video and written education and decision aids. SO: Population Health Management 15:37-45.
4. Baker DW, DeWalt DA, Schillinger D et al. (2011) The effect of progressive, reinforcing telephone education and counseling versus brief educational intervention on knowledge, self-care behaviors and heart failure symptoms. SO: Journal of Cardiac Failure 17:789-796.
5. Lofvenmark C, Karlsson MR, Edner M et al. (2011) A group-based multi-professional education programme for family members of patients with chronic heart failure: effects on knowledge and patients' health care utilization. Patient Education & Counseling 85:e162-e168.
6. DeWalt DA, Schillinger D, Ruo B et al. (2012) Multisite randomized trial of a single-session versus multisession literacy-sensitive self-care intervention for patients with heart failure. SO: Circulation 125:2854-2862.
7. Davis KK, Mintzer M, Dennison-Himmelfarb CR et al. (2012) Targeted intervention improves knowledge but not self-care or readmissions in heart failure patients with mild cognitive impairment. SO: European Journal of Heart Failure 14:1041-1049.
8. Kelder JC CMMT. (2011) Quantifying the added value of BNP in suspected heart failure in general practice: an individual patient data meta-analysis. Heart 97:959-963.

9. Fu S, Luo L, Ye P et al. (2013) The ability of NT-proBNP to detect chronic heart failure and predict all-cause mortality is higher in elderly Chinese coronary artery disease patients with chronic kidney disease. *Clinical Interventions In Aging* 8:409-417.
10. Gariani K, Delabays A, Perneger TV et al. (2011) Use of brain natriuretic peptide to detect previously unknown left ventricular dysfunction in patients with acute exacerbation of chronic obstructive pulmonary disease. *Swiss Medical Weekly* 141:w13298.
11. Ouanes I, Jalloul F, Ayed S et al. (2012) N-terminal proB-type natriuretic peptide levels aid the diagnosis of left ventricular dysfunction in patients with severe acute exacerbations of chronic obstructive pulmonary disease and renal dysfunction. *Respirology* 17:660-666.
12. Kelder JC et al . (9-12-2011) The diagnostic value of physical examination and additional testing in primary care patients with suspected heart failure. *Circulation* 124:2865.
13. Kotecha D, Ngo K, Walters JA et al. (2011) Erythropoietin as a treatment of anemia in heart failure: Systematic review of randomized trials. *American Heart Journal* 161:822-831.
14. Avni T, Leibovici L, and Gafer-Gvili A. (2012) Iron supplementation for the treatment of chronic heart failure and iron deficiency: systematic review and meta-analysis. [Review]. *European Journal of Heart Failure* 14:423-429.
15. Kapoor M, Schleinitz MD, Gemignani A et al. (1-3-2013) Outcomes of patients with chronic heart failure and iron deficiency treated with intravenous iron: a meta-analysis. [Review]. *Cardiovascular & Hematological Disorders - Drug Targets* 13:35-44.
16. Gutzwiller FS, Pfeil AM, Comin-Colet J et al. (9-10-2013) Determinants of quality of life of patients with heart failure and iron deficiency treated with ferric carboxymaltose: FAIR-HF sub-analysis. *International Journal of Cardiology* 168:3878-3883.
17. Gutzwiller FS, Schwenkglenks M, Blank PR et al. (2012) Health economic assessment of ferric carboxymaltose in patients with iron deficiency and chronic heart failure based on the FAIR-HF trial: an analysis for the UK. *European Journal of Heart Failure* 14:782-790.

18. Maurer MS, Teruya S, Chakraborty B et al. (2013) Treating anemia in older adults with heart failure with a preserved ejection fraction with epoetin alfa: single-blind randomized clinical trial of safety and efficacy. *SO: Circulation.Heart Failure* 6:254-263.
19. McCullough PA, Barnard D, Clare R et al. (2013) Anemia and associated clinical outcomes in patients with heart failure due to reduced left ventricular systolic function. *Clinical Cardiology* 36:611-620.
20. Swedberg K, Young JB, Anand IS et al. (2013) Treatment of anemia with darbepoetin alfa in systolic heart failure. *SO: New England journal of medicine* 368:1210-1219.
21. Cittadini A, Marra AM, Arcopinto M et al. (2013) Growth hormone replacement delays the progression of chronic heart failure combined with growth hormone deficiency: an extension of a randomized controlled single-blind study. *JACC Heart Failure* 1:325-330.
22. Doehner W, Todorovic J, Kennecke C et al. (29-11-2012) Improved insulin sensitivity by the angiotensin receptor antagonist irbesartan in patients with systolic heart failure: a randomized double-blinded placebo-controlled study. *International Journal of Cardiology* 161:137-142.
23. Ogino K, Kinugasa Y, Kato M et al. (15-2-2014) Spironolactone, not furosemide, improved insulin resistance in patients with chronic heart failure. *International Journal of Cardiology* 171:398-403.
24. O'Meara E, Khairy P, Blanchet MC et al. (2012) Mineralocorticoid receptor antagonists and cardiovascular mortality in patients with atrial fibrillation and left ventricular dysfunction: insights from the Atrial Fibrillation and Congestive Heart Failure Trial. *SO: Circulation.Heart failure* 5:586-593.
25. Taheri S, Mortazavi M, Pourmoghadas A et al. (2012) A prospective double-blind randomized placebo-controlled clinical trial to evaluate the safety and efficacy of spironolactone in patients with advanced congestive heart failure on continuous ambulatory peritoneal dialysis. *Saudi Journal of Kidney Diseases & Transplantation* 23:507-512.
26. Pitt B, Kober L, Ponikowski P et al. (2013) Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: a randomized, double-blind trial. *European Heart Journal* 34:2453-2463.

27. Hidalgo R, Martí-Carvajal AJ, Kwong-Joey SW et al. (2012) Pharmacological interventions for treating heart failure in patients with Chagas cardiomyopathy. SO: Cochrane Database of Systematic Reviews .
28. Lainscak M, Podbregar M, Kovacic D et al. (2011) Differences between bisoprolol and carvedilol in patients with chronic heart failure and chronic obstructive pulmonary disease: a randomized trial. *Respiratory Medicine* 105 Suppl 1:S44-S49.
29. Stout M, Tew GA, Doll H et al. (2012) Testosterone therapy during exercise rehabilitation in male patients with chronic heart failure who have low testosterone status: a double-blind randomized controlled feasibility study. *American Heart Journal* 164:893-901.
30. Anker SD CCJFGea. (2009) Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 36:2436-2448.
31. Beckers PJ, Denollet J, Possemiers NM et al. (2010) Maintaining physical fitness of patients with chronic heart failure: a randomized controlled trial. *European Journal of Cardiovascular Prevention & Rehabilitation* 17:660-667.
32. Kitzman DW, Brubaker PH, Morgan TM et al. (1-11-2010) Exercise training in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. *Circulation: Heart Failure* 3:659-667.
33. Yeh GY, McCarthy EP, Wayne PM et al. (25-4-2011) Tai chi exercise in patients with chronic heart failure: a randomized clinical trial. *Archives of Internal Medicine* 171:750-757.
34. Sbruzzi G, Ribeiro RA, Schaan BD et al. (2010) Functional electrical stimulation in the treatment of patients with chronic heart failure: A meta-analysis of randomized controlled trials. *European Journal of Cardiovascular Prevention and Rehabilitation* 17:254-260.
35. Taylor RS, Sagar VA, Davies EJ et al. (2014) Exercise-based rehabilitation for heart failure. SO: Cochrane Database of Systematic Reviews .
36. Plentz RD, Sbruzzi G, Ribeiro RA et al. (2012) Inspiratory muscle training in patients with heart failure: meta-analysis of randomized trials. [Review]. *Arquivos Brasileiros de Cardiologia* 99:762-771.

37. Smart NA, Giallauria F, and Dieberg G. (20-8-2013) Efficacy of inspiratory muscle training in chronic heart failure patients: a systematic review and meta-analysis. [Review]. *International Journal of Cardiology* 167:1502-1507.
38. Adamopoulos S, Schmid J-P, Dendale P et al. (2014) Combined aerobic/inspiratory muscle training vs. aerobic training in patients with chronic heart failure: The Vent-HeFT trial: A European prospective multicentre randomized trial. *European Journal of Heart Failure* 16:574-582.
39. Marco E, Ramirez-Sarmiento AL, Coloma A et al. (2013) High-intensity vs. sham inspiratory muscle training in patients with chronic heart failure: a prospective randomized trial. *European Journal of Heart Failure* 15:892-901.
40. Laoutaris ID, Adamopoulos S, Manginas A et al. (1-9-2013) Benefits of combined aerobic/resistance/inspiratory training in patients with chronic heart failure. A complete exercise model? A prospective randomised study. *International Journal of Cardiology* 167:1967-1972.
41. Murad K, Brubaker PH, Fitzgerald DM et al. (2012) Exercise training improves heart rate variability in older patients with heart failure: a randomized, controlled, single-blinded trial. *SO: Congestive heart failure* 18:192-197.
42. Edelmann F, Gelbrich G, Düngen HD et al. (2011) Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study. *SO: Journal of the American College of Cardiology* 58:1780-1791.
43. Belardinelli R, Georgiou D, Cianci G et al. (16-10-2012) 10-year exercise training in chronic heart failure: a randomized controlled trial. *Journal of the American College of Cardiology* 60:1521-1528.
44. Whellan DJ, Nigam A, Arnold M et al. (2011) Benefit of exercise therapy for systolic heart failure in relation to disease severity and etiology-findings from the Heart Failure and A Controlled Trial Investigating Outcomes of Exercise Training study. *SO: American Heart Journal* 162:1003-1010.
45. Witham MD, Fulton RL, Greig CA et al. (2012) Efficacy and cost of an exercise program for functionally impaired older patients with heart failure: a randomized controlled trial. *SO: Circulation.Heart failure* 5:209-216.

46. Anagnostakou V, Chatzimichail K, Dimopoulos S et al. (2011) Effects of interval cycle training with or without strength training on vascular reactivity in heart failure patients. *Journal of Cardiac Failure* 17:585-591.
47. Chrysohoou C, Tsitsinakis G, Vogiatzis I et al. (2014) High intensity, interval exercise improves quality of life of patients with chronic heart failure: a randomized controlled trial. *Qjm* 107:25-32.
48. Freyssin C, Verkindt C, Prieur F et al. (2012) Cardiac rehabilitation in chronic heart failure: effect of an 8-week, high-intensity interval training versus continuous training. *Archives of Physical Medicine & Rehabilitation* 93:1359-1364.
49. Guiraud T, Labrunee M, Gaucher-Cazalis K et al. (2013) High-intensity interval exercise improves vagal tone and decreases arrhythmias in chronic heart failure. *Medicine & Science in Sports & Exercise* 45:1861-1867.
50. Iellamo F, Manzi V, Caminiti G et al. (10-9-2013) Matched dose interval and continuous exercise training induce similar cardiorespiratory and metabolic adaptations in patients with heart failure. *International Journal of Cardiology* 167:2561-2565.
51. Koufaki P, Mercer TH, George KP et al. (2014) Low-volume high-intensity interval training vs continuous aerobic cycling in patients with chronic heart failure: a pragmatic randomised clinical trial of feasibility and effectiveness. *Journal of Rehabilitation Medicine* 46:348-356.
52. Smart NA and Steele M. (2012) A comparison of 16 weeks of continuous vs intermittent exercise training in chronic heart failure patients. *Congestive Heart Failure* 18:205-211.
53. Mezzani A, Grassi B, Jones AM et al. (1-9-2013) Speeding of pulmonary VO₂ on-kinetics by light-to-moderate-intensity aerobic exercise training in chronic heart failure: clinical and pathophysiological correlates. *International Journal of Cardiology* 167:2189-2195.
54. Ozasa N, Morimoto T, Bao B et al. (2012) Effects of machine-assisted cycling on exercise capacity and endothelial function in elderly patients with heart failure. *SO: Circulation Journal* 76:1889-1894.
55. Servantes DM, Pelcerman A, Salvetti XM et al. (2012) Effects of home-based exercise training for patients with chronic heart failure and sleep apnoea: a randomized comparison of two different programmes. *Clinical Rehabilitation* 26:45-57.

56. Shen YQ, Jiang JF, Wang LM et al. (2011) [The effects of aerobic exercise on cardiac output during exercise in patients with chronic heart failure]. SO: Zhonghua xin xue guan bing za zhi 39:700-705.
57. Hayes K, Leet AS, Bradley SJ et al. (2012) Effects of exercise training on exercise capacity and quality of life in patients with a left ventricular assist device: a preliminary randomized controlled trial. SO: Journal of Heart and Lung Transplantation 31:729-734.
58. Laoutaris ID, Dritsas A, Adamopoulos S et al. (2011) Benefits of physical training on exercise capacity, inspiratory muscle function, and quality of life in patients with ventricular assist devices long-term postimplantation. SO: European Journal of Cardiovascular Prevention and Rehabilitation 18:33-40.
59. Keast ML, Slovinec-D'Angelo ME, Nelson CR et al. (2013) Randomized trial of Nordic walking in patients with moderate to severe heart failure. SO: Canadian journal of cardiology 29:1470-1476.
60. Myers J, Gademan M, Brunner K et al. (2012) Effects of high-intensity training on indices of ventilatory efficiency in chronic heart failure. Journal of Cardiopulmonary Rehabilitation & Prevention 32:9-16.
61. Ng SM, Wang CW, Ho RT et al. (2012) Tai chi exercise for patients with heart disease: a systematic review of controlled clinical trials. [Alternative Therapies in Health & Medicine 18:16-22.
62. Besson D, Joussain C, Gremeaux V et al. (2013) Eccentric training in chronic heart failure: feasibility and functional effects. Results of a comparative study. Annals of Physical & Rehabilitation Medicine 56:30-40.
63. ák P, Tomandl J, Spinarova L et al. (2012) Effects of neuromuscular electrical stimulation and aerobic exercise training on arterial stiffness and autonomic functions in patients with chronic heart failure. SO: Artificial organs 36:920-930.
64. Kitzman DW, Brubaker PH, Herrington DM et al. (2013) Effect of endurance exercise training on endothelial function and arterial stiffness in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. SO: Journal of the American College of Cardiology 62:584-592.

65. Guimarães GV, Carvalho VO, Bocchi EA et al. (2012) Pilates in heart failure patients: a randomized controlled pilot trial. *SO: Cardiovascular Therapeutics* 30:351-356.
66. Smart NA, Dieberg G, and Giallauria F. (15-7-2013) Functional electrical stimulation for chronic heart failure: a meta-analysis. [Review]. *International Journal of Cardiology* 167:80-86.
67. Karavidas A, Driva M, Parissis JT et al. (2013) Functional electrical stimulation of peripheral muscles improves endothelial function and clinical and emotional status in heart failure patients with preserved left ventricular ejection fraction. *American Heart Journal* 166:760-767.
68. Donner AF, Correa SG, Brunetto S et al. (2012) Nutritional orientation, knowledge and quality of diet in heart failure: randomized clinical trial. *SO: Nutrición Hospitalaria* 27:441-448.
69. McKeag NA, McKinley MC, Harbinson MT et al. (2014) The effect of multiple micronutrient supplementation on left ventricular ejection fraction in patients with chronic stable heart failure: A randomized, placebo-controlled trial. *JACC: Heart Failure* 2:308-317.
70. Philipson H, Ekman I, Forslund HB et al. (2013) Salt and fluid restriction is effective in patients with chronic heart failure. *European Journal of Heart Failure* 15:1304-1310.
71. Gao D, Ning N, Niu X et al. (2011) Trimetazidine: a meta-analysis of randomised controlled trials in heart failure. [Review]. *Heart* 97:278-286.
72. Swedberg K, Komajda M, Bohm M et al. (11-9-2010) Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. [E *Lancet* 376:875-885.
73. Xu M, Yuan G, and Wei F. (2010) Effect of atorvastatin in patients with chronic heart failure - Insights from randomized clinical trials. *Archives of Medical Science* 6:866-873.
74. Zhang L, Zhang S, Jiang H et al. (2011) Effects of statin treatment on cardiac function in patients with chronic heart failure: a meta-analysis of randomized controlled trials. *Clinical Cardiology* 34:117-123.

75. Zhang L, Zhang S, Jiang H et al. (2010) Effects of statin therapy on inflammatory markers in chronic heart failure: a meta-analysis of randomized controlled trials. *Archives of Medical Research* 41:464-471.
76. Ghio S, Scelsi L, Latini R et al. (2010) Effects of n-3 polyunsaturated fatty acids and of rosuvastatin on left ventricular function in chronic heart failure: a substudy of GISSI-HF trial. *European Journal of Heart Failure* 12:1345-1353.
77. Fu S, Zhang J, Menniti-Ippolito F et al. (2011) Huangqi injection (a traditional chinese patent medicine) for chronic heart failure: A systematic review. *PLoS ONE* 6.
78. Zheng H, Chen Y, Chen J et al. (2011) Shengmai (a traditional Chinese herbal medicine) for heart failure. *Shengmai for heart failure. Cochrane Database of Systematic Reviews*: 10.1002./14651858.CD005052.
79. Zhou X and Chen J. (2014) Is treatment with trimetazidine beneficial in patients with chronic heart failure? *PLoS ONE [Electronic Resource]* 9:e94660.
80. Bohm M, Borer J, Ford I et al. (2013) Heart rate at baseline influences the effect of ivabradine on cardiovascular outcomes in chronic heart failure: analysis from the SHIFT study. *Clinical Research in Cardiology* 102:11-22.
81. Borer JS, Bohm M, Ford I et al. (2012) Effect of ivabradine on recurrent hospitalization for worsening heart failure in patients with chronic systolic heart failure: the SHIFT Study. *European Heart Journal* 33:2813-2820.
82. Borer JS, Bohm M, Ford I et al. (1-2-2014) Efficacy and safety of ivabradine in patients with severe chronic systolic heart failure (from the SHIFT study). *American Journal of Cardiology* 113:497-503.
83. Komajda M, Bohm M, Borer J et al. (2013) Influence of background treatment with mineralocorticoid receptor antagonists on ivabradine's effects in patients with chronic heart failure. *European Journal of Heart Failure* 15:79-84.
84. Swedberg K, Komajda M, Bohm M et al. (29-5-2012) Effects on outcomes of heart rate reduction by ivabradine in patients with congestive heart failure: is there an influence of beta-blocker dose?: findings from the SHIFT (Systolic Heart failure treatment with the I(f) inhibitor ivabradine Trial) study. *Journal of the American College of Cardiology* 59:1938-1945.

85. Tardif J-C, Omeara E, Komajda M et al. (2011) Effects of selective heart rate reduction with ivabradine on left ventricular remodelling and function: Results from the SHIFT echocardiography substudy. *European Heart Journal* 32:2507-2515.
86. Tavazzi L, Swedberg K, Komajda M et al. (10-12-2013) Clinical profiles and outcomes in patients with chronic heart failure and chronic obstructive pulmonary disease: an efficacy and safety analysis of SHIFT study. *International Journal of Cardiology* 170:182-188.
87. Tavazzi L, Swedberg K, Komajda M et al. (2013) Efficacy and safety of ivabradine in chronic heart failure across the age spectrum: insights from the SHIFT study. *European Journal of Heart Failure* 15:1296-1303.
88. Griffiths A, Paracha N, Davies A et al. (1-7-2014) The cost effectiveness of ivabradine in the treatment of chronic heart failure from the UK National Health Service perspective. *Heart* 100:1031-1036.
89. Volterrani M, Cice G, Caminiti G et al. (2011) Effect of Carvedilol, Ivabradine or their combination on exercise capacity in patients with Heart Failure (the CARVIVA HF trial). SO: *International Journal of Cardiology* 151:218-224.
90. Kosmala W, Holland DJ, Rojek A et al. (2013) Effect of If-channel inhibition on hemodynamic status and exercise tolerance in heart failure with preserved ejection fraction: a randomized trial. SO: *Journal of the American College of Cardiology* 62:1330-1338.
91. Gullestad L, Ueland T, Kjekshus J et al. (2012) Galectin-3 predicts response to statin therapy in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA). *European Heart Journal* 33:2290-2296.
92. Rogers JK, Jhund PS, Perez A-C et al. (2014) Effect of rosuvastatin on repeat heart failure hospitalizations: The CORONA trial (controlled rosuvastatin multinational trial in heart failure). *JACC: Heart Failure* 2:289-297.
93. Horwich TB, Middlekauff HR, Maclellan WR et al. (2011) Statins do not significantly affect muscle sympathetic nerve activity in humans with nonischemic heart failure: a double-blind placebo-controlled trial. SO: *Journal of Cardiac Failure* 17:879-886.
94. Wang J-Q, Wu G-R, Wang Z et al. (2014) Long-term Clinical Outcomes of Statin Use for Chronic Heart Failure: A Meta-analysis of 15 Prospective Studies. *Heart Lung and Circulation* 23:105-113.

95. Zhang S, Zhang L, Sun A et al. (2011) Efficacy of statin therapy in chronic systolic cardiac insufficiency: a meta-analysis. [Review]. *European Journal of Internal Medicine* 22:478-484.
96. Aleksova A, Masson S, Maggioni AP et al. (2013) n-3 polyunsaturated fatty acids and atrial fibrillation in patients with chronic heart failure: the GISSI-HF trial. *European Journal of Heart Failure* 15:1289-1295.
97. Xin W, Wei W, and Li X. (2012) Effects of fish oil supplementation on inflammatory markers in chronic heart failure: a meta-analysis of randomized controlled trials. *BMC Cardiovascular Disorders* 12:77.
98. Solomon SD, Zile M, Pieske B et al. (2012) The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *SO: Lancet* 380:1387-1395.
99. Faris RF, Flather M, Purcell H et al. (2012) Diuretics for heart failure. *Cochrane Database of Systematic Reviews* 2:CD003838.
100. Piano MR, Prasun MA, Stamos T et al. (2011) Flexible diuretic titration in chronic heart failure: where is the evidence?.. *Journal of Cardiac Failure* 17:944-954.
101. Miyata M, Sasaki T, Ikeda Y et al. (2012) Comparative study of therapeutic effects of short- and long-acting loop diuretics in outpatients with chronic heart failure (COLD-CHF). *Journal of Cardiology* 59:352-358.
102. TORAFIC Investigators Group. (2011) Effects of prolonged-release torasemide versus furosemide on myocardial fibrosis in hypertensive patients with chronic heart failure: a randomized, blinded-end point, active-controlled study. *Clinical Therapeutics* 33:1204-1213.
103. Masuyama T, Tsujino T, Origasa H et al. (2012) Superiority of long-acting to short-acting loop diuretics in the treatment of congestive heart failure. *Circulation Journal* 76:833-842.
104. Pitt B, Latini R, Maggioni AP et al. (2011) Neurohumoral effects of aliskiren in patients with symptomatic heart failure receiving a mineralocorticoid receptor antagonist: the Aliskiren Observation of Heart Failure Treatment study. *SO: European Journal of Heart Failure* 13:755-764.

105. Matsuzaki M, Hori M, Izumi T et al. (2011) Efficacy and safety of tolvaptan in heart failure patients with volume overload despite the standard treatment with conventional diuretics: a phase III, randomized, double-blind, placebo-controlled study (QUEST study). SO: Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy 25 Suppl 1:S33-S45.
106. Matsuzaki M, Hori M, Izumi T et al. (2011) Effects of tolvaptan on volume overload in Japanese patients with heart failure: results of a phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. SO: Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy 25 Suppl 1:S19-S31.
107. Udelson JE, Bilsker M, Hauptman PJ et al. (2011) A multicenter, randomized, double-blind, placebo-controlled study of tolvaptan monotherapy compared to furosemide and the combination of tolvaptan and furosemide in patients with heart failure and systolic dysfunction. *Journal of Cardiac Failure* 17:973-981.
108. Ghali JK, Orlandi C, and Abraham WT. (2012) The efficacy and safety of lixivaptan in outpatients with heart failure and volume overload: results of a multicentre, randomized, double-blind, placebo-controlled, parallel-group study. SO: *European journal of heart failure* 14:642-651.
109. Silvetti S, Greco T, Di Prima AL et al. (2014) Intermittent levosimendan improves mid-term survival in chronic heart failure patients: meta-analysis of randomised trials. *Clinical Research in Cardiology* 103:505-513.
110. Malfatto G, Della RF, Villani A et al. (2012) Intermittent levosimendan infusions in advanced heart failure: favourable effects on left ventricular function, neurohormonal balance, and one-year survival. *Journal of Cardiovascular Pharmacology* 60:450-455.
111. Packer M, Carson P, Elkayam U et al. (2013) Effect of amlodipine on the survival of patients with severe chronic heart failure due to a nonischemic cardiomyopathy: results of the PRAISE-2 study (prospective randomized amlodipine survival evaluation 2). *JACC Heart Failure* 1:308-314.
112. Amin A, Mahmoudi E, Navid H et al. (2013) Is chronic sildenafil therapy safe and clinically beneficial in patients with systolic heart failure? SO: *Congestive Heart Failure* 19:99-103.

113. Redfield MM, Chen HH, Borlaug BA et al. (2013) Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. SO: JAMA : the journal of the American Medical Association 309:1268-1277.
114. Guazzi M, Vicenzi M, and Arena R. (2012) Phosphodiesterase 5 inhibition with sildenafil reverses exercise oscillatory breathing in chronic heart failure: a long-term cardiopulmonary exercise testing placebo-controlled study. European Journal of Heart Failure 14:82-90.
115. -Hood, William B, Dans AL et al. (2014) Digitalis for treatment of heart failure in patients in sinus rhythm. SO: Cochrane Database of Systematic Reviews .
116. Hashim T, Elbaz S, Patel K et al. (2014) Digoxin and 30-day all-cause hospital admission in older patients with chronic diastolic heart failure. American Journal of Medicine 127:132-139.
117. Gheorghiade M, Patel K, Filippatos G et al. (2013) Effect of oral digoxin in high-risk heart failure patients: a pre-specified subgroup analysis of the DIG trial. European Journal of Heart Failure 15:551-559.
118. Toma M, McAlister FA, Coglianese EE et al. (1-5-2012) Testosterone supplementation in heart failure: a meta-analysis. [Review]. Circulation: Heart Failure 5:315-321.
119. Balderas MK, Castillo ML, Orea TA et al. (2012) Improvement of ventricular function in systolic heart failure patients with oral L-citrulline supplementation. SO: Cardiology Journal 19:612-617.
120. Carvalho AP, Rassi S, Fontana KE et al. (2012) Influence of creatine supplementation on the functional capacity of patients with heart failure. SO: Arquivos brasileiros de cardiologia 99:623-629.
121. Deftereos S, Giannopoulos G, Panagopoulou V et al. (2014) Anti-inflammatory treatment with colchicine in stable chronic heart failure: a prospective, randomized study. JACC Heart Failure 2:131-137.
122. Lip-Gregory YH and Shantsila E. (2014) Anticoagulation versus placebo for heart failure in sinus rhythm. SO: Cochrane Database of Systematic Reviews .

123. Hopper I, Skiba M, and Krum H. (2013) Updated meta-analysis on antithrombotic therapy in patients with heart failure and sinus rhythm. [Review]. *European Journal of Heart Failure* 15:69-78.
124. Flammer AJ, Sudano I, Wolfrum M et al. (2012) Cardiovascular effects of flavanol-rich chocolate in patients with heart failure. *SO: European Heart Journal* 33:2172-2180.
125. Gomes ME, El MS, Lenders JW et al. (2011) High dose ascorbic acid does not reverse central sympathetic overactivity in chronic heart failure. *Journal of Clinical Pharmacy & Therapeutics* 36:546-552.
126. Oxberry SG, Torgerson DJ, Bland JM et al. (2011) Short-term opioids for breathlessness in stable chronic heart failure: a randomized controlled trial. *European Journal of Heart Failure* 13:1006-1012.
127. Van Tassel BW, Arena R, Biondi-Zoccai G et al. (15-1-2014) Effects of interleukin-1 blockade with anakinra on aerobic exercise capacity in patients with heart failure and preserved ejection fraction (from the D-HART pilot study). *American Journal of Cardiology* 113:321-327.
128. Zhou Q, Qin WZ, Liu SB et al. (2014) Shengmai (a traditional Chinese herbal medicine) for heart failure. *SO: Cochrane Database of Systematic Reviews* .
129. Xu T-Y, Lv B-N, Peng H-S et al. (2011) Meglumine adenosine cyclophosphate for chronic heart failure: A systematic review. *Chinese Journal of Evidence-Based Medicine* 11:1395-1401.
130. Hartog JW, Willemsen S, van Veldhuisen DJ et al. (2011) Effects of alagebrium, an advanced glycation endproduct breaker, on exercise tolerance and cardiac function in patients with chronic heart failure. *European Journal of Heart Failure* 13:899-908.
131. McMurray et al. (11-9-0014) Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. *N Engl J Med* 371:993-1004.
132. Vizzardi E, D'Aloia A, Giubbini R et al. (1-11-2010) Effect of spironolactone on left ventricular ejection fraction and volumes in patients with class I or II heart failure. *American Journal of Cardiology* 106:1292-1296.

133. Zannad F, McMurray JJ, Krum H et al. (6-1-2011) Eplerenone in patients with systolic heart failure and mild symptoms. *New England Journal of Medicine* 364:11-21.
134. Hu L-J, Chen Y-Q, Deng S-B et al. (2013) Additional use of an aldosterone antagonist in patients with mild to moderate chronic heart failure: A systematic review and meta-analysis. *British Journal of Clinical Pharmacology* 75:1202-1212.
135. Krum H, Shi H, Pitt B et al. (2013) Clinical benefit of eplerenone in patients with mild symptoms of systolic heart failure already receiving optimal best practice background drug therapy: analysis of the EMPHASIS-HF study. *SO: Circulation.Heart Failure* 6:711-718.
136. Swedberg K, Zannad F, McMurray JJ et al. (2012) Eplerenone and atrial fibrillation in mild systolic heart failure: results from the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure) study. *SO: Journal of the American College of Cardiology* 59:1598-1603.
137. Eschalier R, McMurray JJ, Swedberg K et al. (22-10-2013) Safety and efficacy of eplerenone in patients at high risk for hyperkalemia and/or worsening renal function: analyses of the EMPHASIS-HF study subgroups (Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure). *Journal of the American College of Cardiology* 62:1585-1593.
138. Vardeny O, Cavallari LH, Claggett B et al. (2013) Race influences the safety and efficacy of spironolactone in severe heart failure. *SO: Circulation.Heart failure* 6:970-976.
139. Vardeny O, Wu DH, Desai A et al. (2012) Influence of baseline and worsening renal function on efficacy of spironolactone in patients With severe heart failure: insights from RALES (Randomized Aldactone Evaluation Study). *SO: Journal of the American College of Cardiology* 60:2082-2089.
140. Simone G, Chinali M, Mureddu GF et al. (2011) Effect of canrenone on left ventricular mechanics in patients with mild systolic heart failure and metabolic syndrome: the AREA-in-CHF study. *SO: Nutrition, metabolism, and cardiovascular diseases : NMCD* 21:783-791.
141. Deswal A, Richardson P, Bozkurt B et al. (2011) Results of the Randomized Aldosterone Antagonism in Heart Failure with Preserved Ejection Fraction trial (RAAM-PEF). *SO: Journal of Cardiac Failure* 17:634-642.

142. Edelmann F, Wachter R, Schmidt AG et al. (2013) Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: The Aldo-DHF randomized controlled trial. *JAMA - Journal of the American Medical Association* 309:781-791.
143. Tang AS WGTMeal. (2010) Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 363:2385-2395.
144. Al-Majed NS, McAlister FA, Bakal JA et al. (15-3-2011) Meta-analysis: cardiac resynchronization therapy for patients with less symptomatic heart failure. *Annals of Internal Medicine* 154:401-412.
145. Wells G PRHJeal. (2011) Cardiac resynchronization therapy: a meta-analysis of randomized controlled trials. *CMAJ* 183:421-429.
146. Huang Y, Wu W, Cao Y et al. (3-12-2010) All cause mortality of cardiac resynchronization therapy with implantable cardioverter defibrillator: a meta-analysis of randomized controlled trials. [Review]. *International Journal of Cardiology* 145:413-417.
147. 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* 6:805-812.
148. Foley PW, Patel K, Irwin N et al. (2011) Cardiac resynchronisation therapy in patients with heart failure and a normal QRS duration: the RESPOND study. *SO: Heart (British Cardiac Society)* 97:1041-1047.
149. Gold MR, Thébault C, Linde C et al. (2012) Effect of QRS duration and morphology on cardiac resynchronization therapy outcomes in mild heart failure: results from the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) study. *SO: Circulation* 126:822-829.
150. Goldenberg I, Hall WJ, Beck CA et al. (2011) Reduction of the risk of recurring heart failure events with cardiac resynchronization therapy: MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy). *SO: Journal of the American College of Cardiology* 58:729-737.

151. Kutiyifa V, Solomon SD, Bourgoun M et al. (2013) Effects of cardiac resynchronization therapy on left ventricular mass and wall thickness in mild heart failure patients in MADIT-CRT. SO: Heart Rhythm 10:354-360.
152. Lenarczyk R, Kowalski O, Sredniawa B et al. (2012) Implantation feasibility, procedure-related adverse events and lead performance during 1-year follow-up in patients undergoing triple-site cardiac resynchronization therapy: a substudy of TRUST CRT randomized trial. SO: Journal of Cardiovascular Electrophysiology 23:1228-1236.
153. Lopez AN, Rossignol P, Iraqi W et al. (2012) Association of galectin-3 and fibrosis markers with long-term cardiovascular outcomes in patients with heart failure, left ventricular dysfunction, and dyssynchrony: insights from the CARE-HF (Cardiac Resynchronization in Heart Failure) trial. SO: European Journal of Heart Failure 14:74-81.
154. Mathew J, Katz R, St.John SM et al. (2012) Chronic kidney disease and cardiac remodelling in patients with mild heart failure: Results from the REsynchronization reVERses Remodeling in Systolic Left vEntricular Dysfunction (REVERSE) study. European Journal of Heart Failure 14:1420-1428.
155. Martin DO, Day JD, Lai PY et al. (2012) Atrial support pacing in heart failure: results from the multicenter PEGASUS CRT trial. SO: Journal of Cardiovascular Electrophysiology 23:1317-1325.
156. Sims DB, Mignatti A, Colombo PC et al. (2011) Rate responsive pacing using cardiac resynchronization therapy in patients with chronotropic incompetence and chronic heart failure. Europace 13:1459-1463.
157. Campbell P, Takeuchi M, Bourgoun M et al. (2013) Right ventricular function, pulmonary pressure estimation, and clinical outcomes in cardiac resynchronization therapy. SO: Circulation.Heart Failure 6:435-442.
158. Giraldi F, Cattadori G, Roberto M et al. (2011) Long-term effectiveness of cardiac resynchronization therapy in heart failure patients with unfavorable cardiac veins anatomy comparison of surgical versus hemodynamic procedure. SO: Journal of the American College of Cardiology 58:483-490.
159. Khan FZ, Virdee MS, Palmer CR et al. (2012) Targeted left ventricular lead placement to guide cardiac resynchronization therapy: the TARGET study: a randomized, controlled trial. SO: Journal of the American College of Cardiology 59:1509-1518.

160. Kristiansen HM, Vollan G, Hovstad T et al. (2012) A randomized study of haemodynamic effects and left ventricular dyssynchrony in right ventricular apical vs. high posterior septal pacing in cardiac resynchronization therapy. SO: European Journal of Heart Failure 14:506-516.
161. Ronn F, Kesek M, Karp K et al. (2011) Right ventricular lead positioning does not influence the benefits of cardiac resynchronization therapy in patients with heart failure and atrial fibrillation. Europace 13:1747-1752.
162. Saba S, Marek J, Schwartzman D et al. (2013) Echocardiography-guided left ventricular lead placement for cardiac resynchronization therapy: results of the Speckle Tracking Assisted Resynchronization Therapy for Electrode Region trial. SO: Circulation.Heart Failure 6:427-434.
163. Ritter P, Delnoy PP, Padeletti L et al. (2012) A randomized pilot study of optimization of cardiac resynchronization therapy in sinus rhythm patients using a peak endocardial acceleration sensor vs. standard methods. SO: Europace 14:1324-1333.
164. Mihalcz A, Kassai I, Kardos A et al. (2012) Comparison of the efficacy of two surgical alternatives for cardiac resynchronization therapy: trans-apical versus epicardial left ventricular pacing. SO: Pacing and clinical electrophysiology : PACE 35:124-130.
165. Rogers DP, Lambiase PD, Lowe MD et al. (2012) A randomized double-blind crossover trial of triventricular versus biventricular pacing in heart failure. SO: European Journal of Heart Failure 14:495-505.
166. Russell SJ, Tan C, O'Keefe P et al. (2012) Optimized temporary bi-ventricular pacing improves haemodynamic function after on-pump cardiac surgery in patients with severe left ventricular systolic dysfunction: a two-centre randomized control trial. SO: European Journal of Cardio-thoracic Surgery 42:e146-e151.
167. Beeler R, Schoenenberger AW, Bauer P et al. (2014) Improvement of cardiac function with device-based diaphragmatic stimulation in chronic heart failure patients: The randomized, open-label, crossover Epiphrenic II Pilot Trial. European Journal of Heart Failure 16:342-349.
168. Ruschitzka F, Abraham WT, Singh JP et al. (10-10-2013) Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. New England Journal of Medicine 369:1395-1405.

169. Thibault B, Harel F, Ducharme A et al. (2013) Cardiac resynchronization therapy in patients with heart failure and a QRS complex <120 milliseconds: the Evaluation of Resynchronization Therapy for Heart Failure (LESSER-EARTH) trial. SO: Circulation 127:873-881.
170. Potapov E, Meyer D, Swaminathan M et al. (2011) Inhaled nitric oxide after left ventricular assist device implantation: a prospective, randomized, double-blind, multicenter, placebo-controlled trial. SO: Journal of Heart and Lung Transplantation 30:870-878.
171. Ekman I, Kjellstrom B, Falk K et al. (2011) Impact of device-guided slow breathing on symptoms of chronic heart failure: a randomized, controlled feasibility study. European Journal of Heart Failure 13:1000-1005.
172. Fisher SA, Brunskill SJ, Doree C et al. (2014) Stem cell therapy for chronic ischaemic heart disease and congestive heart failure. Cochrane Database of Systematic Reviews 4:CD007888.
173. Cheng K, Wu F, and Cao F. (2013) Intramyocardial autologous cell engraftment in patients with ischaemic heart failure: a meta-analysis of randomised controlled trials. Heart, Lung & Circulation 22:887-894.
174. Bartunek J, Behfar A, Dolatabadi D et al. (11-6-2013) Cardiopoietic stem cell therapy in heart failure: the C-CURE (Cardiopoietic stem Cell therapy in heart failURE) multicenter randomized trial with lineage-specified biologics. Journal of the American College of Cardiology 61:2329-2338.
175. Dos-Santos RR, Rassi S, Feitosa G et al. (2012) Cell therapy in chagas cardiomyopathy (Chagas arm of the multicenter randomized trial of cell therapy in cardiopathies study): A multicenter randomized trial. SO: Circulation 125:2454-2461.
176. Perin EC, Willerson JT, Pepine CJ et al. (25-4-2012) Effect of transendocardial delivery of autologous bone marrow mononuclear cells on functional capacity, left ventricular function, and perfusion in chronic heart failure: the FOCUS-CCTRN trial. JAMA 307:1717-1726.
177. Povsic TJ, O'Connor CM, Henry T et al. (2011) A double-blind, randomized, controlled, multicenter study to assess the safety and cardiovascular effects of skeletal myoblast implantation by catheter delivery in patients with chronic heart failure after myocardial infarction. American Heart Journal 162:654-662.

178. Heldman AW, DiFede DL, Fishman JE et al. (2014) Transendocardial mesenchymal stem cells and mononuclear bone marrow cells for ischemic cardiomyopathy: The TAC-HFT randomized trial. *JAMA - Journal of the American Medical Association* 311:62-73.
179. Campbell AJ, Ferrier K, and Neill AM. (2012) Effect of oxygen versus adaptive pressure support servo-ventilation in patients with central sleep apnoea-Cheyne Stokes respiration and congestive heart failure. *SO: Internal Medicine Journal* 42:1130-1136.
180. Hetland A, Haugaa KH, Olseng M et al. (2013) Three-month treatment with adaptive servoventilation improves cardiac function and physical activity in patients with chronic heart failure and cheyne-stokes respiration: a prospective randomized controlled trial. *Cardiology* 126:81-90.
181. Miyata M, Yoshihisa A, Suzuki S et al. (2012) Adaptive servo ventilation improves Cheyne-Stokes respiration, cardiac function, and prognosis in chronic heart failure patients with cardiac resynchronization therapy. *Journal of Cardiology* 60:222-227.
182. Randerath WJ, Nothofer G, Priegnitz C et al. (2012) Long-term auto-servoventilation or constant positive pressure in heart failure and coexisting central with obstructive sleep apnea. *SO: Chest* 142:440-447.
183. Yoshihisa A, Suzuki S, Yamaki T et al. (2013) Impact of adaptive servo-ventilation on cardiovascular function and prognosis in heart failure patients with preserved left ventricular ejection fraction and sleep-disordered breathing. *SO: European Journal of Heart Failure* 15:543-550.
184. Ferrante D, Varini S, Macchia A et al. (27-7-2010) Long-term results after a telephone intervention in chronic heart failure: DIAL (Randomized Trial of Phone Intervention in Chronic Heart Failure) follow-up. *Journal of the American College of Cardiology* 56:372-378.
185. Koehler F, Winkler S, Schieber M et al. (3-5-2011) Impact of remote telemedical management on mortality and hospitalizations in ambulatory patients with chronic heart failure: the telemedical interventional monitoring in heart failure study. *Circulation* 123:1873-1880.

186. Tompkins C and Orwat J. (2010) A randomized trial of telemonitoring heart failure patients. *Journal of Healthcare Management* 55:312-322.
187. Chaudhry SI MJCJ. (2010) Telemonitoring in patients with heart failure. *N Engl J Med* 363:2301-2309.
188. Abraham WT, Adamson PB, Bourge RC et al. (2011) Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. *Lancet* 377:658-666.
189. Inglis SC, Clark RA, McAlister FA et al. (2011) Which components of heart failure programmes are effective? A systematic review and meta-analysis of the outcomes of structured telephone support or telemonitoring as the primary component of chronic heart failure management in 8323 patients: Abridged Cochrane Review. *European Journal of Heart Failure* 13:1028-1040.
190. Radhakrishnan K and Jacelon C. (2012) Impact of telehealth on patient self-management of heart failure: a review of literature. [Review]. *Journal of Cardiovascular Nursing* 27:33-43.
191. Dendale P, De KG, Troisfontaines P et al. (2012) Effect of a telemonitoring-facilitated collaboration between general practitioner and heart failure clinic on mortality and rehospitalization rates in severe heart failure: the TEMA-HF 1 (TElemonitoring in the MAnagement of Heart Failure) study. *European Journal of Heart Failure* 14:333-340.
192. Krum H, Forbes A, Yallop J et al. (2013) Telephone support to rural and remote patients with heart failure: the Chronic Heart Failure Assessment by Telephone (CHAT) study. *Cardiovascular therapeutics* 31:230-237.
193. Seto E, Leonard KJ, Cafazzo JA et al. (2012) Mobile phone-based telemonitoring for heart failure management: a randomized controlled trial. *SO: Journal of Medical Internet Research* 14:e31.
194. Lyngå P, Persson H, Hägg MA et al. (2012) Weight monitoring in patients with severe heart failure (WISH). A randomized controlled trial. *SO: European Journal of Heart Failure* 14:438-444.
195. Boyne JJ, Vrijhoef HJ, Crijns HJ et al. (2012) Tailored telemonitoring in patients with heart failure: results of a multicentre randomized controlled trial. *SO: European Journal of Heart Failure* 14:791-801.

196. Koehler F, Winkler S, Schieber M et al. (29-11-2012) Telemedicine in heart failure: pre-specified and exploratory subgroup analyses from the TIM-HF trial. *International Journal of Cardiology* 161:143-150.
197. Landolina M, Perego GB, Lunati M et al. (2012) Remote monitoring reduces healthcare use and improves quality of care in heart failure patients with implantable defibrillators: the evolution of management strategies of heart failure patients with implantable defibrillators (EVOLVO) study. *SO: Circulation* 125:2985-2992.
198. Zanaboni P, Landolina M, Marzegalli M et al. (2013) Cost-utility analysis of the EVOLVO study on remote monitoring for heart failure patients with implantable defibrillators: randomized controlled trial. *SO: Journal of medical Internet research* 15:e106.
199. Thokala et al. (1-9-2013) Telemonitoring after discharge from hospital with heart failure: cost-effectiveness modelling of alternative service designs. *BMJ* 3.
200. Maeda JLK. (2010) Evidence-Based Heart Failure Performance Measures and Clinical Outcomes: A Systematic Review. *Journal of Cardiac Failure* 16:411-418.
201. Eurlings LW, van Poel PE, Kok WE et al. (14-12-2010) Management of chronic heart failure guided by individual N-terminal pro-B-type natriuretic peptide targets: results of the PRIMA (Can PRO-brain-natriuretic peptide guided therapy of chronic heart failure IMprove heart fAilure morbidity and mortality?) study. *Journal of the American College of Cardiology* 56:2090-2100.
202. Persson H, Erntell H, Eriksson B et al. (2010) Improved pharmacological therapy of chronic heart failure in primary care: a randomized Study of NT-proBNP Guided Management of Heart Failure--SIGNAL-HF (Swedish Intervention study--Guidelines and NT-proBNP AnaLysis in Heart Failure). *European Journal of Heart Failure* 12:1300-1308.
203. Li P, Luo Y, and Chen YM. (2013) B-type natriuretic peptide-guided chronic heart failure therapy: a meta-analysis of 11 randomised controlled trials. [Review]. *Heart, Lung & Circulation* 22:852-860.
204. Savarese G, Trimarco B, DelleGrottaglie S et al. (2013) Natriuretic Peptide-Guided Therapy in Chronic Heart Failure: A Meta-Analysis of 2,686 Patients in 12 Randomized Trials. *PLoS ONE* 8.

205. Troughton RW, Frampton CM, Brunner-La Rocca HP et al. (14-6-2014) Effect of B-type natriuretic peptide-guided treatment of chronic heart failure on total mortality and hospitalization: an individual patient meta-analysis. *European Heart Journal* 35:1559-1567.
206. Karlstrom P, Alehagen U, Boman K et al. (2011) Brain natriuretic peptide-guided treatment does not improve morbidity and mortality in extensively treated patients with chronic heart failure: responders to treatment have a significantly better outcome. *European Journal of Heart Failure* 13:1096-1103.
207. Shah MR, Califf RM, Nohria A et al. (2011) The STARBRITE trial: a randomized, pilot study of B-type natriuretic peptide-guided therapy in patients with advanced heart failure. *SO: Journal of cardiac failure* 17:613-621.
208. Bhardwaj A, Rehman SU, Mohammed AA et al. (2012) Quality of life and chronic heart failure therapy guided by natriuretic peptides: results from the ProBNP Outpatient Tailored Chronic Heart Failure Therapy (PROTECT) study. *American Heart Journal* 164:793-799.
209. Gaggin HK, Mohammed AA, Bhardwaj A et al. (2012) Heart failure outcomes and benefits of NT-proBNP-guided management in the elderly: results from the prospective, randomized ProBNP outpatient tailored chronic heart failure therapy (PROTECT) study. *Journal of Cardiac Failure* 18:626-634.
210. Januzzi JL, Jr., Rehman SU, Mohammed AA et al. (25-10-2011) Use of amino-terminal pro-B-type natriuretic peptide to guide outpatient therapy of patients with chronic left ventricular systolic dysfunction. *Journal of the American College of Cardiology* 58:1881-1889.
211. Sanders-van WS, Maeder MT, Nietlispach F et al. (2014) Long-term results of intensified, N-terminal-pro-B-type natriuretic peptide-guided versus symptom-guided treatment in elderly patients with heart failure: five-year follow-up from TIME-CHF. *Circulation: Heart Failure* 7:131-139.
212. Sanders-van WS, Muzzarelli S, Neuhaus M et al. (2013) Safety and tolerability of intensified, N-terminal pro brain natriuretic peptide-guided compared with standard medical therapy in elderly patients with congestive heart failure: results from TIME-CHF. *European Journal of Heart Failure* 15:910-918.

213. Laramee P, Wonderling D, Swain S et al. (2013) Cost-effectiveness analysis of serial measurement of circulating natriuretic peptide concentration in chronic heart failure. *Heart* 99:267-271.
214. Ueland T, Dahl CP, Kjekshus J et al. (1-3-2011) Osteoprotegerin predicts progression of chronic heart failure: results from CORONA. *Circulation: Heart Failure* 4:145-152.
215. Ma C, Chen J, Yang J et al. (2014) Quantitative assessment of left ventricular function by 3-dimensional speckle-tracking echocardiography in patients with chronic heart failure: a meta-analysis. *Journal of Ultrasound in Medicine* 33:287-295.
216. Jones J, Thomson P, Lauder W et al. (2013) Reflexology has no immediate haemodynamic effect in patients with chronic heart failure: a double blind randomised controlled trial. *Complementary Therapies in Clinical Practice* 19:133-138.
217. Oyama J, Kudo Y, Maeda T et al. (2013) Hyperthermia by bathing in a hot spring improves cardiovascular functions and reduces the production of inflammatory cytokines in patients with chronic heart failure. *Heart & Vessels* 28:173-178.
218. Ermen A, Hermanson MP, Moran JM et al. (2013) Double dose vs. standard dose influenza vaccination in patients with heart failure: a pilot study. *SO: European Journal of Heart Failure* 15:560-564.
219. -Kanorski?-SG, Tregubov VG, and -Pokrovski?-VM. (2012) [Advantages of quinapril therapy in patients with arterial hypertension and functional class III chronic heart failure with preserved left ventricular ejection fraction]. *SO: Kardiologiia* 52:31-37.
220. Yamamoto K, Origasa H, and Hori M. (2013) Effects of carvedilol on heart failure with preserved ejection fraction: the Japanese Diastolic Heart Failure Study (J-DHF). *SO: European Journal of Heart Failure* 15:110-118.
221. Rector TS, Carson PE, Anand IS et al. (2012) Assessment of long-term effects of irbesartan on heart failure with preserved ejection fraction as measured by the minnesota living with heart failure questionnaire in the irbesartan in heart failure with preserved systolic function (I-PRESERVE) trial. *SO: Circulation.Heart failure* 5:217-225.

222. Hu DY, Huang J, Cai NS et al. (2012) A multi-center, double-blind, randomized, parallel group study to evaluate the effects of two different doses of losartan on morbidity and mortality in Chinese patients with symptomatic heart failure intolerant of angiotensin converting enzyme inhibitor treatment. SO: Chinese Medical Journal 125:3868-3874.
223. Heran BS, Musini VM, Bassett K et al. (2012) Angiotensin receptor blockers for heart failure. [Review]. Cochrane Database of Systematic Reviews 4:CD003040.
224. Aleksova A, Masson S, Maggioni AP et al. (2012) Effects of candesartan on left ventricular function, aldosterone and BNP in chronic heart failure. Cardiovascular Drugs and Therapy 26:131-143.
225. Gasanin E, Dragutinovi?-I, Bankovi?-D et al. (2013) Effects of combination of AT1-antagonist candesartan cilexetil and ACE-inhibitors in patients with congestive heart failure. SO: Srpski arhiv za celokupno lekarstvo 141:29-34.
226. Borghi C, Cosentino ER, Rinaldi ER et al. (1-7-2013) Effect of zofenopril and ramipril on cardiovascular mortality in patients with chronic heart failure. American Journal of Cardiology 112:90-93.
227. Bohm M, Swedberg K, Komajda M et al. (11-9-2010) Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. Lancet 376:886-894.
228. Desai RV, Guichard JL, Mujib M et al. (10-2-2013) Reduced right ventricular ejection fraction and increased mortality in chronic systolic heart failure patients receiving beta-blockers: insights from the BEST trial. International Journal of Cardiology 163:61-67.
229. White M, Desai RV, Guichard JL et al. (2012) Bucindolol, systolic blood pressure, and outcomes in systolic heart failure: a prespecified post hoc analysis of BEST. Canadian Journal of Cardiology 28:354-359.
230. Fiuzat M, Wojdyla D, Kitzman D et al. (17-7-2012) Relationship of beta-blocker dose with outcomes in ambulatory heart failure patients with systolic dysfunction: results from the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial. Journal of the American College of Cardiology 60:208-215.

231. Marazzi G, Volterrani M, Caminiti G et al. (2011) Comparative long term effects of nebivolol and carvedilol in hypertensive heart failure patients. *Journal of Cardiac Failure* 17:703-709.
232. Funck-Brentano C, van Veldhuisen DJ, van de Ven LL et al. (2011) Influence of order and type of drug (bisoprolol vs. enalapril) on outcome and adverse events in patients with chronic heart failure: a post hoc analysis of the CIBIS-III trial. *European Journal of Heart Failure* 13:765-772.
233. Schou M, Gustafsson F, Videbaek L et al. (2013) Extended heart failure clinic follow-up in low-risk patients: a randomized clinical trial (NorthStar). *SO: European Heart Journal* 34:432-442.
234. Heisler M, Halasyamani L, Cowen ME et al. (2013) Randomized controlled effectiveness trial of reciprocal peer support in heart failure. *Circulation: Heart Failure* 6:246-253.
235. Ditewig JB, Blok H, Havers J et al. (2010) Effectiveness of self-management interventions on mortality, hospital readmissions, chronic heart failure hospitalization rate and quality of life in patients with chronic heart failure: A systematic review. *Patient Education and Counseling* 78:297-315.
236. Smeulders ES, van Haastregt JC, Ambergen T et al. (2010) Nurse-led self-management group programme for patients with congestive heart failure: randomized controlled trial. *Journal of Advanced Nursing* 66:1487-1499.
237. Peters-Klimm F, Campbell S, Hermann K et al. (2010) Case management for patients with chronic systolic heart failure in primary care: The HICMan exploratory randomised controlled trial. *Trials* 11 , 2010. Article Number:56.