



New Zealand  
[ Guideline ]  
for the  
Management of  
Chronic Heart Failure  
2009 Update

**Endorsed by:**

The Cardiac Society  
of Australia  
and New Zealand



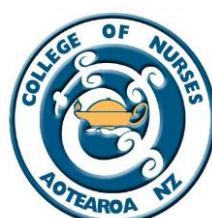
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Pacific Islands  
Heartbeat  
Programme



**New Zealand Guideline for the  
Management of Chronic Heart Failure  
2009 Update**

**National Heart Foundation of New Zealand**

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## **Introduction**

### **Objectives**

The aim of this guideline is to reduce morbidity and mortality from chronic heart failure (HF). It is also hoped that patients' understanding and satisfaction with their health care will be improved.

### **Scope**

This guideline makes recommendations relating to the management of patients with chronic HF. There is commentary on diagnosis in order to define the population of patients to whom this guideline refers. The National Heart Foundation of New Zealand has previously published guidelines for the management of patients with HF in 1997 and 2001. This current guideline updates the 2001 version with specific focus on updates relating to diagnosis, pharmacotherapy, device-based therapies, HF management programmes and palliative care. The patient resources have been extensively updated and are available on-line or from the National Heart Foundation. A web-based version of this guideline is available at [www.heartfoundation.org.nz](http://www.heartfoundation.org.nz)

### **Disclaimer**

The National Heart Foundation of New Zealand and the Cardiac Society of Australia and New Zealand have produced this tool for health professionals and people with HF. Interpretation of the health professional section by those without appropriate health training is not recommended, other than at the request of, or in consultation with, a relevant health professional.

This guideline are not intended to replace clinical judgment. Treatment should take into account co-morbidities, drug tolerance, lifestyle, living circumstances, cultural issues and patient preferences. When prescribing medication, clinicians should observe usual contraindications, be mindful of potential adverse drug interactions and allergies, monitor responses and ensure regular review.

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## Aims of Heart Failure Guideline Revision

The aims of this focused update were:

1. to provide updated evidence-based recommendations for the management (including diagnosis and therapy) of patients with HF in New Zealand;
2. to provide improved patient resources to enhance patient education and self-management;
3. to provide an on-line resource for health professionals and patients to allow widespread access to the guideline information and resources.

This guideline does not cover management of patients with acute decompensated HF. However, for patients hospitalised with new onset or an exacerbation of pre-existing HF many of the management approaches covered in this guideline should be considered prior to discharge. The New Zealand Heart Failure Registry is a quality improvement initiative which can provide ongoing audit and facilitate improvement in patient management. Hospitals are encouraged to contribute to this registry.

## Process

The previous versions of this guideline were published by the National Heart Foundation in 1997 and revised in 2001.<sup>1, 2</sup> A systematic search of the external literature was undertaken to identify explicitly developed evidence-based guidelines on the management of HF. The following guidelines were reviewed:

1. American College of Cardiology and American Heart Association 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult.<sup>3</sup>
2. Heart Failure Society of America 2006 Comprehensive Heart Failure Practice Guideline.<sup>4</sup>
3. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand Guidelines for the Prevention, Detection and Management of Chronic Heart Failure in Australia, 2006.<sup>5</sup>
4. European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008.<sup>6</sup>
5. 2009 Focused Update: American College of Cardiology Foundation/American Heart Association Guidelines for the Diagnosis and Management of Heart Failure in Adults.<sup>7</sup>

The 2001 New Zealand National Heart Failure guideline served as the key national resource and has been updated.<sup>2</sup> The following topics were selected for further review and evaluation of the external evidence:

- the diagnosis of HF; in particular the role of brain natriuretic peptide (BNP) in diagnosis;
- revision of the section on pharmacotherapy;
- the role of device-based therapies (primary implantable cardioverter defibrillator and biventricular pacing);
- the role of exercise in HF;
- the role of palliative care in HF;
- the role of disease management approaches.

Systematic Medline searches of the literature were undertaken by reviewers experienced in guideline development, with the assistance of medical librarians as required. Papers were reviewed and critiqued by a member of the guideline team and strength of evidence assigned according to a standard quality-rating scale (Table 1). Final decisions regarding each paper and the recommendations of the guideline were established by consensus.

## Grading of Evidence

The grading methodology used in this guideline is shown in Table 1.

**Table 1. Levels of Evidence for Clinical Interventions and Grades of Recommendation**

LEVEL OF STUDY DESIGN EVIDENCE	GRADE OF RECOMMENDATION
I Evidence obtained from a systematic review of all relevant randomised controlled trials (RCTs)	A Rich body of high-quality randomised controlled trial (RCT) data
II Evidence obtained from at least one properly designed randomised controlled trial	B Limited body of RCT data or high-quality non-RCT data
III-I Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method)	C Limited evidence
III-2 Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies, or interrupted time series with a control group	D No evidence available - panel consensus judgement
III-3 Evidence obtained from comparative studies with historical control, 2 or more single-arm studies, or interrupted time series with a parallel control group	
IV Evidence obtained from case series, either post-test or pre-test and post-test	

**Source:** The levels of evidence and grades of recommendations are adapted from the National Institute of Health and Medical Research Council levels of evidence for clinical interventions and the US National Institute of Health clinical guidelines. Details can be found at [www.nhlbi.nih.gov/guidelines/index.htm](http://www.nhlbi.nih.gov/guidelines/index.htm).

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## Epidemiology of Heart Failure

HF is a significant and increasing global public health problem. In the United States, HF is estimated to affect approximately 5.7 million people, account for 1.1 million hospital admissions each year and cost in excess of US\$32 billion annually.<sup>8</sup> The diagnosis of HF continues to be associated with poor quality of life, high morbidity and mortality despite contemporary HF management.<sup>9,15</sup> Once admitted to hospital, patients experience high rates of subsequent HF hospitalisation<sup>16</sup> and mortality.<sup>9,10</sup> One-year mortality rates after initial hospital admission for HF are between 25 and 35%.<sup>13</sup>

In New Zealand, there are approximately 12,000 hospital admissions, of approximately 5,500 patients, for HF each year.<sup>17</sup> The average length of stay is 5 days and overall costs associated with HF account for 1.5-2% of the total health budget, thus representing a significant burden to the NZ healthcare system.<sup>18</sup> Despite a decline in mortality through the 1990s, HF mortality in NZ has been sustained over the last 5 years and remains high (20% at 6 months and 30% at 12 months).<sup>18</sup> HF among Māori occurs on average 10-15 years earlier than for non-Māori. Mortality from HF is approximately 8 times higher among Māori males aged 45-64 years than among non-Māori and approximately 3½ times higher among Māori aged >65 years. A similar excess mortality rate is also observed for Māori females. Hospital admissions for HF are 8 to 9 times higher among Māori compared with non-Māori.<sup>19</sup>

The prevalence of HF is increasing as the population ages and the proportion of the population over the age of 65 years increases.<sup>20</sup> The US Census estimates that there will be 40 million Americans aged 65 years and older by 2010. In New Zealand, with a population of approximately 4 million people, it is projected that the proportion of the population over 65 years of age will increase from 12% in 2001, to 14% in 2011 and 18% in 2021.<sup>21</sup> Assuming that the prevalence of HF is approximately 10% in those aged >65 years, it can be expected that the number of people affected by HF will increase by approximately 50% over the next few decades. This increase in prevalence will increase the burden that HF places on healthcare resources.

## Definition of Heart Failure

HF is a complex clinical syndrome occurring as the end result of a variety of different forms of heart disease. There are many different definitions and classifications of HF but a simple, practical definition of the syndrome of HF is that it is characterised by typical symptoms such as shortness of breath, exercise limitation and fatigue, and clinical signs of peripheral and/or pulmonary congestion, and secondary to abnormalities of cardiac structure and function.<sup>22</sup> The syndrome of HF results in significant impairment of quality of life (QOL), more so than many other chronic diseases,<sup>23</sup> and is associated with high morbidity and mortality. HF frequently occurs in the setting of preserved left ventricular (LV) ejection fraction (LVEF)<sup>24, 25</sup> and thus a practical clinical definition of the syndrome,<sup>22</sup> rather than relying on a single factor such as impaired LVEF, allows identification of the broad group of patients affected by this condition.

The 2001 American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines for the Evaluation and Management of Chronic Heart Failure developed a new approach to the classification of HF.<sup>26</sup> This classification took the perspective of HF as part of the spectrum of cardiovascular disease from patients at high risk of developing HF but who do not at that stage have any structural heart disease (Stage A, e.g. patients with hypertension and/or coronary artery disease), through to patients with structural heart disease but without symptoms of HF (Stage B, e.g. patients with LV hypertrophy or prior myocardial infarction), to patients with symptoms of HF (Stage C) and end-stage HF (Stage D). In this classification, patients with the clinical syndrome of symptomatic HF fall within Stages C and D. This classification is useful because it clearly defines HF as a clinical syndrome occurring in patients with structural heart disease. It also recognises the importance of risk factors and structural heart disease in an asymptomatic patient and that therapy directed towards these abnormalities may help to prevent or delay the onset of the syndrome of HF.

## Diagnosis of Heart Failure

HF is a clinical syndrome characterised by symptoms, clinical signs and some abnormality of cardiac structure and/or function.<sup>22</sup> Patients presenting with suspected HF should undergo a full clinical assessment including history and examination. Investigations may aid the overall clinical assessment but it is important to recognise that no single test will reliably identify HF and the diagnosis requires careful integration of all available information.

### 1. Clinical evaluation

#### Recommendations

**Evaluation for heart failure should be undertaken in all patients who complain of new-onset shortness of breath on exertion, orthopnoea or paroxysmal nocturnal shortness of breath unless history and physical examination clearly indicate a non-cardiac cause for their symptoms.**

**The most specific signs of heart failure are elevated jugular venous pressure, a third heart sound and a laterally displaced apical impulse, and these are virtually diagnostic in a patient with compatible symptoms.**

*Level of evidence IV: Grade of recommendation D*

#### Clinical Practice Points

- Diagnosis of the clinical syndrome of heart failure can be difficult, especially in patients who are elderly, obese or have co-morbidities, and when a patient presents with milder symptoms in the community.
- Careful attention should be given to obtaining history of causative factors for heart failure, including any of the following:
  - hypertension;
  - myocardial infarction;
  - valvular heart disease;
  - atrial fibrillation (AF).
- Exertional shortness of breath and ankle swelling are common symptoms which can be due to a variety of conditions and, alone, have low specificity for heart failure.
- Orthopnoea and paroxysmal nocturnal shortness of breath are features of more marked decompensation and are more specific for heart failure.
- The presence of more than one physical sign, such as an elevated jugular venous pressure, third heart sound and pulmonary crepitations, increases the likelihood of heart failure.

## Supporting Evidence

### Clinical history

Early recognition of the clinical syndrome of HF is important to allow prompt implementation of evidence-based therapies. While the diagnosis can be difficult, especially in primary care (see below), suspicion should be high when patients with possible causative risk factors for HF present with appropriate symptoms. A careful clinical history is an important part of the assessment of suspected HF. Shortness of breath on exertion is often the earliest symptom followed by paroxysmal nocturnal shortness of breath, oedema, cough and orthopnoea.<sup>27</sup> Fatigue is a frequent symptom, and may become more clinically evident when shortness of breath is less marked or has improved. A history of hypertension, previous myocardial infarction, cardiac murmur or other heart disease, in conjunction with the above symptoms, points toward a diagnosis of HF. A careful history of prior or current alcohol and drug use should be sought. Importantly, many patients with impaired LV function have no symptoms. In one report, 20% of patients with a LVEF <40% exhibited no clinical criteria for HF.<sup>28</sup> Conversely, the symptoms listed above are not always due to HF.

Symptoms suggestive of HF include:

- shortness of breath on exertion;
- lower extremity oedema;
- decreased exercise tolerance;
- paroxysmal nocturnal shortness of breath;
- orthopnoea;
- unexplained confusion or fatigue in elderly;
- nausea or abdominal pain (ascites or hepatic engorgement).

### **Physical examination**

In many patients with early symptoms of HF, even with moderate-to-severe LV systolic dysfunction, there are few abnormal physical findings. A pathological third heart sound (S3) is the most sensitive physical sign, and may be present in two-thirds of patients with LVEF <30%.<sup>29</sup> Rales and/or a displaced apical impulse are present in about one-third of patients.<sup>27</sup> Jugular venous distension and peripheral oedema appear to be less sensitive signs.<sup>27</sup>

The specificities of physical signs are less well defined but an elevated jugular venous pressure and a third heart sound are probably the most specific clinical signs of HF. Lower extremity oedema is a relatively non-specific finding, common in older people, and usually due to chronic venous insufficiency.<sup>30</sup>

Abnormal physical findings in HF include:

- tachycardia, irregular pulse;
- elevated jugular venous pressure or positive hepato-jugular reflux;
- a third heart sound;
- laterally displaced apical impulse;
- pulmonary rales that do not clear with coughing;
- peripheral oedema.

### **Clinical assessment in primary care**

Diagnosis of HF presenting in primary care can be particularly difficult. Symptoms and signs have limited sensitivity and specificity.<sup>31</sup> Patients are often elderly with co-morbidity. The clinical syndrome of HF is particularly difficult to diagnose in the elderly and in the presence of accompanying respiratory disease.<sup>31</sup> Symptoms may be mild, routine clinical assessment lacks specificity and investigations, such as echocardiography, may not be readily available. Over-diagnosis of HF in the community is well-documented. Only one-quarter to one-third of patients whose general practitioners suspect HF have the diagnosis confirmed on further cardiological assessment.<sup>31-33</sup> Brain natriuretic peptide (BNP) has a particular role to assist in the assessment of patients with suspected HF in the community (see next section).

### **Clinical assessment of functional capacity**

A well-established clinical schema for assessing functional capacity is the New York Heart Association (NYHA) Functional Classification. This is based on the degree of limitation of the patient's lifestyle (Table 2). It is a useful shorthand method for recording functional status and is helpful for inter-patient comparisons and for monitoring response to therapy. However classifying HF on the basis of exercise intolerance examines only one facet of HF symptomatology. Many symptoms of HF (e.g. fatigue) are impossible to quantify.

**Table 2. New York Heart Association Functional Classification**

<b>Class I:</b>	Patients with cardiac disease but without resulting limitation in physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, shortness of breath or anginal pain.
<b>Class II:</b>	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, shortness of breath or anginal pain.
<b>Class III:</b>	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, shortness of breath or anginal pain.
<b>Class IV:</b>	Patients with cardiac disease resulting in an inability to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency or of anginal pain are present at rest. If any physical activity is undertaken discomfort is increased.

### **Investigations**

Investigations are generally required to assist in the diagnosis of HF. The specific tests chosen may depend in part upon the location and acuity of the patient presentation. For example, a patient presenting with florid pulmonary oedema in the hospital setting may require rapid investigation whereas a patient with milder symptoms of suspected HF in the community may require investigation to assist in ruling in/ruling out this diagnosis to facilitate appropriate further evaluation.

It is important that each investigation be integrated into the full array of information available on the patient. A sensible sequence of investigations will facilitate prompt diagnosis. Useful investigations are considered below.

#### ***Electrocardiogram (ECG)***

A normal ECG makes the diagnosis of HF highly unlikely.<sup>34</sup> While this high negative predictive value may be useful, many patients with suspected HF will have a variety of abnormalities on the ECG, thus the ECG alone cannot be used to definitely confirm the diagnosis of HF. Major features on the ECG seen in patients with HF include left axis deviation, AF, bundle branch block, LV hypertrophy and pathological Q-waves.<sup>34</sup>

#### ***Chest X-ray***

Important radiographic abnormalities associated with HF include pulmonary vascular redistribution, cardiomegaly (cardiothoracic ratio >0.5), pleural effusions and interstitial oedema.

## 2. Brain natriuretic peptide (BNP)

### Recommendations

**Brain natriuretic peptide assists in the diagnosis of patients presenting with symptoms of suspected heart failure.**

**Level of evidence II: Grade of recommendation A**

### Clinical Practice Points

- BNP-32 and NT-proBNP are both useful tests to aid clinical decision-making in patients presenting with symptoms of suspected heart failure. Suggested values for BNP are as follows:

	<b>Heart failure unlikely (Rule out test)</b>	<b>Heart failure likely (Rule in or confirm test)</b>
<b>BNP-32</b>	<100 pg/mL (approx. 30 pmol/L)	>500 pg/mL (approx. 145 pmol/L)
<b>NT-proBNP</b>	<300 pg/mL (approx. 35 pmol/L)	Recommended age-adjusted optimal cut points: Age <50yrs: 450 pg/mL ( $\approx$ 50 pmol/L) Age 50-75 yrs: 900 pg/mL ( $\approx$ 100 pmol/L) Age >75 yrs: 800 pg/mL ( $\approx$ 210 pmol/L)

- Intermediate or “grey zone” values can be considered as those that fall above the cut points for ruling out heart failure but below those cut points for confirming heart failure (see above table):
  - Age stratification for NT-proBNP reduces the likelihood of a grey zone value;
  - BNP levels may be elevated in the absence of heart failure due to atrial fibrillation, chronic obstructive pulmonary disease, acute coronary syndromes, pulmonary embolism, pulmonary hypertension or renal impairment;
  - BNP levels may be normal or only marginally elevated even if heart failure is present in patients who are obese, or who have recently been commenced on diuretic therapy (it is recommended that the blood test for NT-proBNP is done prior to commencing diuretics in a patient presenting with new symptoms), or in those who have had very sudden onset of [“flash”] pulmonary oedema.
- Patients with grey zone NT-proBNP levels who present with symptoms and/or signs with good specificity for heart failure (such as paroxysmal nocturnal shortness of breath and/or an elevated jugular venous pressure) are likely to have heart failure.
- Patients in whom the diagnosis of heart failure is obvious from clinical assessment and other tests, such as chest X-ray, do not require BNP testing for diagnosis.
- While use of BNP can aid in the early assessment of patients with suspected heart failure, this biomarker does not replace the need for cardiac imaging in a patient with confirmed heart failure.

### Supporting Evidence

BNP, one of a family of related peptides, has important roles in the management of patients with HF including diagnosis, assessing prognosis, and potentially in guiding therapy.<sup>35</sup> BNP is released from the heart in proportion to transmural wall stress and has multiple actions including natriuresis, diuresis, peripheral vasodilatation and modulation of vasoconstrictor neurohormonal systems. The precursor (pro-hormone) pro-BNP, is cleaved within the heart to 2 fragments; BNP-32, the active hormone and an inactive aminoterminal portion, NT-proBNP. Both are stable in EDTA anti-coagulated whole blood for up to 3 days, and commercial assays are available for both.

Both BNP-32<sup>36</sup> and NT-proBNP<sup>37</sup> are of value in the assessment of patients with symptoms of suspected HF. As with other investigations, the BNP measurement should not be taken in isolation but should be incorporated with the patient assessment (history and physical

examination), ECG and chest x-ray to assist with the diagnosis of the clinical syndrome of HF. BNP levels rise with age, and are affected by gender, co-morbidity (particularly renal dysfunction) and drug therapy, and thus must be interpreted in clinical context. In general terms BNP can be interpreted as follows (for specific values, see Table 3):

- A normal BNP level makes the diagnosis of HF unlikely (rule out test)
- A high BNP level makes the diagnosis of HF very likely (rule in or confirm test)
- Intermediate values of BNP require careful interpretation, in light of patients age (consider age-adjusted cut-off values) and co-existing conditions.

**Table 3. Clinical use of BNP-32 and NT-proBNP**

	Heart failure unlikely <i>(Rule out test)</i>	Heart failure likely <i>(Rule in or confirm test)</i>
<b>BNP-32</b>	<100 pg/mL (approx. 30 pmol/L)	>500 pg/mL (approx. 145 pmol/L)
<b>NT-proBNP</b>	<300 pg/mL (approx. 35 pmol/L)	Recommended age-adjusted optimal cut points: Age <50yrs: 450 pg/mL ( $\approx$ 50 pmol/L) Age 50-75 yrs: 900 pg/mL ( $\approx$ 100 pmol/L) Age >75 yrs: 800 pg/mL ( $\approx$ 210 pmol/L)

Some patients such as those presenting with acute “flash” pulmonary oedema, may present with clear clinical evidence of HF but initially have relatively normal, or lower than expected, levels of BNP.

#### **Specific notes regarding NT-proBNP<sup>37, 38</sup>**

Intermediate or “grey zone” values can be considered as those that fall above the cut points for ruling out HF (<300 pg/mL [approx. 35 pmol/L]) but below those cut points for ruling in HF (Table 3). Several factors are important to evaluate when considering patients with grey zone BNP levels:<sup>38</sup>

- Age stratification reduces the likelihood of a grey zone value (to <15% of tests);
- NT-proBNP levels may be elevated in the absence of HF due to AF, chronic obstructive pulmonary disease, acute coronary syndromes, pulmonary embolism, pulmonary hypertension;
- NT-proBNP levels may be low even if HF is present in patients who are obese, or who have recently been commenced on diuretic therapy (it is recommended that the blood test for NT-proBNP is done prior to commencing diuretics in a patient presenting with new symptoms);
- Patients with grey zone NT-proBNP levels who present with symptoms and/or signs with good specificity for HF (such as paroxysmal nocturnal shortness of breath and/or an elevated jugular venous pressure) are more likely to have HF.

#### **Specific notes regarding BNP-32<sup>36</sup>**

If the BNP is <100 pg/mL (approx. 30 pmol/L), then HF is unlikely (negative predictive value 90%). If the BNP is >500 pg/mL (approx. 145 pmol/L), then HF is highly likely (positive predictive value 90%). For patients with grey zone BNP levels, between 100 and 500 pg/mL, then several factors should be considered including: right ventricular failure associated with cor pulmonale, pulmonary embolism or renal failure. BNP-32 levels may also be low in patients who are obese and in patients presenting with flash pulmonary oedema.<sup>36</sup>

#### **Other laboratory investigations**

Other laboratory investigations are required both to assist in the diagnosis of HF, evaluate for potential causes and to monitor patients clinical status during therapeutic interventions. These include:

- Full blood count: HF due to, or aggravated by, anaemia;
- Serum creatinine: renal dysfunction, either primary or secondary to cardio-renal syndrome;
- Serum sodium and potassium: monitoring in context of HF management;
- Serum albumin: oedema secondary to low serum albumin in nephrotic syndrome;

- Thyroid function tests: HF due to or aggravated by hypo/hyperthyroidism;
- Urinalysis: proteinuria due to nephropathy/nephritic syndrome, or red blood cells/casts due to glomerulonephritis.

Once HF is considered to be the cause of the patient's presenting symptoms then further specific work-up should be considered, including echocardiography for assessment of cardiac structure and function. Patients in whom the diagnosis is unlikely (*rule out* test) do not need echocardiography but require re-evaluation and consideration of other causes of the presentation.

### **Echocardiography**

Imaging of the heart for a patient with HF is a crucial part of the evaluation. While use of BNP can aid in the early assessment of patients with suspected HF, this biomarker does not replace the need for cardiac imaging in a patient with confirmed HF. Sensible use of BNP can improve selection of patients in whom HF appears likely and who will require further investigation, including with echocardiography.

In New Zealand the initial cardiac imaging modality for patients with HF will most commonly be echocardiography. The echocardiographic evaluation of patients with known or suspected HF should include assessment of:

- LV size;
- Presence or absence of LV hypertrophy;
- LV systolic function, commonly with assessment of LVEF;
- LV regional wall motion abnormalities (if present suggesting underlying coronary artery disease);
- LV diastolic function, commonly using a combination of mitral and tissue Doppler, and left atrial size;
- Right ventricular size and systolic function;
- Exclusion of significant valve disease.

It is recognised that echocardiography is not widely available in many areas in New Zealand. "Open-Access" echocardiography for primary care practitioners has been promoted in many areas. However, there is no randomised controlled clinical trial evidence that the provision of this service alters outcome or is cost-effective. The use of BNP as a rule out test for patients presenting in primary care with suspected HF is simple and accessible, and can avoid the need for echocardiography. Despite limitations with access to echocardiography, it is still recommended as part of the assessment of patients with the syndrome of HF.

## Aetiology of Heart Failure

HF should never be the complete or final diagnosis. The aetiology of HF and the presence of exacerbating factors or other diseases that have an important influence on management should be carefully considered. The extent to which the cause of HF should be pursued by further investigation will depend on the patient's life expectancy, the likelihood that the cause is remediable, whether knowing the cause will influence management, and the resources available.

Aetiological factors for HF are listed in Table 4. Coronary artery disease (commonly complicated by myocardial infarction) is the primary cause of HF in approximately 70% of patients.<sup>39</sup> Abnormalities of LV systolic function are often present in such patients, usually manifest as low LVEF. In the elderly, accurate diagnosis is more difficult and may be obscured by multiple other diagnoses. Hypertension, hypertrophy, and myocardial fibrosis may be more important causes of HF in the elderly and can occur in the presence of preserved LVEF. Often there is uncertainty over which factor dominates.

The cardiomyopathies are conditions resulting in structural and functional abnormalities of cardiac muscle (in the absence of coronary artery disease, hypertension, or valve disease). New classification of the cardiomyopathies has been proposed by the European Society of Cardiology in 2008.<sup>40</sup> This classification has abandoned the distinction between primary and secondary cardiomyopathies, and instead has adopted groupings based on specific morphological and functional phenotypes, with further sub-classification into familial and non-familial forms. In general, the evaluation of specific forms of cardiomyopathies will require specialist referral and is not dealt with further in this Guideline.

**Table 4. Causative factors in the development of heart failure**

- |  |
|--|
| <ul style="list-style-type: none"><li>• Coronary artery disease</li><li>• Hypertension</li><li>• Endocrine disorders, e.g. diabetes, hypo/hyperthyroidism, acromegaly, Cushing's syndrome, aldosteronism, phaeochromocytoma</li><li>• Valvular heart disease</li><li>• Alcohol</li><li>• Cardiomyopathies<sup>40</sup></li><li>• Familial cardiomyopathy</li><li>• Infections, such as viral myocarditis</li><li>• Congenital heart disease</li><li>• Infiltrative conditions, such as sarcoidosis, amyloidosis, haemochromatosis</li><li>• Drugs, such as cytotoxic agents</li><li>• Nutritional, such as obesity, thiamine deficiency</li><li>• Chronic arrhythmias, e.g. uncontrolled AF, or bradycardia (complete heart block)</li></ul> |
|--|

## Precipitating or Exacerbating Factors

It is important to identify and treat any reversible factors, which may be exacerbating the symptoms of HF. Patients hospitalised with an exacerbation of HF should be thoroughly assessed for any factor(s) that may have contributed to the exacerbation. These factors include:

- poor compliance with current management regime;
- anaemia;
- co-existing infections, such as pneumonia;
- arrhythmias, especially AF;
- concomitant drugs, such as nonsteroidal anti-inflammatory drugs, calcium channel blockers, corticosteroids and liquorice;
- alcohol excess;
- renal dysfunction and/or renal artery stenosis;
- pulmonary embolism;
- unrecognised myocardial infarction;
- excess salt intake.

## **Criteria for Specialist Referral**

In many patients with HF extensive investigations may not be appropriate due to age and multiple concomitant medical conditions. The criteria for specialist referral cannot be based on evidence from randomised controlled trials as the interventions evaluated in such trials are usually applied to subsets of patients with established diagnoses. Consequently, the recommendations for referral outlined below are based on consensus opinion. Clinicians should rely on their clinical judgement and when in doubt should err on the side of referral. Undertaking specialist referral should not delay initiation of appropriate treatment for patients with symptomatic HF.

There are certain patients who may benefit from consideration of further investigation. Of particular note are:

- the onset of HF in younger patients (in whom transplantation may be considered);
- those whose history suggests severe myocardial ischaemia or significant valvular disease where further investigation and intervention (revascularisation) may be indicated.

In these cases specialist referral is recommended.

Specialist referral may also be considered in the following situations where:

- the diagnosis is uncertain;
- the aetiology is uncertain;
- arrhythmia (such as AF or ventricular arrhythmias) are apparent;
- in those with sudden onset of HF;
- those who have an inadequate response to treatment;
- the indication for anticoagulation is uncertain.

## Treatment of Heart Failure

Patients with the clinical syndrome of HF frequently have symptoms of shortness of breath, poor exercise capacity and impaired quality of life (QOL). Hospital admissions are frequent and after a first hospital admission for HF in New Zealand annual mortality rates remain high (approximately 30% at one year). Early diagnosis of the clinical syndrome of HF allows appropriate management strategies to be instigated to improve patients' QOL and clinical outcomes.

Much of the evidence underpinning the recommendations for treatment is from randomised controlled trials that have involved patients with HF and impaired LV systolic function (typically LVEF <35-45%). Evidence-based recommendations among this group of patients includes pharmacotherapy (with angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers (ARBs), beta-blockers and aldosterone antagonists), and device-based therapies (including implantable defibrillators and biventricular pacing). However, 30-50% of patients with the syndrome of HF will have relatively normal LVEF; so called "HF with preserved LVEF". Currently, the results of randomised trials of pharmacotherapy (ACE inhibitors and ARBs) in such patients have been disappointing. Consequently, the recommendations for treatment for patients with HF with preserved LVEF reflect consensus opinion, rather than being evidence-based.

HF is a chronic condition that requires long-term management, and patient self-care strategies are vitally important to improve outcomes. Evidence is now available from randomised controlled trials that a wide range of patients with HF can gain significant ongoing and long-term benefits from improved self management. Exercise is an important aspect of HF management. A structured approach to healthcare delivery, commonly incorporating a HF nurse specialist and a multidisciplinary team, for patients with HF is associated with improved clinical outcomes.

Patients with HF often have important co-morbidities such as coronary artery disease, AF, respiratory disease, and diabetes. To maximise outcomes it is important to consider HF management along with the management of other co-existing conditions.

## Heart Failure Disease Management

There is now clear evidence, from multiple randomised controlled trials, that chronic disease management interventions improve outcomes for patients with HF. Different models of healthcare delivery have been assessed and should be adapted to the local healthcare environment.

### Recommendations

**A structured approach to chronic disease management is recommended for patients with heart failure, especially for those at high risk, such as those with recent hospitalisation.**

*Level of evidence I: Grade of recommendation A*

### Clinical Practice Points

- Management interventions for patients with heart failure commonly involve the following aspects of care:
  - comprehensive education and involvement of the patient and family/support people;
  - social support;
  - focus on patient self-management strategies;
  - attention to compliance with healthcare and self management;
  - optimisation of medical therapy;
  - structured follow-up (often in shared-care settings with hospital and primary care);
  - more intensive disease management strategies for patients recently hospitalised with heart failure who are particularly vulnerable (such as those with English as a second language, multiple previous hospital admissions or from lower socioeconomic conditions);
  - interventions may commence during a hospital admission and continue with early, planned and structured follow-up to address the needs of the patient.
- Any structured programme/intervention should have flexibility and be able to be adapted according to the needs of the individual patients and the local healthcare environment.
- The heart failure nurse specialist has a key role in management and often will work as part of a multidisciplinary team.
- Remote monitoring (telemonitoring) may be considered for some patients.
- Adequate funding is required to sustain such management interventions.

### Supporting Evidence

The effectiveness of different management approaches for improving outcomes for patients with HF has been examined in multiple randomised controlled trials. These trials have involved different interventions, differing patient groups, and included various components of the Chronic Care Model. Within the trials there is often overlap in the interventional strategy, for example, combining educational interventions with clinical follow-up and telephone monitoring. However, it is convenient to consider the trials in general categories based on their predominant intervention:

- disease management strategies. These may involve:
  - hospital-based clinics (usually multidisciplinary);
  - home-based interventions (usually multidisciplinary);
  - primary care-based interventions;
- telemonitoring or structured telephone support (remote monitoring);
- self management and educational interventions;
- social support.

Several systematic reviews of these trials have been performed over recent years. These reviews have included similar trials but have had different foci of analysis. Three recent

systematic reviews are outlined below in more detail. These reviews appear scientifically robust and provide an appropriate summary of the effects of these interventions.

### Disease management

Five systematic reviews of disease management interventions for HF have been performed.<sup>41-45</sup> The most recent and robust systematic review included 29 multidisciplinary HF management trials involving 5,039 patients.<sup>41</sup> There was significant heterogeneity between the trials in this review. Furthermore, it is not necessarily appropriate to combine the results from trials where the interventions have important differences. Thus, the trials were grouped according to the structure of the main intervention, as follows.

#### *Multidisciplinary heart failure clinic & multidisciplinary intervention (not clinic-based)*

These interventions reduced all-cause mortality – risk ratio (RR) 0.75 (95% confidence interval [CI] 0.59-0.96), number needed to treat (NNT) was 17, and the decrease in all-cause mortality was observed whether or not a HF clinic was involved in the intervention. Multidisciplinary interventions also reduced HF hospital readmissions, RR 0.73 (95% CI 0.63-0.87).

#### *Telephone/telemonitoring*

This systematic review did address telephone follow-up/telemonitoring, although a subsequent meta-analysis has addressed this in more detail (see below). No effect was observed for telephone follow-up alone on total mortality (RR 0.91, 95% CI 0.65-1.29), although there was a reduction in HF readmissions (RR 0.75, 95% CI 0.57-0.99).

#### *Self-Care/Educational activities*

Relatively small numbers of patients have been involved in studies of self-care interventions alone (without other components to the intervention) at the time of this meta-analysis. There was no demonstrable effect of these interventions on total mortality (RR 1.14, 95% CI 0.67-1.94), although HF readmissions appeared to be reduced (RR 0.66, 95% CI 0.52-0.83).

A subsequent meta-analysis in 2006 combined the results from 36 randomised trials of disease management programmes for patients with HF involving 8,341 patients.<sup>42</sup> This systematic review analysed all trials combined, despite significant heterogeneity in the design of the trials. From this meta-analysis, all-cause mortality was reduced by the disease management interventions (absolute risk difference 3%, 95% CI -1%, -5%, NNT over 6 months = 33). All-cause readmissions were also reduced (absolute risk difference 8%, 95% CI -5%, -11, NNT 13).

A further study has been published since these meta-analyses were completed. The DEAL-HF study assessed the effects of a combined physician and nurse-directed HF management programme (based in out-patient clinics) compared with a usual care group.<sup>46</sup> This study, involving 240 patients, demonstrated a reduction in the combined endpoint of HF readmissions and all-cause mortality (absolute risk reduction [ARR] 19%, NNT over 1 year = 5).

In summary, multidisciplinary interventions appear to reduce mortality and HF readmissions. Education alone had no effect on mortality, but decreased HF readmissions (however, it is important to note the relatively small number of studies and patients). Each intervention had some differences in structure, but common themes emerged which should be considered when planning to implement such programmes:

- multidisciplinary nature of intervention: including congestive HF nurse specialist role, doctors in primary-secondary-tertiary care, pharmacists, social workers, and occupational therapists;
- multi-faceted: including critical pathways, implementation of evidence-based guidelines (including drug therapy), importance of reminders/feedback;
- patient-centred: including education, self-management, and structured follow-up.

## **Structure of heart failure management interventions**

### *Increased access to primary care alone*

A study by Weinberger et al.<sup>47</sup> involving 1,396 patients with chronic lung disease, diabetes or HF (13%), showed that close follow-up by a primary care practitioner and nurse resulted in an increase in hospital admissions. This may have been a result of increased recognition of previously undetected problems, lack of a disease-specific protocol or lack of specialist involvement. No other trials specifically addressing increased access to primary care services alone have been performed.

### *Home-based interventions*

Several randomised trials have assessed the effects of home-based multidisciplinary programmes for patients with HF. The first of these studies by Rich et al.<sup>48</sup> demonstrated that a nurse-directed, multidisciplinary intervention reduced hospital admissions and improved quality of life (QOL) in high-risk, elderly patients with HF. Subsequent studies, involving a wider range of lower risk patients with HF, have shown similar results, with reduced hospital readmissions and improved QOL.<sup>49-51</sup> Overall, the data from these studies suggest that home-based, nurse-directed management programmes can have a significant impact for patients with HF. Home visits appear to be an important part of the design of these programmes. Many patients with HF are elderly and access to hospital-based clinics may be difficult. Home visiting allows the provision of education and other strategies within the context of the patient's own surroundings and allows tailoring of the programme to the individual patient.

Further benefit may be achieved by strategies that combine hospital- and home-based interventions. For example, a study of nurse-directed hospital discharge planning and subsequent home follow-up of elderly patients, including those with HF, showed that hospital readmissions were reduced over 6 months of follow-up.<sup>52</sup>

### *Hospital-based interventions*

Hospital discharge planning alone has been shown to decrease hospital readmissions in short-term follow-up (6 weeks),<sup>53</sup> although the effects of this intervention did not appear to be sustained. These results were reinforced by the finding of a virtual elimination of hospital readmissions in management and control groups in a management study that involved careful stability criteria before hospital discharge.<sup>54</sup> Three randomised controlled trials have assessed the effect of predominantly hospital-based out-patient management programmes for patients with HF.<sup>54-56</sup> Overall, the hospital outpatient-based management interventions alone appear to be less effective than the home-based or integrated care programmes. Such interventions may need to include intervention during the initial hospitalisation, involvement of primary care, and home visiting.

### *Integrating management with secondary care, primary care and the patient*

Two randomised trials have specifically addressed the issue of integrated management involving the patient with primary and secondary care.<sup>57, 58</sup> The first of these trials involved 197 patients admitted to hospital with an exacerbation of HF.<sup>57</sup> The management approach involved integration of care between a hospital HF clinic (with nurse specialist and cardiologist), the patient's general practitioner and the patient/family. Education, follow-up and support were key components of the study. This intervention did not decrease the time to first readmission for the combined endpoint of death and all-cause readmission, but there were significant improvements in QOL and a 26% reduction in total hospital admission rate.

The study by Kasper et al.<sup>58</sup> used a similar approach, with a multidisciplinary team of a HF nurse, cardiologist, another nurse to coordinate telephone follow-up and the primary care practitioner. The inclusion criteria for this study selected patients at high risk for readmission, using one or more clinical criteria such as age >70 years, LVEF <35%, aetiology of HF, severe hypertension, one prior admission for HF in the last year and other clinical markers. This study was unique in that the HF nurse was able to initiate and titrate pharmacological therapy. The primary outcome of the number of deaths and HF readmissions over 6 months was reduced from 72 in the control group to 50 in the intervention group. This result, while clinically

meaningful, only reached a p value of 0.09. QOL and percentage of patients receiving target dosages of HF therapy and adhering to dietary recommendations were significantly improved with the intervention.

The data from these two studies are consistent, showing reduced readmissions and improved QOL. Cost analyses from these studies suggest that, overall, this benefit is cost-neutral over 6-12 months of follow-up.<sup>57, 58</sup>

### **Telemonitoring or structured telephone support (remote monitoring)**

Telemonitoring refers to the transfer of physiological data such as blood pressure, weight, ECG and oxygen saturation through telephone or digital cable from home to healthcare provider. An alternative approach is structured telephone support between patients and healthcare provider(s) which may or may not include transfer of physiological data. Two systematic reviews of telemonitoring interventions for HF have been performed.<sup>59, 60</sup> The most recent of these combined 14 randomised controlled trials, involving 4,264 patients: 4 trials involved telemonitoring, 9 trials structured telephone support, and 1 trial both interventions.<sup>59</sup> These interventions reduced all-cause mortality (risk reduction 0.8, 95% CI 0.69-0.92), and reduced HF readmissions (risk reduction 0.79, 95% CI 0.69-0.89).

In summary, remote monitoring reduces all-cause mortality and HF readmissions, although it does not decrease all-cause admissions. QOL, costs, and patient/provider acceptability are infrequently reported in these studies. Telemonitoring is a means of systematically organising effective care, and it is likely that a significant part of the effects are associated with triage of patients by telemonitoring nurse at first signs of worsening HF and intervention thereafter by primary care physician.

### **Self management and educational support**

Self-management programmes aim to enable patients to assume a primary role in managing their condition, including, for example, monitoring their own symptoms, adjusting medications and deciding when additional medications may be required. Self-management strategies are commonly incorporated into multidisciplinary interventions and telemonitoring. However, some studies have specifically addressed self management alone, the results from which have been incorporated in a recent systematic review that reported the impact of self management for patients with congestive HF.<sup>61</sup> This review identified 6 randomised controlled trials involving 857 patients: there was no reduction in all-cause mortality (odds ratio [OR] 0.93, 95% CI 0.57-1.51; p=0.76), although there were significant reductions in all-cause (OR 0.59, 95% CI 0.44-0.80; p=0.001) and HF-specific readmissions (OR 0.44, 95% CI 0.27-0.71; p=0.001). The main limitation of these data is that there are relatively few trials with small numbers of patients from which to draw firm conclusions.

Since these meta-analyses were published, there have been few other studies assessing management strategies for patients with HF. The Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart failure (COACH) trial involved 1023 patients who were randomised to either continue under the care of a cardiology clinic, or to one of two intervention programmes consisting of education and support from a nurse.<sup>62</sup> During the 18 months of the study there were no differences between the 3 groups of patients in the combined endpoint of death or HF readmission, or in all-cause mortality. This study may have been confounded by the nature of the intervention design, with all patients continuing under specialist follow-up, and thus potentially receiving additional care to that which would have been provided in other settings. The implications of the results from this study are uncertain, given these methodological limitations. However, it does reinforce the need to carefully consider the structure of planned interventions in detail to maximise clinical benefit.

### **Social Support**

In most HF disease management programmes it is recognised that support resources for patients with HF are important. A recent overview of the literature regarding the impact of social support for patients with HF has been undertaken.<sup>63</sup> This analysis identified 17 studies that

investigated the relationship between social support and different clinical outcomes in patients with HF. Data from the studies were not formally combined, instead summary conclusions were made based on groupings of the studies. Several studies found relationships between social support and hospital readmissions and mortality, although relationships with QOL were less certain. However, it is difficult to draw firm conclusions regarding the impact of social support alone on clinical outcomes for patients with HF due to the relatively sparse literature in this area. This analysis was limited in its ability to draw more definitive conclusions due to the inadequate trial data in this area.

## **Non-Pharmacological Management**

### **Introduction**

Non-pharmacological interventions are an important component of HF management. These interventions relate to the patient understanding their condition, symptom recognition and control, and understanding that their treatment often involves the use of complex drug regimes, diet and other lifestyle modification. This requires the patient to acknowledge, understand and take ownership of their condition, and manage it to slow progression of the disease.

### **Patient self-care management**

Self-care management support is an important element of high-quality care for the HF patient as discussed in the previous section. Patient self-care includes a range of actions aimed at maintaining clinical stability, avoiding behaviours that worsen the condition and detecting early symptoms of deterioration.<sup>64</sup> Self-care can significantly improve symptoms, functional capacity, well-being and outcomes. Effective self-care behaviours require education and counselling from healthcare professionals.<sup>65</sup> Evidence suggests that programmes teaching self-management skills are more effective than information-only patient education in improving clinical outcomes.<sup>66</sup>

Effective communication between providers and patients is at the centre of any HF self-management intervention. It is only through effective communication that health professionals can determine the level of patient understanding, educate appropriately and empower the patient to achieve sustained behavioural change where appropriate. Behavioural changes might include the use of cognitive behavioural therapy, health beliefs model and motivational interviewing. However, it is important to appreciate that some patients with HF may have cognitive impairment that could include memory and attention deficit.

Recommendations related to self-care management are generally derived from expert consensus opinion rather than documented evidence. Many aspects of self-care management are incorporated into the HF management programmes (see Management Programmes section of this guideline).

### **Communication and discussion of prognosis**

Patients and their families or caregivers should be educated regarding the cause of HF, why symptoms occur, rationale for drug treatment, self-care measures and prognosis. Psychological adaptation may be as important for the patient as aspects of physical functioning.<sup>67</sup> It is important that patients and their families understand the prognosis of HF; this can enhance adherence to treatment and assist decisions about future plans. In advanced cases, practitioners should discuss patients' healthcare preferences and desires regarding resuscitation.

The sub sections following are set out in-line with the patient hand book "Staying well with heart failure" and not necessarily in order of importance.

## Provide structured education and support

### Recommendations

**Self-management initiatives, either individually or in groups, can improve adherence to treatment and outcomes in patients with heart failure.**

*Level of evidence II: Grade of recommendation C*

### Clinical Practice Points

- A structured and supported programme is the standard strategy for all patients.
- Ideally a structured and supported programme would be delivered by health professionals trained in heart failure management.
- Heart failure nurse specialists can provide important support for education of patients with heart failure. With support and training, primary care nurses are well placed to deliver a structured programme of education. Resources such as the Heart Foundation's "Staying well with heart failure" can facilitate effective patient education and enhance self-management.
- Where possible the family/whanau should be included in a structured and supported education programme.

Good adherence to treatment can improve well-being, morbidity and mortality in patients with HF.<sup>68</sup> However, only 20-60% of patients adhere to prescribed treatment<sup>69, 70</sup> and many misunderstand or cannot recall recommendations on management.<sup>71</sup> Strong relationships between healthcare professionals and patients, as well as active social support, can improve adherence. Family participation in patient education programmes is recommended. Patients should be educated about the beneficial effects, side effects and dosages of their medications. The time course and delay of the beneficial effects of standard combination therapy should also be understood.

## Symptom recognition and weight monitoring

### Recommendations

**Weight monitoring is advised as part of regular self-care management programmes in patients with heart failure.**

*Level of evidence III-3: Grade of recommendation C*

### Clinical Practice Points

- Provide educational material that helps the patient understand their condition and related symptoms.
- Patients should weigh themselves on a regular basis, preferably daily and at the same time of day, in order to assess their condition and gain an indication as to when they should seek medical intervention.
- Provide a clear action plan as to when a patient should seek medical help in the face of deteriorating symptoms such as weight gain, shortness of breath, peripheral oedema, or other symptoms.

Symptoms of deterioration in HF can vary considerably between patients.<sup>72</sup> Increases in body weight in many patients are associated with fluid retention and deterioration. Patients and caregivers should learn to recognise symptoms of deterioration, and patients should weigh themselves to monitor weight change as part of a regular daily routine. A suitable target weight range should be decided after clinical assessment by a health professional. In the case of unexpected weight gain over 2-3 days, patients should be advised on appropriate action

including who to contact for review. Some patients may be able to self-titrate diuretics in response to weight change. However, specific advice and the appropriate management plan should be individualised for each patient.

## Adherence to drug treatment

### Recommendations

All patients should understand the reasons for taking their prescribed drugs, the dosing and potential side effects.

*Level of evidence IV: Grade of recommendation C*

### Clinical Practice Points

- Patients should be given clear written information on all drugs.
- Patients should be asked on subsequent visits whether they believe they are experiencing any adverse side effects, and whether they have missed any doses of their medication.
- Patients should be asked whether they are taking any un-prescribed/herbal medications.
- Patients should be advised about the use of analgesics. In particular the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with heart failure may be associated with adverse effects and is generally contraindicated.

Adherence to prescribed drugs can be as low as 20% after two years and many patients do not have a clear understanding of the importance or rationale for taking their drugs. A chronic care programme that includes individualised education and related written documentation has proven to make a significant difference to adherence rates. However, this may be challenging in patients with cognitive impairment, or the 20% of New Zealand adults who are illiterate.

## Smoking

### Recommendations

An ABC approach to smoking cessation should be used for all patients with heart failure who smoke.

*Level of evidence IV: Grade of recommendation C*

### Clinical Practice Points

- All patients should be asked if they smoke.
- If they do, brief advice should strongly encourage the patient to quit.
- Patients should be referred to smoking cessation services and appropriate treatment prescribed (refer to NZ Smoking Cessation Guidelines; [www.moh.govt.nz](http://www.moh.govt.nz)).
- If the spouse, partner and/or family/whanau smoke, they should also be strongly encouraged to stop smoking to avoid the risk to the patient of secondhand smoke and to avoid undermining any cessation attempts by the patient.

The effects of smoking cessation have not been evaluated prospectively in patients with HF. However, observational studies support the relationship between smoking cessation and decreased morbidity and mortality.<sup>73, 74</sup> It is recommended that patients be motivated to stop smoking and receive appropriate support for cessation. Further information on smoking cessation can be obtained from the NZ Smoking Cessation Guidelines 2007 ([http://www.nzgg.org.nz/guidelines/0148/nz\\_smoking\\_cessation\\_guidelines.pdf](http://www.nzgg.org.nz/guidelines/0148/nz_smoking_cessation_guidelines.pdf))

## Immunisation

### Recommendations

Influenza and pneumococcal vaccination should be considered for all patients with heart failure.

*Level of evidence IV: Grade of recommendation C*

### Clinical Practice Points

- A yearly patient recall should be entered into the ‘patient management system’ that flags when an annual immunisation is due.

Annual influenza vaccination, and pneumococcal vaccination, is recommended for patients with HF without contraindications.<sup>75</sup>

## Diet, nutrition and fluids

### Recommendations

Dietary sodium should be restricted, excessive fluid intake avoided and alcohol intake limited in patients with heart failure.

*Level of evidence IV: Grade of recommendation C*

### Clinical Practice Points

- In general, strict fluid restriction in all patients with mild to moderate heart failure does not appear to confer clinical benefit; however, patients should be advised to avoid excessive fluid intake
- Patients should be advised how to assess the salt content in foods by reading food labels and advised to avoid foods that have high salt content.
- Practical ways to avoid salt include:
  - reducing commercially prepared, processed or instant foods;
  - avoid adding salt when cooking;
  - avoid adding salt to food on the table.
- Advise moderate alcohol intake of only 1-2 glasses of wine per day or equivalent or, in cases of alcohol-induced cardiomyopathy, abstinence.

A healthy, balanced dietary pattern is important for patients with HF. Dietary sodium restriction is generally recommended, particularly when diuretic requirements are high. Excessive intake of salt should be avoided and patients should be educated about the salt content of common foods. Fluid restriction, to 1.5-2 L/day, may be required in patients with severe HF and especially in those with hyponatremia. Alcohol intake should be limited to 1-2 drinks per day and abstinence is very important for patients with alcohol-related cardiomyopathy.<sup>76</sup> Prevention of malnutrition can become increasingly relevant in advanced HF.

## **Exercise**

Meta-analyses<sup>77-80</sup>, systematic reviews (SRs)<sup>81, 82</sup> and one large randomised controlled trial (RCT)<sup>83, 84</sup> assessing the efficacy of exercise training in patients with HF report improvements in exercise capacity, and health-related quality of life (HRQOL). Effects of exercise on major clinical endpoints (death and all-cause readmission to hospital) are less certain with, at best, a modest benefit.<sup>80, 85</sup>

The following recommendations are considered to be appropriate for the New Zealand population and, where possible, are evidence based. Recommendations with lower levels of evidence grading are made with consideration of an individual's safety and are to some degree pragmatic to enhance implementation and maintenance of an exercise programme. For the purposes of these guidelines, physical activity is defined as "any bodily movement produced by skeletal muscles that results in energy expenditure beyond resting expenditure".<sup>86</sup> In contrast, exercise is defined as "a subset of physical activity that is planned, structured, repetitive, purposeful in the sense that improvement or maintenance of physical fitness is the objective".<sup>86</sup>

### **Patient selection**

In general, "stable HF" refers to patients who have stable cardiac symptoms, and who are receiving optimal HF therapy (see pharmacotherapy/device-based therapies recommendations). Patients should be referred to an exercise programme after assessment by an appropriate health professional (e.g. medical practitioner, HF nurse specialist) providing the patient is stable. Patients with stable HF who present with absolute contraindications (Table 5) should not participate in an exercise programme, while those with relative contraindications (Table 5) to exercise may be able to participate in exercise training if the benefits outweigh the risks (medical review recommended).

**Table 5. Contraindications to exercise training.**

<b>Absolute contraindications to exercise training:</b> <sup>87</sup>
<ul style="list-style-type: none"><li>• Progressive worsening of exercise tolerance or shortness of breath at rest or on exertion over the prior 3-5 days;</li><li>• Significant ischaemia at low rates (&lt;2 metabolic equivalents [METS], ≈50 watts [W]);</li><li>• Uncontrolled diabetes;</li><li>• Acute systemic illness or fever;</li><li>• Recent embolism;</li><li>• Thrombophlebitis;</li><li>• Active pericarditis or myocarditis;</li><li>• Moderate to severe aortic stenosis;</li><li>• Regurgitant valvular heart disease requiring surgery;</li><li>• Myocardial infarction within previous 3 weeks;</li><li>• New-onset AF.</li></ul>
<b>Relative contraindications to exercise training:</b> <sup>87</sup>
<ul style="list-style-type: none"><li>• Worsening fluid retention; for example, ≥2kg increase in body mass over previous 1-3 days;</li><li>• New York Heart Association Functional Class IV;</li><li>• Concurrent continuous or intermittent dobutamine therapy;</li><li>• Decrease in systolic blood pressure with exercise;</li><li>• Complex ventricular arrhythmia at rest or appearing with exertion;</li><li>• Supine resting heart rate ≥100 beats per minute;</li><li>• Pre-existing co morbidities.</li></ul>

### **Specific situations – choice of programme**

Ideally patients with stable HF should participate in a supervised exercise programme. An individualised programme should be prescribed after undertaking a comprehensive assessment incorporating patient values and choice. Where a supervised exercise programme is not available (or a patient chooses not to participate) then patients with stable HF should be encouraged to participate in an individualised, unsupervised, home/community exercise programme.

### **Specific patient groups**

In very sedentary patients, or after an episode of worsening HF or concurrent illness, patients should be provided with written information on maintaining/improving activity and options to progress to a supervised (or unsupervised) exercise programme once their acute episode resolves.

Patients with stable HF who are older adults, who have concurrent diseases, or who have had an implantable cardioverter defibrillator device (ICD) implanted should be strongly considered for exercise programmes during optimisation of medical therapy or when receiving optimal medical therapy.

### **1. Supervised exercise programme**

It is currently not known if there is an ideal range of exercise parameters (Frequency, Intensity, Type and Time [of session]; FITT) for the prescription of exercise for patients with HF. The recommendations below have been synthesised from highest quality literature, including systematic reviews and randomised controlled trials. They should be used as a framework for developing an exercise programme and not as an exact prescription. A patient's response during and immediately after an exercise session, and over the next few days, will allow modification of the exercise regime.

The majority of research has focused on the efficacy of aerobic exercise prescription. More recently the use of resistance training in patients with HF (either alone or in addition to aerobic exercise) has been investigated, although at present the evidence to justify the routine inclusion of resistance training is inconclusive.<sup>81</sup> These guidelines have a focus on aerobic prescription but with some statements (including safety) on resistance training, reflecting available data. The benefits of exercise are mainly related to exercise capacity and HRQOL.

## Recommendations

A supervised exercise programme is recommended for all patients with stable heart failure. An individualised exercise programme should be prescribed after undertaking a comprehensive assessment incorporating patient values and choice.

*Level of evidence II: Grade of recommendation B*

## Clinical Practice Points

- A supervised exercise programme is the ideal strategy for all patients with stable heart failure.
- An unsupervised programme may be the most appropriate strategy in a subgroup of patients.
- A comprehensive clinical assessment should be undertaken prior to commencing an exercise programme.
- Patient-centred / “SMART” goals need to be established prior to commencement of an exercise programme, and modified over time as appropriate.
- Provide the patient with information on their exercise programme in an appropriate format, including:
  - the benefits of undertaking exercise;
  - that it is OK, safe and appropriate to feel a little more breathless when exercising;
  - when to stop exercising and seek assistance from a health professional;
  - when not to exercise.
- Incorporate strategies to enhance adherence:
  - value patient choice of exercise;
  - provide a written exercise plan;
  - revisit patient goals and modify as appropriate;
  - encourage maintenance of an exercise diary;
  - ensure a positive and personal message from all health professionals;
  - provide a fun and engaging environment.
- Prescribe an aerobic exercise programme (see below for specifics):
  - follow the FITT strategy;
  - progress exercise training dependent on individual patient response;
  - incorporate home-based exercise component;
  - possible addition of dynamic resistance exercise training, in response to specific testing and patient goals, may be clinically indicated.
- Careful monitoring of patients before, during and after an exercise session is required.
- Prepare for progressing to an unsupervised maintenance home-based/community programme.
- Enable and support progression to a unsupervised home-community based exercise programme:
  - health professional to identify and liaise with local programmes to enhance a smooth and safe transition;
  - consistent positive messages from healthcare providers to encourage exercise as part of daily life;
  - regular review by health professional (e.g. 3-monthly or as clinically indicated) through primary care and other health professionals.
- Exercise programmes should be reviewed, and temporarily stopped or modified, when a patient’s clinical status changes.

## **Expansion of Clinical Practice Points: “How to”**

During a supervised exercise programme, patients with HF are encouraged and supported to integrate exercise into their daily routine. A supervised programme involves face-to-face contact, often in a group environment, with health professionals such as physiotherapists who have expertise in exercise prescription and the management of patients with chronic diseases. Staff-to-patient ratios and staff mix can be variable depending on local clinical environment and facilities. A minimum of two health professionals should be present during a group exercise session. Once the supervised programme has been completed patients should be encouraged to maintain a home- or community-based unsupervised programme.

A comprehensive clinical assessment should be undertaken prior to commencing an exercise programme, this includes assessment of the following:

- absolute and relative contraindication to exercise (Table 5);
- presence of concurrent conditions and their severity;
- current level of activity (using a sub-maximal exercise test such as the Six Minute Walk Test or the Incremental Shuttle Walk Test);
- maximal exercise test (with or without peak oxygen consumption [peak VO<sub>2</sub>]);
- self-reported exercise capacity;
- perceived and actual barriers to exercise.

### **Aerobic training exercise programme prescription**

*Warm up:* 5-10 min; rhythmical action of large muscle groups.

*“F” frequency:* approximately 2-3 supervised sessions per week, progressing to a total of 5-6 days per week (which may include some unsupervised sessions).

*“I” intensity:* 50-75% of peak VO<sub>2</sub>. However, this information is not often directly or readily available in the routine clinical setting. Other methods of intensity assessment that have also been used in research and are commonly used in combination clinically are approximately 11-14 on the Borg Rating of Perceived Exertion (6-20) scale or approximately 50-80% of Heart Rate Reserve (HRR), defined as: [50-80% of (maximum HR – resting heart rate)] + resting heart rate. Note that heart rate-based methods of intensity may not be accurate in patients with more advanced disease, those on beta-blockers, or in patients with an irregular heart rate.

*“T” type:* this should be aerobic exercise, the most common forms of which are walking, circuits, stationary cycling (“exercycle”) and treadmill. Other options include functional activities such as step-ups, with progress to stair climbing.

*“T” time of session:* aim for 30-40 minutes of continuous exercise. At the initiation of a new programme, short intervals (“snacks”) of 2, 3 or 5 minutes are appropriate, progressing to more continuous exercise.

*Cool down:* approximately 5-10 minutes.

The programme should be available for about 3-6 months, but needs to be individualised for each patient.

### **Possible addition of resistance training**

If potential muscle weakness is identified as a factor limiting functional activities then further evaluation should be completed, including assessment of absolute and relative contraindications to exercise<sup>88</sup> and assessment of relevant muscle groups using one repetition maximum (1RM).

## **Exercise prescription for resistance training**

Initial prescription for resistance training

*"F"* frequency: 1-2 times per week (avoiding consecutive days).

*"I"* intensity: 40-50% 1RM of 1-2 sets with 5-10+ repetitions per set with at least a 1- to 3-minute rest between sets.

*"T"* type: dynamic resistance (through muscle range using free weights or mechanical resistance for 3-5 muscle groups). Avoid static resistance training and breath-holding.

Muscle strength and ability to complete the desired functional activity need to be reassessed. Progression should consist of an increase in the number of repetitions at the same percentage of 1RM, followed by an increase in the percentage of 1RM (to 60-70%) with a lower number of repetitions then slowly increase number of repetitions.

## **Monitoring**

The following should be assessed prior to each session:

- measure resting blood pressure and heart rate, checking for significant changes;
- undue general fatigue since the last exercise session;
- excessive musculoskeletal soreness since the last exercise session;
- changes in drug regime since the last exercise session;
- signs of worsening HF, including change in symptoms and increasing fluid retention (including weight gain and increased ankle swelling).

Ideally, sore muscles and undue general fatigue should be avoided, but if they do occur, a reduction in the intensity and/or duration of the exercise session is indicated. Patients whose clinical status changes should be reviewed and their exercise programme temporarily stopped or modified.

Monitoring during an exercise session should include:

- supervision to ensure patients do not train above the recommended intensity;
- use of the Borg Rating of Perceived Exertion (6-20) scale;
- detection of a slight increase in breathlessness only; breathlessness should not be excessive;
- detection of slight sweating;
- Talk Test.

In addition, unhealthy competition should be avoided during exercise sessions.

After each exercise session, the patient's heart rate should return to their normal resting level, and appropriate fluid replacement should be encouraged (noting any fluid restrictions).

## **Progression of supervised exercise prescription**

Commencement of programme:

- lower intensity, shorter duration;
- habitually sedentary or severely debilitated persons will need to have a longer warm up, start at a lower intensity, and may benefit from interval training ("snacks").

Improvement:

- when able to complete "dose" of exercise at a lower perceived rating of exertion first increase duration then slowly increase intensity;
- encourage patients to self monitor the intensity of their exercise;
- incorporate pertinent functional activities such as stair climbing and sit to stand;
- introduce and incorporate a home exercise component into the programme (e.g. a progressive walking programme on unsupervised days with self monitoring of intensity).

## **Progression to unsupervised home- or community-based exercise programme**

Discuss potential options with the patient, such as an individual home-based exercise programme, exercising with a friend or like-minded individuals or joining a local community group or gym. It is important to establish patient-centred goals, provide a written exercise programme establishing clear exercise parameters, provide written safety instructions (including when to stop exercising and when to seek professional advice). Health professionals should identify and liaise with appropriate exercise programmes in each patient's local community to enable a smooth and safe transition between programmes. The following groups and resources may be useful:

- Church groups
- Heart Foundation – Affiliated Heart Clubs, [www.heartfoundation.org.nz](http://www.heartfoundation.org.nz)
- SPARC
- Green prescription
- Tai Chi (group/out of house/partially subsided)  
<http://www.acc.co.nz/preventing-injuries/at-home/older-people/information-for-older-people/modified-tai-chi-classes/index.htm>

## **Supporting Evidence**

The supporting evidence for the current recommendation is from several smaller randomised, controlled trials that have been incorporated into systematic reviews and meta-analyses. More recently, one larger randomised, controlled trial has been published. The current recommendations are from a synthesis of all this available evidence, and have considered effects on patient clinical status, HRQOL, as well as more standard endpoints of survival and hospital readmission.

### **Meta-analyses and systematic reviews**

The first systematic review (SR)<sup>82</sup>, including literature up to December 2000, suggested that short-term training in a subgroup of patients with HF had both physiological and HRQOL benefits. Since then six meta-analyses<sup>77-80, 85, 89</sup> and one SR<sup>81, 82</sup> have been conducted. Key characteristics of the meta-analysis and SR's are presented in Appendix 1. In general, the methods were appropriate and transparent, including pre-determined criteria to assess the quality of individual studies. All but one SR<sup>81</sup> and one meta-analysis<sup>78</sup> included studies that used either aerobic or resistance training, or a combination of the two, and did not differentiate in their analysis. It should be noted that some individual studies appear across multiple literature reviews. Many of the analyses identified that the quality of individual studies varied. Study participants were not usually blinded to treatment allocation, as this is difficult to achieve in an exercise intervention study. Across all the analyses there was underrepresentation of females, older adults, and those with concurrent diseases. Descriptions of ethnicity were limited. Interventions were summarised and key parameters of exercise prescription were reported.

The results of the meta-analysis are reported in Appendix 1. Outcome measures consistently identified were exercise capacity (peak VO<sub>2</sub> or VO<sub>2max</sub> and the Six Minute Walk Test), HRQOL, cardiac performance measures, hospitalisation and mortality. Exercise training was consistently associated with significant improvements in peak VO<sub>2</sub>/VO<sub>2max</sub> and distance walked in the Six Minute Walk Test in patients with HF. Overall, exercise training favoured an improvement in HRQOL. Data from these meta-analyses on the effects of exercise on major clinical endpoints such as mortality and hospitalisation are limited due to the relatively small number of patients and events. The most robust meta-analysis<sup>85</sup> reported reduction in mortality and in a combined endpoint of mortality and hospitalisation. Cost effectiveness as an outcome measure was not addressed.

In the majority of individual studies the exercise training was supervised, or initially supervised and then some progressed to home-based with some contact (phone or home visit). At present there is no consensus on exercise prescription parameters. In the majority of the studies patients completed aerobic training 3-5 times per week at a prescribed intensity between 50-

80% of peak  $\text{VO}_2$ , or 50-80% of maximum heart rate reserve; time per session was 30-60 minutes and the average exercise programme duration was three months. One meta-analysis<sup>80</sup> reported that improvements in  $\text{VO}_{2\text{max}}$  were greater for training programmes of higher intensity and longer total length.

With respect to the inclusion of resistance training, one meta-analysis<sup>78</sup> suggested that resistance training alone or in combination with aerobic training does not further improve outcomes under study. This meta-analysis did not address HRQOL or strength/functional related outcomes. Furthermore the most recent SR<sup>81</sup> specifically investigated the efficacy of moderate-to-high resistance training alone or in combination with an aerobic exercise programme. The authors concluded that there was not enough evidence to routinely include resistance training.

In summary, data from meta-analyses and SR's support modest benefits of exercise training on HRQOL and exercise capacity, achieved with an emphasis on aerobic training.

#### **Individual randomised controlled trial**

In addition to the meta-analysis and the SR's, results are available from one recent randomised controlled trial – the HF-ACTION Trial.<sup>83, 84</sup> This study involved 2,331 patients with HF and LVEF  $\leq 35\%$ .<sup>83, 84</sup> Patients were randomised to usual care (including advice to complete 30 minutes of moderate-intensity exercise on most days of the week) or exercise training, which consisted of an initial supervised aerobic exercise programme (36 sessions) that progressed to an unsupervised home exercise programme. Due to the inherent nature of the trial design and intervention, study investigators and patients were not blinded to the intervention allocation. The primary analysis reported no statistically significant effects on the major clinical endpoints of all-cause mortality or all-cause hospitalisation. In a pre-specified supplementary analysis that adjusted for prognostic baseline characteristics there was a modest reduction in all-cause mortality and all-cause hospitalisation which reached statistical significance. In addition, at 3 months there were improvements in exercise capacity (Six Minute Walk Test, peak  $\text{VO}_2$  and exercise time) and in HRQOL in the exercise group compared with the control group.

#### **Summary**

Exercise training in patients with stable HF with low LVEF is associated with a modest improvement of major clinical endpoints including all-cause mortality or hospitalisation, and modest improvements in HRQOL and exercise capacity.

## **2. Specific situations**

Specific situations and specific patient groups require special consideration for recommendations regarding exercise.

### **A. Unsupervised exercise programme**

The majority of evidence supports patients with HF undertaking a supervised (face-to-face) exercise programme for the duration of the programme or being initially supervised then continuing with an unsupervised programme. One meta-analysis partially addressed whether home-based exercise is safe and effective for improving exercise capacity and HRQOL in patients with HF.<sup>77</sup> Five of the included studies initially had a period of supervision and six of the studies maintained contact either by home visits or phone calls. The studies demonstrated that a home-based exercise programme was safe and resulted in improvement in exercise capacity, although there was no effect on HRQOL. In the New Zealand environment, supervised exercise programmes may either not be available or patients may prefer a different environment and chose not to participate in a supervised programme. If either is the case it is recommended that patients ideally would participate in supervised sessions (albeit for a brief time) not only to receive specific individualised advice and enhance understanding, but also to develop self-monitoring strategies before proceeding with unsupervised exercise.

## Recommendations

**Patients with stable heart failure should be encouraged to undertake an individualised, unsupervised home or community exercise programme when a supervised programme is unavailable (or if the patient chooses not to participate).**

*Level of evidence IV: Grade of recommendation D*

## Clinical Practice Points

- A comprehensive clinical assessment should be undertaken prior to commencing an exercise programme.
- Patient-centred / “SMART” goals need to be established prior to commencement of an exercise programme, and modified over time as appropriate.
- Provide the patient with information on their exercise programme in an appropriate format, including:
  - the benefits of undertaking exercise;
  - that it is OK, safe and appropriate to feel a little more breathless when exercising;
  - when to stop exercising and seek assistance from a health professional;
  - when not to exercise.
- Incorporate strategies to enhance adherence:
  - value patient choice of exercise;
  - provide a written exercise plan;
  - revisit patient goals and modify as appropriate;
  - encourage maintenance of an exercise diary;
  - ensure a positive and personal message from all health professionals;
- Prescribe an aerobic exercise programme (see below for specifics):
  - follow the FITT strategy;
  - progress exercise training dependent on individual patient response;
  - incorporate home-based exercise component.
- Facilitate knowledge of self-monitoring strategies:
  - during exercise, ensure training is at the recommended intensity, and not above;
  - post-exercise recovery and rehydration.
- Prepare for, enable and support progression in the exercise programme.

### Expansion of Clinical Practice Points: “How to”

A comprehensive clinical assessment should be undertaken prior to commencing an exercise programme, this includes assessment of the following:

- absolute and relative contraindication to exercise (Table 5);
- presence of co-morbidities and their severity;
- current level of activity (using a sub-maximal exercise test such as the Six Minute Walk Test or the Incremental Shuttle Walk Test);
- maximal exercise test (with or without peak oxygen consumption [peak VO<sub>2</sub>])
- self-reported exercise capacity;
- perceived and actual barriers to exercise.

## **Aerobic training exercise programme prescription**

*Warm up:* 5-10 min; rhythmical action of large muscle groups.

*“F” frequency:* approximately 2-3 times per week initially, progressing to a total of 5-6 days per week.

*“I” intensity:* aim for mild-to-moderate intensity walking – patients should experience a mild increase in breathlessness, but still be able to “walk and talk”. This intensity equates to a score of approximately 11-14 on the Borg Rating of Perceived Exertion (6-20) scale.

*“T” type:* this should be aerobic exercise.

*“T” time of session:* aim for 30 minutes of continuous exercise. At the initiation of a new programme, short intervals (“snacks”) of 2, 3 or 5 minutes are appropriate, progressing to more continuous exercise.

*Cool down:* approximately 5-10 minutes.

### **Self monitoring strategies**

During exercise sessions, ensure patients are training at the recommended intensity and not above:

- Borg Rating of Perceived Exertion (6-20) Scale;
- slight increase in breathlessness only, not excessive breathlessness;
- slight sweating;
- Talk Test.

In addition, unhealthy competition should be avoided during exercise sessions.

After each exercise session, the patient’s heart rate should return to their normal resting level, and appropriate fluid replacement should be encouraged (noting any fluid restrictions).

### **Progression of exercise prescription**

Commencement of programme:

- lower intensity, shorter duration;
- habitually sedentary or severely debilitated persons will need to have a longer warm up, start at a lower intensity, and may benefit from interval training (snacks).

Improvement:

- when able to complete “dose” of exercise at a lower perceived rating of exertion first increase duration (to 40 minutes or more) then slowly increase intensity (to 13-14 on the Borg Rating of Perceived Exertion (6-20) Scale);
- encourage patients to self monitor the intensity of their exercise;
- incorporate pertinent functional activities such as stair climbing and sit to stand.

## **B. After an episode of worsening heart failure or concurrent illness, or in very sedentary patients**

When patients with HF have episodes of worsening disease or exacerbation of another illness they may require hospital admission or a period of “rest” at home. During the episode of care, physical activity can decline which is associated with further general cardiovascular and muscular deconditioning. Once the patient becomes stable, an initial assessment should be completed and appropriate advice given on increasing activity (whilst in hospital or at home). The normally very sedentary patient who undertakes vigorous physical activity may be more at risk of adverse cardiac events.<sup>90</sup> It is therefore of utmost importance that patients are assessed and advised appropriately, slowly increasing their physical activity.

### **Recommendations**

**Written information on maintaining or improving physical activity, and options to progress exercise rehabilitation, should be provided to patients who have experienced an acute episode of worsening heart failure or other illness, or in those who are very sedentary.**

*Level of evidence IV: Grade of recommendation D*

### **Clinical Practice Points**

- Identify the level of current physical activity and the limiting factors.
- Informal assessment of walking:
  - assess patient’s ability to achieve self-reported activity;
  - monitor/identify breathlessness and other limiting factors (e.g. osteoarthritis of the hip).
- Assess the local environment (home and surrounding areas) with respect to the patient’s normal daily activities.
- Provide the patient with information on their exercise programme in an appropriate format, including:
  - the benefits of undertaking exercise;
  - that it is OK, safe and appropriate to feel a little more breathless when exercising;
  - when to stop exercising and seek assistance from a health professional’;
  - when not to exercise.
- Incorporate strategies to enhance adherence:
  - value patient choice of exercise;
  - provide a written exercise plan;
  - revisit patient goals and modify as appropriate;
  - encourage maintenance of an exercise diary;
  - ensure a positive and personal message from all health professionals;
  - provide a fun and engaging environment.
- Initiate physical activity/exercise programme:
  - start slowly, with current walking distance;
  - aim for 20-30 minutes of continuous walking in 1 session.
- Have options for progression:
  - to a supervised (ideal) or unsupervised programme;
  - document the outcome of discussions;
  - provide referrals as appropriate.

## **Expansion of Clinical Practice Points: “How to”**

### **Identification of present activity**

The aim is to identify how much activity the patient is currently undertaking and to identify any limiting factors (e.g. osteoarthritis). This information can be obtained by questioning the patient:

- How far are you walking at present?
- What stops you from doing more? Breathlessness? Legs aching? How long does it take to recover?
- How often are you doing this today?
- Are you using a walking aid at present?
- Do you normally have a walking aid?
- Have you tried any steps? If so, how many steps can you do without stopping?
- Are you showering without help?
- Can you dress without stopping?

In addition, it is important to assess the patient’s usual environment, including their home and sounding area in the context of their ability to achieve normal daily activities. Relevant lead-in questions might include:

- Are there any steps at entry to home?
- Any there any steps inside your home? If yes, how many and where?
- Can you carry something up a flight of stairs without stopping?
- How long is your driveway? Is it flat or on a slope?
- Describe your local area. Is it flat, hilly or a combination?
- Do you have any exercise equipment at home (e.g. a bike)?
- Do you normally garden, rake or weed?
- Do you normally do housework?
- Do you have any hobbies?
- Do you avoid certain activities (e.g. stairs, carrying, vacuuming, walking outside)?

### **Initiating activity/exercise**

The approach taken to increasing physical activity will depend on the patient’s current level of activity. It is recommended that the following steps be followed:

- start with present walking distance (time) + activities (daily);
- slowly increase time (distance) of walking + activities (daily);
- set a walking distance target;
- once the patient can complete the target walking distance comfortably (i.e. with less breathlessness and fatigue) then set a new distance/time target;
- aim for 20-30 minutes of walking in one continuous session.

### **Progression to supervised or unsupervised exercise programme**

This should be discussed with the patient and their relevant support persons. Details of supervised and unsupervised exercise programmes are provided in separate sections of this guideline. The outcome of discussions needs to be documented, with referral provided as appropriate.

### **3. Specific patient groups**

The majority of studies have been undertaken in patients with stable HF of mild-to-moderate severity (NYHA class II–III) who are in their fifth to six decade of life and have no or few concurrent conditions.<sup>77–81, 85, 89</sup> Specific populations of patients with HF have therefore been under-represented in these studies. As a result, it is uncertain whether HF patients who also have concurrent diseases, are older than those studied, or who have undergone implantation of an ICD will have the same response to treatments, in terms of efficacy, tolerability and safety, as patients recruited to participate in clinical trials. However, there is increasing evidence that patients with common concurrent conditions (coronary heart disease, chronic obstructive pulmonary disease, type II diabetes, renal failure, obesity and osteoarthritis), older patients, and those with an ICD also experience positive health improvements when undertaking exercise programmes.

### **Recommendations**

**An exercise programme should be strongly considered for heart failure patients who have concurrent diseases, an ICD or who are of older age, and are receiving optimal medical therapy, or while medical therapy is being optimised.**

**Level of evidence IV: Grade of recommendation D**

### **Clinical Practice Points**

- Refer to Clinical Practice Points for supervised exercise programme.
- Modifications will need to be made when prescribing and monitoring exercise programmes in specific patient groups.
- In heart failure patients with concurrent diseases, identify and liaise with health professional and consumer support organisations as appropriate:
  - Chronic Obstructive Pulmonary Disease – Asthma and Respiratory Foundation of New Zealand ([www.asthmanz.co.nz](http://www.asthmanz.co.nz))
  - Diabetes – Diabetes New Zealand ([www.diabetes.org.nz](http://www.diabetes.org.nz))
  - Renal Failure – New Zealand Kidney Foundation ([www.nzkidneyfoundation.co.nz](http://www.nzkidneyfoundation.co.nz))
  - Osteoarthritis – Arthritis New Zealand ([www.arthritis.org.nz](http://www.arthritis.org.nz))
  - Coronary Heart Disease – National Heart Foundation ([www.heartfoundation.org.nz](http://www.heartfoundation.org.nz))
- In patients who have had an ICD device inserted:
  - the multidisciplinary team should address fear/anxiety, with ongoing encouragement and reassurance during the programme as appropriate.
  - the individual patient's maximal cut-off heart rate should be identified after liaison with appropriate health professionals (cardiologist/cardiac technician/electrophysiologist). For many patients pharmacological management (such as with beta-blockers) will mean that the estimated training heart rate will remain below the maximal cut-off heart rate.
  - if a patient had an ICD inserted <6 weeks ago, the patient's prescribed exercise programme should avoid lifting arms above shoulder level and resistance training.
  - initially a heart rate monitor could be used to identify the patient's heart rate during exercise and then the Borg Rating of Perceived Exertion (6-20) scale can be introduced to reduce the need for a heart rate monitor.
  - six weeks after ICD implantation, the patient should be encouraged gently to obtain a full range of shoulder motion.
- In older adults, identify and liaise with health professional and consumer support organisations as appropriate:
  - Age Concern ([www.ageconcern.org.nz](http://www.ageconcern.org.nz))
  - Osteoporosis New Zealand ([www.bones.org.nz](http://www.bones.org.nz))

## **Supporting Evidence**

### **Older adult patients with heart failure**

A multifactorial approach to the prevention of falls has been recommended<sup>91</sup>, given that approximately 30% of adults aged >65 years will fall in a 12-month period<sup>92</sup> and that HF is associated with an increase risk of fractures, particularly hip fractures.<sup>93</sup> Undertaking an appropriate exercise programme is one component that has been identified as being important in effective fall-prevention strategies. Data from a meta-analysis showed that incorporation of an individually prescribed exercise programme was associated with a 35% reduction in the number of falls and fall-related injuries in older adults.<sup>94</sup>

### **Patients with an implantable cardioverter defibrillator (ICD)**

After the insertion of an ICD some patients may lack confidence to undertake or recommence exercise. One small randomised, controlled, crossover study investigated the effects of a 12-week cardiac rehabilitation programme in patients who had received an ICD.<sup>95</sup> Reported benefits compared with baseline included an improvement in exercise duration, a reduction in the Hospital Anxiety and Depression scale scores, and no ICD discharges during exercise sessions. In addition, the HF-ACTION randomised controlled trial provided more reassurance on the safety of exercise training in HF patients with an ICD.<sup>83</sup> Of the participants allocated to supervised exercise training, 42% had an ICD in place and only one had an ICD discharge which meant they did not reach target exercise parameters.

### **Patients with concurrent diseases**

Patients with HF often have multiple coexisting medical conditions, the number and complexity of which may increase with increasing age.<sup>96, 97</sup> Common concurrent conditions in patients with HF include chronic obstructive pulmonary disease and diabetes. To locate consumer and health professional information see Clinical Practice Points above. Table 6 identifies SR's regarding exercise rehabilitation in specific subgroups of patients that are commonly present in patients with HF.

**Table 6. Systematic reviews of the efficacy of exercise in patients with concurrent disease**

<b>Chronic Obstructive Pulmonary Disease</b>
<ul style="list-style-type: none"><li>Lacasse Y, Goldstein R, Lasserson TJ, &amp; Martin S. (2006). Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2006, Issue 4. Art. No.: CD003793. DOI: 10.1002/14651858.CD003793.pub2.</li></ul>
<b>Type II Diabetes</b>
<ul style="list-style-type: none"><li>Thomas, D., Elliott, E., &amp; Naughton, G. (2006). Exercise for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD002968. DOI: 10.1002/14651858.CD002968.pub2</li></ul>
<b>Renal Failure</b>
<ul style="list-style-type: none"><li>Cheema, B., &amp; Singh, M. (2005). Exercise training in patients receiving maintenance haemodialysis: A systematic review of clinical trials, American Journal of Nephrology, 25, 352-364.</li></ul>
<b>Osteoarthritis</b>
<ul style="list-style-type: none"><li>Lange, A., Vanwanseele, B., &amp; Singh, M. (2008). Strength training for treatment of osteoarthritis of the knee: A systematic Review. Arthritis and Rheumatism, 59, 1488-1494.</li><li>Hernandez-molina, G., Reichenbach, S., Zhang, B., Lavalley, M., &amp; Felson, D. (2008). Effect of therapeutic exercise for hip osteoarthritis pain: Meta-analysis. Arthritis and Rheumatism, 59, 1221-1228.</li></ul>
<b>Coronary Heart Disease</b>
<ul style="list-style-type: none"><li>Jolliffe J, Rees K, Taylor RRS, Thompson DR, Oldridge N, &amp; Ebrahim S. (2001). Exercise-based rehabilitation for coronary heart disease. Cochrane Database of Systematic Reviews Issue 1. Art. No.: CD001800. DOI: 0.1002/14651858.CD001800.</li></ul>
<b>Obesity</b>
<ul style="list-style-type: none"><li>Shaw KA, Gennat HC, O'Rourke P, &amp; Del Mar C. (2006). Exercise for overweight or obesity. Cochrane Database of Systematic Reviews Issue 4. Art. No.: CD003817. DOI: 10.1002/14651858.CD003817.pub3.</li></ul>

## **Pharmacotherapy**

Much of the evidence underpinning the recommendations for treating patients with HF comes from randomised controlled clinical trials that have involved patients with HF with impaired LV systolic function (typically LVEF <35-45%). Evidence-based recommendations for this group of patients includes pharmacotherapy (with ACE inhibitors, ARBs, beta-blockers and aldosterone antagonists), and device-based therapies (including implantable defibrillators and biventricular pacing). However, 30-50% of patients with the syndrome of HF will have relatively normal LV function; so called “HF with preserved LVEF”. To date, the results of randomised trials of pharmacotherapy in this patient group have been disappointing. As a consequence, the recommendations for treating patients with HF and preserved LV function are largely consensus opinion, rather than evidence based.

# Pharmacotherapy for patients with heart failure and low LVEF (LV systolic dysfunction)

## Angiotensin-converting enzyme (ACE) inhibitors

ACE inhibitors improve symptoms of HF, decrease hospital admissions, and improve LV function and survival. ACE inhibitor therapy can also prevent progression to HF in patients with asymptomatic LV dysfunction and should therefore be used early in the course of the disease.

### Recommendations

**Angiotensin-converting enzyme inhibitor treatment in appropriate doses should be considered in all patients with heart failure due to LV systolic dysfunction (LVEF <45%).**

*Level of evidence I: Grade of recommendation A*

### Clinical Practice Points

- Consider a low starting dose (e.g. captopril 6.25mg, enalapril 2.5mg) and titrate up to the doses used in randomised, controlled trials (recommended doses: captopril 50mg three times daily; enalapril 10mg twice daily; cilazapril 5mg once daily; quinapril 10mg twice daily). Higher doses may be indicated for some patients (e.g. those with coexisting hypertension).
- Hypotension may occur after the first dose of ACE inhibitors especially if there is pre-existing hypotension, hyponatraemia, or over-diuresis.
- Monitor blood pressure, serum potassium and renal function (prior to starting therapy, and approximately one week after initiation or a change in dose).
- Contraindications to ACE inhibitors:
  - prior ACE inhibitor intolerance;
  - symptomatic hypotension;
  - angioedema (prior angioedema with an ACE inhibitor is an absolute contraindication);
  - serum potassium >5.5 mmol/L;
  - severe aortic stenosis;
  - bilateral renal artery stenosis;
  - serum creatinine >250 µmol/L should trigger assessment of other potentially nephrotoxic drugs, urinalysis, and renal ultrasound with referral to a renal physician prior to commencing an ACE inhibitor where a readily reversible cause of renal impairment is not apparent. Where renal failure is associated with proteinuria, ACE inhibitor therapy slows the rate of progression to end-stage renal failure.
- ACE inhibitor-related cough: a dry, irritating cough may occur with ACE inhibitors. If this recurs on re-challenge then the patient may be eligible for an ARB (losartan or candesartan; refer to PHARMAC Special Authority Criteria for funded access).
- Worsening serum creatinine during treatment may require ACE inhibitor and/or diuretic dose reduction.
- Concomitant use of diuretics is usually required for management of fluid overload.

### Supporting Evidence

The ACE inhibitor enalapril has been shown to reduce mortality in patients with moderate and severe HF in the SOLVD<sup>98</sup> and CONSENSUS<sup>99</sup> trials, respectively. The relative risk reduction versus placebo over 12 months was 31% (absolute risk reduction of 16%) for those with severe HF. In those with mild HF the overall relative risk reduction for enalapril recipients compared with placebo was 16% (absolute risk reduction of 4.5%); the greatest risk reduction in these patients (23%) was seen at 12 months. The survival curves indicate that treatment with enalapril increases survival by approximately 6 months. The effect of captopril on survival in patients with clinical HF has not been studied. Captopril has been shown to improve survival in

the early post-myocardial infarction setting in the presence of reduced LVEF.<sup>100, 101</sup> It is likely that the effects of ACE inhibitors in HF are a class effect and thus no specific ACE inhibitor is recommended.

Both enalapril and captopril have been shown to improve functional status in 40-80% of patients.<sup>98, 99, 102</sup> The average improvement was 0.5-1 NYHA functional class.<sup>30</sup> The SOLVD trial showed a modest reduction in hospitalisation for those with mild to moderate congestive HF (relative risk reduction of 9.5%).<sup>98</sup>

Symptoms are common in HF, but cough and dizziness are slightly (and significantly) more common with ACE inhibitors. In the SOLVD trial 87% of enalapril recipients experienced side effects and the corresponding rate for placebo recipients was 82%.<sup>98</sup> The most common symptoms are dizziness due to hypotension, and cough. The actual average changes in blood pressure are modest, a decrease in systolic blood pressure of 5 mmHg. Symptomatic hypotension is more common in patients who have been over-diuresed, or are hypotensive to begin with. In the CONSENSUS trial (severe HF), 5.5% of patients were withdrawn because of symptomatic hypotension.<sup>99</sup> In general, systolic blood pressure >90 mmHg, without postural hypotension, is acceptable.<sup>103</sup>

Cough is common with ACE inhibitors, but also occurs frequently in patients with HF. It was reported in 37% of patients taking enalapril in the SOLVD trial, and in 31% of those taking placebo. A patient presenting with cough should be carefully assessed for signs of increasing congestion before the cough is attributed to ACE inhibitor therapy. Many patients with a cough attributed to ACE inhibitor therapy can continue with treatment if the cough is not severe and the benefits of treatment are explained.

## Diuretics

Diuretics should be used for the symptomatic relief of pulmonary and systemic venous congestion.

### Recommendations

**Diuretic therapy should be started in patients with heart failure and clinical signs of fluid overload.**

**Level of evidence III-3: Grade of recommendation C**

### Clinical Practice Points

- Target doses of diuretics depend on the identification of a “dry” (or target) body weight.
- Patients should receive appropriate education regarding self-management with body weight monitoring when diuretics are used.
- Adjustment of diuretic dose will depend on a patient’s symptoms and degree of fluid retention (consider target weight to help gauge diuresis).
- Aim to use the minimum diuretic dose required to maintain optimal fluid status (in particular, avoid dehydration from over-diuresis).
- Monitoring of serum creatinine and electrolytes is required during diuretic use; frequency of monitoring will depend on the clinical status of the individual patient.
- Diuretics cause activation of the renin-angiotensin-aldosterone system in patients with mild symptoms of heart failure and thus should be used in combination with an ACE inhibitor.

### Supporting Evidence

There are no data regarding the effects of loop or thiazide diuretics on mortality in patients with HF. However, trials of ACE inhibition, beta-blockade and spironolactone have all been undertaken with the majority of patients receiving background loop diuretic therapy and hence their efficacy is proven as additions to diuretics rather than as lone therapies. There are few studies of the optimal diuretic therapy for HF, and dose requirements may vary depending on the patient’s needs. In mild HF a thiazide may be sufficient (e.g. bendrofluazide 2.5-5mg daily initially).<sup>104</sup>

In general a loop diuretic will be required in moderate or severe HF, or if the patient has failed to respond to thiazide diuretics (e.g. frusemide 40mg daily initially). If the initial dose proves inadequate, greater diuresis is achieved by doubling the dose, with the most benefit seen when the higher dose is given once daily rather than in two divided doses. Diuretic use should be combined with careful clinical monitoring, which usually includes the patient monitoring their own body weight.

A thiazide may be used together with loop diuretics for resistant oedema, but only with extreme caution as this combination can induce profound diuresis.

It is essential to monitor serum potassium, sodium and creatinine levels during diuretic use, usually at least every 3 months, but more frequently during initiation of therapy.

### Diuretics and ACE Inhibitors

Volume depletion from over-diuresis may increase the risk of first-dose hypotension when starting ACE inhibitor therapy. Therefore it is very important to avoid excessive diuresis prior to starting ACE inhibitor therapy. If an ACE inhibitor is used with a diuretic then potassium replacement will generally not be required. Serious hyperkalaemia can occur if potassium-sparing diuretics are used in combination with ACE inhibitors; this combination should only be used under careful supervision (see section regarding use of spironolactone).

## **Angiotensin receptor blockers (ARBs)**

ARBs block angiotensin II type 1 receptors and therefore inhibit the renin-angiotensin-aldosterone system at a point beyond the angiotensin-converting enzyme. ARBs have two main potential areas of use in patients with HF: either as an alternative drug for patients who experience ACE inhibitor-related cough, or in addition to ACE inhibitors in patients with LV systolic dysfunction (LVEF <45%).

### **1. ARBs for patients who cannot tolerate ACE inhibitors due to cough**

#### **Recommendations**

**ARBs should be considered for patients with heart failure and LV systolic dysfunction (LVEF <45%) who are not able to tolerate an ACE inhibitor due to cough.**

***Level of evidence II: Grade of recommendation A***

#### **Clinical Practice Points**

- Cough is common in patients with heart failure and before the cough is attributed to the ACE inhibitor the patient should be carefully assessed for clinical signs of worsening congestion and treated appropriately.
- Initiation of an ARB will depend on the clinical setting:
  - for patients who have not been taking an ACE inhibitor, consider a low starting dose (e.g. candesartan 4-8mg daily, losartan 12.5mg daily) and titrate the dose approximately every 2 weeks (target doses: candesartan 32mg daily, losartan 50mg daily);
  - for patients already receiving an ACE inhibitor, it may be possible to start ARB therapy at a higher dose. This should be individualised for each patient;
  - monitor blood pressure, serum potassium and renal function: prior to starting therapy, and then usually approximately one week after initiation or a change in dose.
- Contraindications to ARBs:
  - prior intolerance of ARB;
  - symptomatic hypotension (consider if reduction in other blood pressure-lowering agents including diuretics, nitrates and calcium antagonists may subsequently allow introduction of ACE inhibitors);
  - serum potassium >5.5 mmol/L;
  - serum creatinine >250 µmol/L (some patients with renal failure may tolerate an ARB but specialist referral is recommended);
  - severe aortic stenosis;
  - bilateral renal artery stenosis.

Losartan and candesartan are currently available (2010) under Special Authority for patients who have been treated with and cannot tolerate an ACE inhibitor due to persistent cough, or if the patient has had angioedema. The current special authority criteria require re-challenge with an ACE inhibitor before approval. In addition, losartan is available under special authority where a “patient is not adequately controlled on maximum tolerated dose of an ACE inhibitor”. Applications can be submitted by any relevant practitioner on the appropriate form which can be accessed at: <http://www.pharmac.govt.nz/Schedule/SAForms>.

#### **Supporting Evidence**

ACE inhibitors and ARBs both inhibit the effects of angiotensin II, but have different mechanisms of action. Cough is a common side effect of ACE inhibitors, but is also common in patients with HF (for example, cough was reported in 37% of those taking enalapril and 31% of those taking placebo in the SOLVD trial).<sup>98</sup> A patient presenting with cough should be carefully assessed for signs of increasing congestion before the cough is attributed to ACE inhibitor therapy. Many patients with a cough attributed to ACE inhibitor therapy can continue with

treatment if the cough is not severe and the benefits of continuing ACE inhibitors are explained. If the cough requires discontinuation of therapy, then an ARB is a suitable alternative.

Initial trials demonstrated that the ARB candesartan was well tolerated, and improved symptoms and exercise capacity in patients with HF with LV systolic dysfunction (LVEF <45%) who were not receiving ACE inhibitors.<sup>105, 106</sup> The CHARM-Alternative Trial was designed to determine whether the ARB candesartan improved outcome in patients with HF with LV systolic impairment who were not taking an ACE inhibitor. CHARM-Alternative enrolled 2,028 patients with HF and LVEF <40%, who were not taking an ACE inhibitor due to prior intolerance (three-quarters of which was due to ACE inhibitor-related cough). Patients were randomised to receive candesartan (target dose 32 mg/day) or placebo and followed for a median of 33 months. The primary endpoint of cardiovascular death or hospital admission for HF occurred in 334 (33%) patients receiving candesartan compared with 406 (40%) patients receiving placebo (hazard ratio 0.70 (95% CI 0.60-0.81), p=0.0004; ARR 7%, NNT = 14). Study drug discontinuation rates were similar in the two treatment groups (candesartan 30% versus placebo 29%). In summary, the CHARM-Alternative trial has demonstrated that clinical outcomes are improved with the use of candesartan for patients with HF and LV systolic dysfunction. The ELITE studies compared captopril and losartan in elderly patients with HF and indicated non-inferiority of ARB's with respect to mortality, plus superior tolerability.<sup>107, 108</sup>

While the trial data reported above are for candesartan, it is reasonable to consider that the benefits are a class effect of the ARBs. Therefore, no specific ARB is recommended in this guideline. The Pharmaceutical Management Agency of New Zealand (PHARMAC) Special Authority criteria need to be fulfilled for candesartan or losartan to be available with appropriate funding. The special authority criteria are updated regularly and can be accessed at:  
<http://www.pharmac.govt.nz/Schedule/SAForms>

## 2. ARBs in addition to ACE inhibitors for patients with heart failure and LV systolic dysfunction

### Recommendations

ARBs may be considered for patients with heart failure with LV systolic dysfunction (LVEF <45%) who remain symptomatic despite appropriate treatment with ACE inhibitors and beta-blockers. Extra caution, with monitoring for adverse effects, is required.

*Level of evidence II: Grade of recommendation A*

### Clinical Practice Points

- It is recommended that patients are treated with optimal doses of ACE inhibitors and beta-blockers prior to considering the addition of an ARB.
- Patients on concomitant spironolactone may be at higher risk of hyperkalaemia, and ARB/ACE inhibitor combination therapy should only be used with extreme caution in such patients.
- Contraindications to ARBs:
  - prior intolerance of ARB;
  - symptomatic hypotension;
  - serum potassium >5.5 mmol/L;
  - serum creatinine >250 µmol/L (some patients with renal failure may tolerate an ARB but specialist referral is recommended);
  - severe aortic stenosis;
  - bilateral renal artery stenosis.
- Losartan and candesartan are currently available (2010) under Special Authority for patients who have been treated with and cannot tolerate an ACE inhibitor due to persistent cough, or if the patient has had angioedema. The current special authority criteria require re-challenge with an ACE inhibitor before approval. In addition, losartan is available under special authority where a “patient is not adequately controlled on maximum tolerated dose of an ACE inhibitor”. Applications can be submitted by any relevant practitioner on the appropriate form which can be accessed at: <http://www.pharmac.govt.nz/Schedule/SAForms>.

### Supporting Evidence

Angiotensin II can be produced by non-angiotensin-converting enzyme pathways in patients with HF, and angiotensin II levels may remain high despite treatment with an ACE inhibitor. Therefore, trials have addressed the role of combined therapy with both ARB and ACE inhibitors in patients with HF with LV systolic dysfunction.

The CHARM-Added Trial was designed to determine whether the ARB candesartan improved outcome in patients with HF with LV systolic impairment who were already treated with an ACE inhibitor.<sup>109</sup> CHARM-Added enrolled 2,548 patients with HF and LVEF <40%, who were already treated with an ACE inhibitor. Patients were randomised to receive candesartan (target dose 32 mg/day) or placebo and followed for median of 41 months. The primary endpoint of cardiovascular death or hospital admission for HF occurred in 483 (38%) patients receiving candesartan compared with 538 (42%) patients receiving placebo (adjusted hazard ratio 0.85, 95% CI 0.75-0.96, p=0.0004; ARR 4.4%, NNT 23). Study drug discontinuation rates were higher in the candesartan group compared with the placebo group (withdrawals for any cause: 24.2% vs 18.3% for candesartan vs placebo, respectively). Withdrawals due to increased creatinine levels and hyperkalaemia were significantly higher in candesartan vs placebo recipients, and there was a nonsignificant trend towards an increase in withdrawals due to hypotension in the candesartan group. In summary, the CHARM-Added trial demonstrated that clinical outcomes were improved with the addition of candesartan in patients with HF and LV systolic dysfunction who were already receiving an ACE inhibitor and a beta-blocker. However, there was an excess of withdrawals due to worsening renal function and

hyperkalaemia. Translation of this clinical trial evidence into clinical practice will require careful patient selection and long-term monitoring to ensure ongoing safety with this combination therapy.

The Valsartan Heart Failure trial (Val-HeFT), involving 5,010 patients, evaluated the effects of the addition of valsartan to standard HF therapy including background ACE inhibitor.<sup>110</sup> While mortality alone was similar with valsartan compared with placebo, valsartan significantly improved the combined endpoint of mortality and morbidity (resuscitated cardiac arrest, hospital admission for HF or receipt of an intravenous inotrope for >4 hours) 723 (28.8%) patients receiving valsartan compared with 801 (32.1%) patients receiving placebo (relative risk 0.87, 95% CI 0.77-0.97, p=0.009; ARR 3.3%, NNT 30 over 23 months). While valsartan is not available for use in New Zealand the results from Val-HeFT are consistent and reinforce the class nature of the effects of ARBs in this setting.

## Beta-Blockers

The rationale for using beta-blockers in patients with HF is now well established. Multiple large-scale clinical trials have provided conclusive evidence of the beneficial effects of beta-blocker therapy on survival in HF.<sup>111-117</sup> As a result, beta-blockers are now an important part of standard care for patients with HF with LV systolic dysfunction (LVEF <45%) in addition to ACE inhibitors, ARBs and diuretics.

### Recommendations

**Beta-blockers should be considered for all patients with heart failure due to LV systolic dysfunction (LVEF <45%).**

*Level of evidence I: Grade of recommendation A*

### Clinical Practice Points

- Patients considered for beta-blocker therapy should have LV systolic dysfunction (LVEF <45%) and be clinically stable on adequate doses of an ACE inhibitor and a diuretic, with mild-to-moderate symptoms (NYHA functional class II-III).
- Patients with overt clinical congestion with unstable symptoms should be treated with ACE inhibitors/diuretics prior to commencing beta-blockers.
- If possible low-dose beta-blocker therapy should be started prior to hospital discharge in patients hospitalised with heart failure.
- Contraindications to beta-blockade:
  - asthma;
  - heart block/sick sinus syndrome (in the absence of a pacemaker);
  - symptomatic hypotension.
- Initiation of beta-blockers in patients with heart failure:
  - start at a low dose (e.g. metoprolol controlled release 23.75mg once daily, or carvedilol 3.125-6.25mg twice daily).
- Dose titration for beta-blocker therapy:
  - in general, the beta-blocker dosage can be increased weekly or fortnightly;
  - check specifically for signs of worsening congestion, hypotension or bradycardia (heart rate <50 beats/minute) at each visit prior to upward dose titration.
  - doubling of the dose approximately every 2 weeks can be achieved for many patients, although slower titration should be considered for some.
- Potential adverse events of beta-blockers in heart failure patients:
  - dizziness: common with the vasodilating beta-blockers such as carvedilol; often decreases with continued treatment;
  - symptomatic hypotension: usually a sign of intolerance (decrease dose or stop therapy).
  - worsening heart failure (mainly increasing congestion): this may be managed by increasing diuretics and continuing with beta-blocker therapy if possible (slower dose titration may be required).
- Target doses:
  - aim for metoprolol controlled release 190mg daily or carvedilol 25mg twice daily (or 50mg twice daily for patients weighing >85kg).
- Managing beta-blockers in patients re-hospitalised with heart failure:
  - for most patients who tolerate initial beta-blocker titration, subsequent worsening heart failure is generally not due to the beta-blocker; dose reduction in this situation is associated with worse prognosis and during such episodes the general aim should be to continue beta-blocker therapy if possible;
  - temporary dose reduction may be required for some patients; for example, those with hypotension. However, efforts should subsequently be made to re-titrate the dose of the beta-blocker upwards.

## **Supporting Evidence**

Approximately 17,500 patients with HF have been entered into 30 randomised clinical trials of beta-blocker therapy<sup>111-117</sup> (this body of clinical trial data is approximately twice the size of that available for ACE inhibitors in patients with HF). The trials have shown conclusively that beta-blockers improve survival, decrease hospitalisations and improve LV function in patients with HF. Clinical evidence of efficacy in HF has only been documented for three beta-blockers: carvedilol,<sup>116</sup> metoprolol<sup>113</sup> and bisoprolol.<sup>111</sup>

The following data for survival benefits are from the total dataset combined in a meta-analysis:<sup>111-115</sup> absolute risk reduction = 4.5% (approximate annual mortality rate 17.4% in placebo-treated patients vs 12.9% in beta-blocker recipients); relative risk reduction = 28% (standard deviation 4%); number needed to treat = 22 (to prevent one death during approximately 1 year of treatment).

Effects on symptoms and exercise tolerance are less consistent, and should not be considered a main aim of beta-blocker therapy, at least in the short-term. The benefits of beta-blockers are *in addition* to the benefits obtained with ACE inhibitor therapy. The role of beta-blockers is in the treatment of patients with chronic HF and there is no place for the use of beta-blockers in the treatment of acute pulmonary oedema. However, once patients are rendered free of frank volume expansion, introduction of beta-blockers should not be delayed.

There is a potential for adverse effects with beta-blockers, particularly during initiation of therapy. Patient selection, timing of therapy and careful dose titration are of key importance (see below).

While clinical evidence of efficacy in HF has been demonstrated with carvedilol,<sup>116</sup> metoprolol<sup>113</sup> and bisoprolol,<sup>111</sup> bucindolol had no effect on survival<sup>115</sup> and xamoterol (a beta-blocker with intrinsic sympathomimetic activity) was shown to increase mortality.<sup>118</sup> To assess the potential differences between carvedilol (additional vasodilator properties) and metoprolol, the COMET (Carvedilol or Metoprolol European Trial) trial was performed in patients with systolic HF; the primary endpoint was the effects of carvedilol and metoprolol on mortality.<sup>119</sup> Treatment with carvedilol resulted in an additional survival benefit (relative risk reduction 17%; p=0.01) over and above short-acting metoprolol tartrate.

The results from COMET have been the subject of considerable debate for several reasons: firstly the preparation of metoprolol (metoprolol tartrate as used in the Metoprolol in Dilated Cardiomyopathy [MDC] trial<sup>120</sup>) was different from that used in the large-scale mortality trial MERIT-HF (metoprolol succinate controlled release/extended release preparation [metoprolol CR/XL]) from which the clinical efficacy of metoprolol compared with placebo was established.<sup>113</sup> Secondly, the heart rate reduction achieved in the MDC trial (15 beats/minute; mean metoprolol tartrate dosage 108 mg/day)<sup>120</sup> was greater than that achieved in COMET (11.7 beats/min; mean metoprolol tartrate dosage 85 mg/day).<sup>119</sup> In MERIT-HF the mean metoprolol CR/XL dosage was 159 mg/day, which is equivalent to approximately 106 mg/day of metoprolol tartrate, and the heart rate reduction achieved in MERIT-HF<sup>113</sup> was 14 beats/min, similar to that seen in the MDC trial.<sup>120</sup> Interestingly, post-hoc analyses from the MERIT-HF trial<sup>121</sup> demonstrated similar survival benefits in subgroups taking low and high doses of metoprolol. However, it should be noted that there were important clinical differences in the patients who received lower dosages; these patients were older, had lower LVEF, worse functional class and higher creatinine levels than those who received higher dosages. Furthermore, a similar mean heart rate at the end of dosage titration was achieved in patients who received higher or lower dosages (although heart rate change per se was not a goal or target of therapy), suggesting that individualisation of the dose of metoprolol was more important than aiming for one dose target in all patients.

A recent analysis from the COMET study demonstrated that the beta-blocker dose, heart rate and systolic blood pressure were independently associated with outcome, but that carvedilol remained superior to metoprolol tartrate in multivariate analysis with no interaction between

these variables.<sup>122</sup> Despite these arguments it is difficult to reliably determine whether the survival benefit demonstrated with carvedilol in COMET would have been similar if metoprolol succinate instead of metoprolol tartrate had been used.

While the results from COMET demonstrated that carvedilol resulted in a greater reduction in mortality than is gained with metoprolol tartrate, these data do not negate the importance of the MERIT-HF<sup>113</sup> and CIBIS-II<sup>111</sup> trials. No clear survival advantage has been demonstrated with carvedilol over metoprolol succinate or bisoprolol, and thus application of any of these evidence-based therapies for patients with HF remains an equal priority.

#### **Beta-blockers in patients with heart failure after acute myocardial infarction (MI)**

Clinical trials in the 1970s and 1980s demonstrated important clinical benefits with beta-blocker therapy in patients after acute MI.<sup>123</sup> These trials were conducted prior to the widespread use of thrombolysis and ACE inhibitor therapy and most excluded patients with overt HF or significant LV dysfunction. The CAPRICORN trial involved patients with LV dysfunction who were treated with ACE inhibitors after acute MI, and demonstrated that all-cause mortality was reduced by 23% with carvedilol therapy, from 15% in the placebo group to 12% in the carvedilol group after 2.5 years of treatment.<sup>115</sup> While the results of the CAPRICORN trial did not achieve conventional statistical significance for the primary endpoint (all-cause mortality or cardiovascular hospitalisation), the reduction in all-cause mortality alone was consistent with other data and resulted in an indication for carvedilol in this patient group. Therefore, carvedilol appears to be safe and effective in patients with LV dysfunction after acute MI.

## Aldosterone antagonists

Aldosterone antagonists have now been demonstrated to confer significant survival benefits and to reduce morbidity when used in combination with ACE inhibitors and loop diuretics in patients with severe HF and severe LV systolic impairment.

### Recommendations

**Low-dose aldosterone antagonists should be considered for patients with severe heart failure (NYHA class III or IV, who have been class IV within the last 6 months) with LVEF ≤35%.**

*Level of evidence II: Grade of recommendation A*

### Clinical Practice Points

- It is recommended that patients receive treatment with an ACE inhibitor (or ARB) and a beta-blocker, both in appropriate doses, prior to starting spironolactone.
- Spironolactone is the aldosterone antagonist commonly used in New Zealand:
  - recommended dose of spironolactone is 25mg once daily. Lower doses (spironolactone 12.5mg once daily) may be considered if adverse effects (see below) occur at the higher dose;
  - eplerenone is an alternative aldosterone antagonist with less oestrogenic side effects but is not currently funded in New Zealand.
- Contraindications to aldosterone antagonists:
  - serum potassium >5.0 mmol/L;
  - serum creatinine >200 µmol/L;
  - for patients at high risk of renal dysfunction, such as the elderly and those with diabetes, spironolactone should not be used if glomerular filtration rate (GFR) is <30 mL/min.
- Concomitant medications:
  - spironolactone is not recommended in patients who are receiving combined treatment with an ACE inhibitor and ARB;
  - nonsteroidal anti-inflammatory agents should not be co-administered with spironolactone.
- Monitoring/Side effects:
  - hyperkalaemia and worsening renal function may occur with spironolactone therapy, and are more common in patients who are elderly and have pre-existing renal dysfunction;
  - serum creatinine and electrolytes should be checked 3-4 days, one week and one month after initiation of therapy and then as indicated by renal function (usually a minimum of every 3 months);
  - hyperkalaemia (serum potassium >5.5 mmol/L) or worsening renal function requires dose reduction or cessation of spironolactone. Manage severe hyperkalaemia or worsening renal function according to standard clinical practice;
  - patients who become ill with intercurrent illness such as diarrhoea and vomiting are at increased risk of renal failure and hyperkalaemia when receiving spironolactone in combination with an ACE inhibitor. It is recommended that patients are instructed to withhold their spironolactone if any such volume-depleting intercurrent illness should develop and to seek medical advice prior to re-starting this therapy (see spironolactone patient information sheet);
  - gynaecomastia and breast pain may occur in approximately 10% of men.

### Supporting Evidence

Previously it has been assumed that suppression of the renin-angiotensin aldosterone system using an ACE inhibitor alone would inhibit the formation of aldosterone. However, aldosterone responds to multiple secretagogues in addition to angiotensin II and levels may increase despite ACE inhibitor therapy (during which alternative pathways for angiotensin II generation

may result in increases in angiotensin II levels in any case).<sup>124</sup> In addition, there has been concern that the concurrent use of an aldosterone antagonist and an ACE inhibitor could lead to dangerous hyperkalaemia.

The RALES trial involved 1663 patients with severe HF (NYHA class III or IV) and LVEF  $\leq 35\%$  (severe LV impairment).<sup>125</sup> Spironolactone (mean dose 25mg once daily) was added to usual therapy, which included ACE inhibitors and loop diuretics. Few patients in this study were receiving beta-blockers. All-cause mortality at two years was reduced from 46% in the placebo group to 35% in the spironolactone group (ARR 11%; NNT to prevent one death over 2 years = 9). In addition, there were fewer hospital admissions, improved symptoms and no significant increase in the risk of hyperkalaemia. However, 10% of male patients experienced gynaecomastia or breast pain, some of whom needed to stop therapy because of these adverse effects.

While there is only one large-scale randomised controlled trial reporting the benefits of spironolactone for patients with HF, the RALES trial was a well-designed study and demonstrated clear benefits.<sup>125</sup> Subsequently, use of this drug for patients with severe HF has become recommended as standard practice.<sup>6</sup> Importantly, a preceding dose-finding study by the RALES investigators demonstrated that spironolactone used in daily doses of 12.5 to 25mg could be co-administered with an ACE inhibitor relatively safely without major increase in the risk of hyperkalaemia.<sup>126</sup> The mean daily dose achieved with spironolactone in the RALES Trial was 25mg once daily. Thus, the recommended dose of spironolactone is 12.5 to 25mg once daily.

Long-term monitoring of renal function and potassium is vitally important for the safe use of spironolactone in patients with HF. Reports of the adverse effects of combination therapy with spironolactone and ACE inhibitors in patients with HF have highlighted that renal failure and serious hyperkalaemia may occur at times of intercurrent illness (especially diarrhoea and vomiting) and worsening HF.<sup>127</sup> Such data reinforce the importance of careful patient selection and monitoring for this combination therapy. In particular, patients should be advised to discontinue their spironolactone at the earliest indication of intercurrent illness and seek medical advice.

Eplerenone is a selective aldosterone antagonist with anti-androgenic effects. Eplerenone has been evaluated in patients with HF and LV systolic dysfunction following acute myocardial infarction. The EPHESUS Trial recruited 6,642 patients within 3-14 days following acute myocardial infarction with LVEF  $\leq 40\%$  and/or clinical HF.<sup>128</sup> During a mean follow-up of 16 months (range 0 to 33 months) mortality was reduced from 16.7% in the placebo group to 14.4% in the eplerenone group (ARR 2.4%; NNT to prevent one death over 1 years = 50). Eplerenone is a potential alternative for use in patients who cannot tolerate spironolactone due to gynaecomastia or breast pain, although it is not currently funded in New Zealand.

## Digoxin

There are two potential clinical situations in which digoxin should be considered for patients with HF.

### 1. Patients with heart failure and co-existing atrial fibrillation (AF)

#### Recommendations

Digoxin should be considered for all patients with heart failure who are in atrial fibrillation.

*Level of evidence III-3: Grade of recommendation C*

#### Clinical Practice Points

- Digoxin is useful to assist with control of ventricular rate in patients with heart failure and atrial fibrillation.
- Digoxin alone may control the ventricular rate at rest but usually does not provide sufficient rate control during exercise.
- Beta-blockers, unless contraindicated, should be used in appropriate doses to assist with rate control.
- Additional agents may be required to adequately control the heart rate, especially during exercise (see section on atrial fibrillation).

## **2. Patients with heart failure who are in sinus rhythm**

The evidence for the clinical efficacy of ACE inhibitors, ARBs, spironolactone and beta-blockers supports the use of these drugs in appropriate doses prior to considering digoxin.

### **Recommendations**

**Digoxin should be considered for patients with heart failure with LV systolic dysfunction (LVEF <45%) who remain symptomatic despite treatment with an ACE inhibitor, diuretics, spironolactone and beta-blockers with the aim of improving symptoms and preventing further clinical deterioration.**

***Level of evidence II: Grade of recommendation B***

### **Clinical Practice Points**

- Patients should receive adequate treatment with other evidence-based therapies (including ACE inhibitors, diuretics, spironolactone and beta-blockers) prior to considering digoxin.
- Loading doses of digoxin are generally not required. Usual dosages:
  - 125-250 µg/day in patients with normal renal function;
  - reduced dosage of 62.5-125 µg/day in the elderly or in those with renal impairment;
  - in practice it will be rare for appropriate digoxin doses to exceed 125 µg/day;
  - digoxin is renally excreted and therefore a lower dosage should be used in patients with renal dysfunction. Renal function should be assessed using estimated glomerular filtration rate (eGFR) as well as serum creatinine (i.e. do not rely on serum creatinine alone).
- Contraindications to digoxin:
  - second or third degree heart block (in the absence of a permanent pacemaker);
  - previous digoxin toxicity.
- Monitoring/Side effects:
  - digoxin levels should be checked after about 1 week of therapy in patients with normal renal function, although steady state may take longer to reach in those with renal impairment. Digoxin levels should be used to monitor for suspected digoxin toxicity. Titration of digoxin to achieve “therapeutic” plasma levels is not required;
  - signs of digoxin toxicity include: confusion, nausea, anorexia, visual disturbance and either tachy- or bradyarrhythmias. Digoxin toxicity should be suspected in a patient presenting with any of the above symptoms, or unusual symptoms, particularly in the elderly;
  - some drugs may increase plasma digoxin levels (e.g. amiodarone, diltiazem, verapamil, antibiotics, quinidine). Reduction of the digoxin dosage should be considered when starting these drugs.

### **Supporting Evidence**

The DIG Trial was a randomised, placebo-controlled trial comparing digoxin (0.25 mg/day) with placebo in patients with HF with LVEF ≤45% who were in sinus rhythm.<sup>129</sup> While this trial showed that overall mortality was not affected in those taking digoxin, both hospitalisation due to worsening HF, and the combined endpoint of death or hospitalisations due to worsening HF were decreased: ARR was approximately 7%. It had been previously shown that when digoxin was withdrawn from patients, exercise tolerance, NYHA class and QOL scores deteriorated.<sup>130</sup> However, given that digoxin does not reduce mortality, patients who are symptomatically well controlled after treatment with ACE inhibitors, diuretics and beta-blockers are unlikely to gain a benefit from the addition of digoxin. There was no clear benefit of digoxin for patients with HF and preserved LVEF in this study.

## **Amiodarone**

Amiodarone is a class III antiarrhythmic, which also has sympatholytic effects on the heart. It has a neutral effect on survival in patients with HF and systolic dysfunction. In HF, amiodarone may be used to maintain sinus rhythm after cardioversion for AF, or to suppress symptomatic ventricular arrhythmias, which are not otherwise controlled by optimal medical therapy. Amiodarone causes frequent, and potentially serious, side effects, mandating careful monitoring of patients.

### **Recommendations**

**Amiodarone is effective for the maintenance of sinus rhythm after cardioversion for atrial fibrillation.**

***Level of evidence I: Grade of recommendation B***

**Amiodarone is recommended in patients with an ICD, otherwise optimally treated, who continue to have symptomatic ventricular arrhythmias.**

**Amiodarone may be used to suppress symptomatic ventricular arrhythmias in patients who are ineligible for an ICD.**

***Level of evidence II: Grade of recommendation B***

### **Clinical Practice Points**

- Treatment should be initiated only under hospital or specialist supervision.
- Contraindications:
  - symptomatic conduction disease;
  - evidence of thyroid dysfunction;
  - concomitant therapy with medicines that may induce torsades de pointes;
  - pregnancy and lactation.
- Precautions:
  - Hypotension;
  - severe respiratory failure;
  - severe or uncompensated heart failure.
- Amiodarone interacts with many other drugs, and potential interactions should be considered when commencing therapy with amiodarone or when new drugs are being prescribed in a patient on amiodarone therapy.
- Amiodarone potentiates warfarin therapy. Warfarin doses should be decreased when commencing amiodarone therapy, and INRs frequently monitored initially.
- Patients should be advised of potential side effects and required monitoring when being initiated on amiodarone. All patients should be advised regarding photosensitivity and prescribed high sun-protection-factor (SPF) sunscreen.
- The chronic administration of amiodarone may increase ventricular defibrillation and/or pacing threshold of pacemakers or implantable cardioverter defibrillator devices. Therefore, testing of the functioning of such devices before and during amiodarone treatment is recommended.

### **Supporting Evidence**

Amiodarone is a class III antiarrhythmic agent which prolongs the action potential duration and hence refractory period of atrial, nodal and ventricular tissues, thereby giving a very broad spectrum of activity. It differs from other class III antiarrhythmics in that it also has a sympatholytic effect on the heart. Amiodarone has a long half life, and accumulates in adipose tissue and highly perfused organs. Measured drug levels do not correlate well with efficacy or adverse events.

Amiodarone is an effective antiarrhythmic, and does not increase mortality in patients with HF and systolic dysfunction.<sup>131-133</sup> It is therefore frequently used when antiarrhythmic therapy is required in this patient group.

### **Atrial fibrillation (AF)**

Small randomised controlled trials suggest that amiodarone is more effective than placebo for conversion of recent onset of AF to sinus rhythm.<sup>134</sup> Dofetilide is a more effective option in patients with HF, but is not available in New Zealand. Amiodarone slows the ventricular rate in patients with AF and this, combined with its modest efficacy at cardioversion, make it a useful acute agent in patients with acute rapid AF and LV dysfunction. Because cardioversion and embolisation may occur, adequate anticoagulation is necessary before commencing amiodarone if AF has been present for more than 48 hours.

In patients with HF and AF, a routine strategy of attempting to achieve and maintain sinus rhythm has not been shown to be superior to controlling ventricular rate and anticoagulation.<sup>135</sup> However in patients who remain symptomatic after adequate rate control, a rhythm control strategy may be pursued. In a substudy of the AFFIRM trial, amiodarone was more effective than other antiarrhythmics studied in maintaining sinus rhythm.<sup>136</sup>

Because of its side effect profile, amiodarone is not an appropriate first-line agent for chronic ventricular rate control. However, amiodarone may be considered when beta-blocker and digoxin therapy is contraindicated or ineffective.

### **Ventricular arrhythmias**

#### *Primary prevention of sudden cardiac death*

Patients with ventricular dysfunction after myocardial infarction are at risk of sudden cardiac death. While amiodarone has been shown to reduce arrhythmic death in this patient group, overall mortality was unaffected.<sup>132</sup> Beta-blockers reduce the risk of sudden cardiac death and total mortality in this patient group and are the first-line therapy.

The GESICA group conducted a large randomised trial of amiodarone (300 mg/day) in patients with symptomatic congestive HF.<sup>131</sup> They showed a reduction in both sudden cardiac death and death from progressive HF. However, the trial was conducted before the routine use of beta-blockers in HF with systolic dysfunction. In the SCD-HeFT trial,<sup>137</sup> patients with cardiomyopathy and mild-to-moderate HF symptoms were randomised to receive an ICD, amiodarone or placebo. 1,310 patients with ischaemic cardiomyopathy and 1,211 patients with non-ischaemic cardiomyopathy were enrolled. Amiodarone did not impact survival in either group of patients and is therefore not recommended for routine primary prevention of sudden cardiac death in patients with cardiomyopathy.

#### *Secondary prevention of sudden cardiac death*

Three randomised prospective trials have compared amiodarone therapy with ICDs for the secondary prevention of sudden cardiac death. The trials were not limited to patients with pre-existing structural heart disease. In the two largest trials, patients with LV systolic dysfunction and conscious symptomatic ventricular tachycardia were included. The largest of these trials, Antiarrhythmics Versus Implantable Defibrillators (AVID)<sup>138</sup> randomised 1,016 patients and demonstrated a clear survival benefit with ICDs compared with antiarrhythmic drugs in this patient group. The Canadian Implantable Defibrillator Study (CIDS)<sup>139</sup> and the Cardiac Arrest Study of Hamburg (CASH)<sup>140</sup> both showed a trend to improved survival with ICDs. ICDs are the therapy of choice for secondary prevention of sudden cardiac death.

#### *Prevention of frequent ICD discharges*

Amiodarone plus beta-blockers is more effective at preventing ICD shocks than either beta-blockers or sotalol alone. However, the risk of adverse events is increased.<sup>141</sup>

## Side effects and monitoring

Adverse effects are common, and occur in up to 50% of amiodarone recipients during long-term therapy. Because of amiodarone's long half life, monitoring for adverse events needs to continue for months after the drug has been stopped. The most common adverse events and recommended monitoring are summarised in Table 7. Most adverse events are reversible with dose reduction or drug withdrawal.

**Table 7. Common adverse events during amiodarone therapy, and monitoring recommendations [adapted from Vassallo P & Trohman RG (2007)]<sup>134</sup>**

System	Monitoring		Possible adverse events and reported frequencies
	Baseline	Follow-up	
<b>Cardiac</b>	ECG	Yearly	- QT prolongation; torsades de pointes - Sinoatrial or conduction system impairment
<b>Skin</b>	Physical examination	As needed for signs/Sx	- Photosensitivity (25-75%) - Blue-grey discolouration (4-9%)
<b>Endocrine</b>	TFTs	6 monthly	- Hyperthyroidism (0.9-2%) - Hypothyroidism (6%)
<b>Hepatic</b>	AST/ALT	6 monthly	- Elevated enzyme levels (15-30%) - Hepatitis and cirrhosis (<3%)
<b>Neurologic</b>	Physical examination	As needed for signs/Sx	Most commonly: - Tremor, ataxia (3-35%) - Peripheral neuropathy (0.3% annually)
<b>Ophthalmologic</b>	Physical examination	As needed for signs/Sx	Corneal microdeposits (>90%) Optic neuropathy ( $\leq$ 1-2%)
<b>Pulmonary</b>	Pulmonary function tests	As needed for signs/Sx	Pulmonary toxicity (1-17%)
	Chest x-ray	Yearly	

ECG = electrocardiogram; TFTs = thyroid function tests; AST = aspartate aminotransferase; ALT = alanine aminotransferase; Sx = symptoms.

## Summary

Amiodarone is an effective antiarrhythmic which does not increase mortality in HF. It has important adverse effects and drug interactions which require careful consideration and ongoing monitoring in all patients on chronic amiodarone therapy.

## Device Therapy

Patients with HF are at increased risk of ventricular arrhythmias and sudden death. Recent trials have demonstrated a survival advantage when an ICD is added to optimal medical treatment, and also for biventricular pacing with and without a defibrillator. The cost-effectiveness of defibrillator treatment in this setting is arguable and is a major factor to take into account when formulating guidelines for device therapy. Furthermore, the relative merits of biventricular pacing alone versus defibrillator treatment alone or combined with biventricular pacing are presently unclear. The following guideline is a compromise which seeks to balance the magnitude of proven benefit to an individual patient against the cost of providing that benefit. It specifically excludes recommendations regarding ICD implantation for familial cardiac conditions with a high risk of sudden death such as the long QT and Brugada syndromes, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy and congenital heart disease.

### 1. Implantable defibrillator for primary prevention

#### Recommendations

A primary ICD should be considered in patients with heart failure who meet the following criteria:

- ischaemic cardiomyopathy ≥1 month after acute myocardial infarction or non-ischaemic cardiomyopathy present for ≥3 months;
- LVEF ≤30% measured ≥3 months after optimal heart failure treatment (maximum tolerated dosages of ACE inhibitors or ARBs, beta-blockers and spironolactone);
- NYHA class II or III;
- no associated disease with a reduced survival expectancy of <18 months;
- age ≤75 years.

*Level of evidence II: Grade of recommendation A*

#### Clinical Practice Points

- Patients should be on maximal heart failure medications, including ACE inhibitors or ARBs, beta-blockers and spironolactone, as tolerated for at least 3 (preferably 6) months.
- LVEF should be quantified ≥3 months after optimisation of heart failure treatment.
- With respect to revascularisation:
  - patients should be assessed to exclude symptoms or findings that would make them a candidate for a revascularisation procedure;
  - if such a procedure has been undertaken then primary ICD placement is usually delayed for at least 3 months to allow for improvement of LV function to be evident.
- Patients with NYHA class IV symptoms are generally not candidates for a primary ICD.
- To be eligible for ICD implantation, patients should not have associated disease with a reduced survival expectancy of <18 months.
- On pragmatic grounds it is recommended that patients undergoing primary ICD implantation should be aged ≤75 years.
- The majority of trial patients implanted with a primary ICD never received therapy from their device: an appropriate shock was delivered in only 21% and 19% of patients in the SCD-HeFT<sup>142</sup> (follow-up 45 months) and MADIT-II<sup>143</sup> (follow-up 19 months) trials, respectively. This suggests that the ability to identify high-risk patients is poor.

#### Supporting Evidence

There are nine randomised trials of primary prevention of sudden death using ICD therapy. Three of these, The Coronary Artery Bypass Graft Patch Trial (1997),<sup>144</sup> the Multicentre Unsustained Tachycardia Trial (1999)<sup>145</sup> and the Multicentre Automatic Defibrillator Trial (1996)<sup>146</sup> have been excluded as ineligible for current practice decisions. The remaining six trials are briefly summarised below; the first two have small patient numbers and therefore have

comparatively lower relevance. Two additional trials address biventricular pacing, with or without an ICD.

- CAT (Primary Prevention of Sudden Death in Idiopathic Dilated Cardiomyopathy): 104 NYHA class II-III patients with recent-onset ( $\leq 9$  months) non-ischaemic cardiomyopathy and LVEF  $\leq 30\%$  were randomised to ICD or control group; there was no survival benefit for the ICD vs control after 5 years.<sup>147</sup>
- AMIOVERT (Amiodarone Versus Implantable Cardioverter-Defibrillator): 103 NYHA class I-III patients with chronic non-ischaemic cardiomyopathy and LVEF  $\leq 35\%$  were randomised to ICD or amiodarone; there was no survival benefit for the ICD over amiodarone after 2 years.<sup>148</sup>
- DEFINITE (Prophylactic Defibrillator Implantation in Patients with Non-ischemic Dilated Cardiomyopathy): 458 NYHA class II-III patients with non-ischaemic cardiomyopathy and LVEF  $\leq 35\%$  were randomised to ICD or control group; there was a non-significant trend to survival benefit for the ICD compared with control after 2.4 years ( $p=0.08$ ).<sup>149</sup>
- DINAMIT (Prophylactic Use of an Implantable Cardioverter-Defibrillator after Acute Myocardial Infarction): 674 NYHA class II-III patients with LVEF  $\leq 35\%$  were randomised to ICD or control group at 6-40 days after acute MI; there was no survival benefit for the ICD vs control after 2.5 years ( $p=0.66$ ).<sup>150</sup>
- MADIT-II (Prophylactic Implantation of a Defibrillator in Patients with Myocardial Infarction and Reduced Ejection Fraction): 1,232 NYHA class I-IV patients with MI not within the previous month and LVEF  $\leq 30\%$  were randomised in a 3:2 ratio to ICD or control group; the absolute survival benefit for the ICD vs control was 5.2% at 20 months ( $p=0.016$ ).<sup>143</sup>
- SCD-HeFT (Amiodarone or an Implantable Cardioverter-Defibrillator for Congestive Heart Failure): 2,521 NYHA class II-III patients with ischaemic or non-ischaemic cardiomyopathy and LVEF  $\leq 35\%$  were randomised to placebo, amiodarone or ICD: there was an absolute survival benefit of 7.2% after 5 years for the ICD compared with placebo ( $p=0.0007$ ). Prespecified subgroup analyses showed no apparent reduction in the risk of death with ICD therapy in NYHA class III patients and a marginally significant trend for improved survival in non-ischaemic congestive HF ( $p=0.06$ ).<sup>142</sup>
- COMPANION (Cardiac-Resynchronisation Therapy with or without an Implantable Defibrillator in Advanced Chronic Heart Failure): 1,520 NYHA class III-IV patients with ischaemic or non-ischaemic cardiomyopathy and LVEF  $\leq 35\%$  were randomised to a control group, biventricular pacing alone or combined with an ICD; there was a survival benefit for the combined therapy group only at 16 months (36% reduction in relative risk of death;  $p=0.004$ ). Biventricular pacing alone was associated with a marginally significant reduction in the risk of death from any cause (adjusted  $p=0.06$ ).<sup>151</sup>
- CARE (The Effect of Cardiac Resynchronisation on Morbidity and Mortality in Heart Failure): 813 NYHA class III or IV patients with ischaemic and non-ischaemic cardiomyopathy and LVEF  $\leq 35\%$  were randomised to biventricular pacing or control group; the absolute survival benefit at 2 years for pacing vs control was 7.1% ( $p<0.002$ ). Calculations suggested that for every nine devices implanted, one death and three hospitalisations for major cardiovascular events were prevented.<sup>152</sup>

### **Cost Effectiveness**

The cost-effectiveness of a prophylactic ICD varies. The most recent study by Sanders et al<sup>153</sup> stated that “the weight of evidence from eight randomized trials is that the prophylactic implantation of an ICD reduces the rate of death from any cause: in the six trials that showed a mortality benefit, we project that the implantation of an ICD adds between 2.12 and 6.21 undiscounted years of life. This increment in life expectancy is substantial as compared with that provided by many other medical interventions, and the incremental cost-effectiveness of the ICD, in appropriately selected patients, is similar to that of other interventions often accepted as cost-effective”.

## 2. Cardiac resynchronisation therapy and/or an ICD

### Recommendations

Resynchronisation pacing should be considered in patients with heart failure who meet the following criteria:

- NYHA class III or IV who are not inotrope dependent
- LVEF  $\leq 35\%$  after  $\geq 6$  weeks of optimal heart failure treatment (maximum tolerated dosages of ACE inhibitors or ARBs, beta-blockers and spironolactone);
- QRS duration  $>149$  ms or 120-149 ms with two additional criteria for dyssynchrony (aortic pre-ejection delay  $>140$  ms, interventricular mechanical delay  $>40$  ms or delayed activation of the posterolateral left ventricular wall);
- sinus rhythm;
- no major cardiovascular event in the previous 6 weeks;
- absence of major co-morbidity likely to seriously and persistently impair quality of life and no associated disease, other than cardiac disease, with a reduced survival expectancy of  $<12$  months;
- age  $\leq 75$  years.

*Level of evidence II: Grade of recommendation A*

### Clinical Practice Points

- The additional benefit of an ICD plus cardiac resynchronisation therapy (biventricular pacing) is presently uncertain.
- Patients should be on maximal heart failure medications, including ACE inhibitors or ARBs, beta-blockers and spironolactone, as tolerated for a minimum of 6 weeks and preferably 3 months.
- LVEF should be quantified after optimisation of heart failure treatment.
- Provided the heart rate is well controlled, selected patients with atrial fibrillation could be considered for biventricular pacing.
- While left bundle branch block is not made a specific inclusion criterion, most trials have only small numbers of patients with right bundle branch block. Until further evidence is presented right bundle branch block should be a contraindication.
- Patients should not have associated disease with a reduced survival expectancy of  $<12$  months.
- On pragmatic grounds it is recommended that patients for cardiac resynchronisation therapy should be aged  $\leq 75$  years.

### Supporting Evidence

In the COMPANION study,<sup>151</sup> pacing alone reduced all-cause mortality by 24% ( $p=0.059$ ), and in the CARE study<sup>154</sup> by 31% ( $p<0.002$ ). Combination therapy (ICD + resynchronisation) in the former study was associated with a greater relative risk reduction of 36% for total mortality ( $p=0.003$ ). The COMPANION authors concluded that “the decision of which of these two therapeutic options is appropriate for a particular setting is best determined on an individual basis by patients and their physicians”.

The authors of the CARE study noted that 7% of the cardiac resynchronisation group died suddenly and estimated that a future study would require 2,600 patients with a 2.5-year follow-up to detect a 5% absolute reduction in the risk of all-cause mortality with the addition of an ICD (combination therapy). At the present time patients should be managed on a case-by-case basis until further trial data are available. However, there is currently poor evidential support for routine combination therapy in patients with severely impaired LV function.

### **Resynchronisation treatment for heart failure**

Prior to COMPANION and CARE, there have been at least 7 smaller trials of cardiac resynchronisation therapy (MUSTIC,<sup>155</sup> PATH-CHF1,<sup>156</sup> PATH-CHFII,<sup>157</sup> MIRACLE,<sup>158</sup> InSync ICD,<sup>159</sup> MIRACLE ICD,<sup>160</sup> CONTAK ICD).<sup>161</sup> In the overview by Al-Khatib et al.<sup>162</sup>, the comment is made that these studies are small, follow-up brief and, as blinding was not possible, outcome assessment unavoidably biased. Two meta-analyses of cardiac resynchronisation therapy trials have been published, one reported a 29% reduction in HF hospitalisation but no change in all-cause mortality,<sup>163</sup> while the second<sup>164</sup> reported a significant improvement in all-cause mortality (odds ratio 0.79, 95% CI 0.66-0.96). The latter analysis, however, included benefit from combined therapy with an ICD. Data from these trials have been strengthened by the results of the two major randomised trials, COMPANION and CARE.

## Management of Patients with Heart Failure with Preserved LVEF

As previously discussed in this guideline, HF is a clinical syndrome with symptoms, usually shortness of breath, fatigue and limitation of functional capacity, due to an underlying abnormality of cardiac structure and function.<sup>165</sup> HF has been traditionally viewed as a failure of heart pump function and LVEF has been widely used to define systolic function, assess prognosis and select patients for therapeutic interventions. Until recently, most clinical trials assessing therapeutic interventions in HF have selected patients on the basis of low LVEF. However, it is recognised that HF can occur in the presence of "normal" systolic function: so-called "HF with preserved ejection fraction (HF-P EF)" which appears to be the case in 30-50% of patients with clinical HF.<sup>166-169</sup>

### Recommendations

**Patients with heart failure with preserved LVEF should receive appropriate non-pharmacological management and be considered for involvement in heart failure management programmes.**

**There is no clear evidence upon which to provide recommendations for pharmacological treatment of patients with heart failure with preserved LVEF.**

*Level of Evidence IV: Grade of recommendation D*

### Clinical Practice Points

- No specific therapeutic agents have yet been shown to reduce morbidity and mortality in patients with heart failure with preserved LVEF.
- Diuretics should be used to treat symptoms of fluid retention. Patients may be particularly susceptible to volume change with diuresis and close monitoring of response to therapy, including blood pressure and renal function, is generally required.
- Effective management of associated conditions should be considered for patients with heart failure with preserved LVEF, including:
  - optimal treatment of hypertension, often this will require multiple blood pressure-lowering drugs to achieve suitable blood pressure control, e.g. blood pressure <130/80 mmHg;
  - adequate rate control and anticoagulation for patients with co-existing atrial fibrillation (see section on Atrial Fibrillation);
  - treatment of co-existing coronary artery disease;
  - tight glycaemic control is commonly recommended in patients with diabetes with heart failure with preserved LVEF, although it should be noted that there is no clear clinical evidence upon which to base this recommendation.
- Patients with heart failure with preserved LVEF should still be considered for involvement in heart failure management programmes and should receive standard non-pharmacological management (see Non-Pharmacological Management section of this guideline).

### Supporting Evidence

Most randomised, controlled trials of therapeutic interventions for patients with HF have involved patients with low LVEF (typically <40-45%). Thus, the treatment for patients with HF-P EF has not been evidenced-based and therefore has reflected individual clinicians' opinions. Recently, clinical trials have been performed to specifically address therapy for patients with HF-P EF crudely defined by adoption of a simple LVEF threshold of 40 or 45%.

- The Candesartan in Heart Failure: Reduction in Mortality and Morbidity (CHARM) Programme specifically involved patients with LVEF >40% in the CHARM-Preserved Study.<sup>170</sup> This study, involving 3,023 patients, demonstrated that candesartan (an ARB) had a modest effect on reducing recurrent admissions for HF, with no effect on cardiovascular mortality.

- The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) study involved 850 patients with HF due to LV diastolic dysfunction (LVEF >40%).<sup>171</sup> Recruitment for this study was difficult and ultimately was underpowered for the primary endpoint of all-cause mortality and HF readmission, although at one year a reduction in HF hospitalisation was observed in the perindopril group.
- The Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) Study involved 4,128 patients aged >60 years with LVEF ≥45%, who were randomised to treatment with irbesartan or placebo.<sup>172</sup> During the 4 years of follow up there was no difference in the primary outcome of all-cause mortality or cardiovascular hospitalisation between the irbesartan and placebo groups.<sup>172</sup>

The results from these 3 trials have been rather disappointing and suggest that the therapeutic hypotheses that apply to patients with HF with low LVEF cannot be expected to provide the same clinical benefits for patients with HF-PEF. Further trials are ongoing but at present there is insufficient evidence upon which to base clear recommendations for any particular therapeutic class.

Many HF management programmes have included some patients with HF-PEF. While the trials are generally too small to draw conclusions from subgroup analyses, the recommendation is that such patients should still be considered for non-pharmacological management (see section in this guideline on Non-pharmacological Management). Diuretics should be used as for patients with HF with low LVEF to treat symptoms associated with fluid retention (see section on Diuretics).

## Concomitant Conditions

### Atrial Fibrillation (AF)

AF is common in patients with HF and is associated with increased morbidity and mortality. AF may be either a cause or consequence of HF. Important clinical considerations are: whether restoration of sinus rhythm should be attempted; achievement of adequate rate control; and necessity for anticoagulation.

AF is present in 10-30% of patients with HF, with a higher incidence in those with more severe disease. AF increases the risk for all-cause mortality and other adverse cardiovascular events in patients with HF, regardless of systolic function.<sup>173-175</sup> Each condition increases the likelihood of the other.<sup>176</sup> HF results in atrial structural and physiologic changes that increase the likelihood of the development and maintenance of AF. AF, by loss of atrial contraction, rapid ventricular response and R-R interval variability, may have significant haemodynamic effects in patients with HF. In addition, a rapid ventricular response may lead to a rate-related cardiomyopathy.

There is a paucity of data on the management of AF in patients with HF, and some aspects of management remain controversial. It is clear, however, that effective management of AF can only be achieved with effective management of HF, and that for the effective treatment of HF, effective management of AF is a necessary component.<sup>177</sup> Potential precipitating factors for AF should be identified and, where possible, controlled. Once this has been achieved, the important clinical considerations are consideration of cardioversion, rate control and prevention of thromboembolism.

Recommendations have been incorporated and adapted from the NZGG guideline for The Management of People with Atrial Fibrillation and Flutter.<sup>178</sup>

## 1. Rate control and rhythm control

### Recommendations

Adequate control of ventricular rate, both at rest and during exercise, is strongly recommended for patients with heart failure.

*Level of evidence II: Grade of recommendation B*

There is no evidence to support the routine use of a rhythm control strategy over rate control with currently available drug therapies.

Pharmacological cardioversion is generally limited to intravenous amiodarone.

Class I antiarrhythmic drugs (disopyramide, flecainide, propafenone) should not be used in patients with heart failure because of their negative inotropic effects and an increased risk of proarrhythmia.

*Level of evidence II: Grade of recommendation A*

Electrical cardioversion may be indicated in the acute setting, when atrial fibrillation and pulmonary oedema have developed over hours.

*Level of evidence II: Grade of recommendation C*

### Clinical Practice Points

- Potential precipitating factors for atrial fibrillation should be considered, and corrected where possible. These include:
  - electrolyte abnormalities;
  - hyperthyroidism;
  - alcohol consumption;
  - uncontrolled hypertension;
  - mitral valve disease;
  - acute pulmonary disease;
  - myocardial ischaemia;
  - chest, and other, infections.
- Patients with heart failure and coexisting atrial fibrillation should be treated with diuretics and ACE inhibitors and this will often reduce the heart rate. Beta-blockers should be added according to the standard guideline recommendations.

#### Rate control

- Rate control should be assessed using the apical heart rate or by ECG. Heart rate obtained from standard measurement of the pulse rate at the radial artery does not adequately reflect the ventricular rate.
- Rate control is achieved when the resting ventricular response is 60-80 beats/min at rest, and 90-115 beats/min during moderate exercise.
- Rate control should be assessed when therapy has been established, and every 2-3 years.
- Digoxin is the first choice of agent for rate control, but may be less effective if sympathetic tone is high.
- Amiodarone is effective for reducing heart rate if digoxin is inadequate, and may effect cardioversion.
- In the acute setting, cautious low-dose short-acting diltiazem may be effective and is generally well-tolerated unless hypotension and/or heart failure are severe.
- Once heart failure is under control, beta-blockers such as metoprolol or carvedilol should be considered according to the guideline recommendations.
- If drug therapy is ineffective or not tolerated, refer selectively for consideration of atrioventricular (AV) nodal ablation and permanent pacemaker implantation.

## **Supporting Evidence**

### **Rate control**

While digoxin has long been a mainstay in the management of AF and HF, there is evidence that it does not adequately control heart rate during exercise or where there is increased sympathetic tone.<sup>179</sup> In addition, digoxin has not been shown to improve overall mortality in patients with HF.<sup>129</sup>

Amiodarone is a suitable alternative agent when rapid rate control is required in the acute setting.<sup>177</sup> However, its significant long-term side effects make it unattractive for ongoing rate control.

The known survival benefits of beta-blockers in HF with LV systolic dysfunction make them attractive agents for AF rate control in HF.<sup>111, 113</sup> In one small randomised, double-blind, crossover study, the combination of digoxin and carvedilol was shown to be superior to either agent alone in terms of rate control, LVEF and patient symptoms.<sup>180</sup> The authors suggested that this demonstrates that both increased vagal tone and reduced sympathetic activation are important for controlling heart rate in patients with HF and AF. There are no data on the safety or efficacy of beta-blockers in acute AF with decompensated HF, and alternative agents should be used in this setting.

Diltiazem induces rapid, sustained heart rate control in the acute setting.<sup>177</sup> Two small studies showed no worsening of HF, although patients need to be carefully monitored for hypotension. Diltiazem is an effective chronic rate-controlling agent. It is efficacious in patients with HF with preserved systolic dysfunction.<sup>181</sup> Because of its negative inotropic effects, the use of diltiazem in patients with systolic dysfunction remains controversial. However, there is some evidence of benefit<sup>182</sup> and the risks of inadequate rate control should be balanced against the potential risks of diltiazem when other agents are not tolerated or are contraindicated.

When AF rate is refractory to medical therapy, atrioventricular (AV) node ablation and permanent pacing should be considered.<sup>183</sup> The optimal pacing site, and the role of biventricular pacing after AV node ablation, are the subject of ongoing investigation.

### **Rhythm control**

The AF-CHF study compared the effects of a routine rhythm-control strategy with a rate-control strategy in patients with HF and LV systolic dysfunction and AF.<sup>184</sup> The rhythm-control strategy involved electrical cardioversion plus antiarrhythmic drug therapy, generally amiodarone, while the rate-control strategy involved a combination of beta-blocker and/or digoxin followed, under certain circumstances, by AV nodal ablation and pacemaker implantation. During an average follow-up of 3 years, 58% of patients in the rhythm-control group had at least one recurrence of AF and 27% were in AF at 4 years. The rhythm-control strategy did not reduce the rate of death from cardiovascular causes compared with a rate-control strategy. Neither were there any beneficial effects on secondary outcomes.

In some clinical circumstances, restoration and maintenance of sinus rhythm may still be considered. The AF recurrence rate after electrical cardioversion is high in patients with HF, and antiarrhythmic drugs will generally be required to try and maintain sinus rhythm.

Class I antiarrhythmics (disopyramide, flecainide, propafenone) are associated with a high risk of proarrhythmia in patients with HF and should not be used in this setting.

Dofetilide is a pure class III agent. The DIAMOND-CHF study enrolled participants with new or worsening HF and at least one episode of shortness of breath in the previous month, and compared dofetilide with placebo.<sup>185</sup> There was no difference in mortality between the two treatment groups, but dofetilide reduced or delayed hospitalisation and significantly increased rates of conversion to sinus rhythm at 1 and 12 months. The incidence of torsades de pointes in the dofetilide group was approximately 2-5%. Dofetilide is not currently available in New

Zealand.

Uncontrolled trials have shown that the class III agent amiodarone may help maintain sinus rhythm after cardioversion.<sup>177</sup> The use of amiodarone in HF patients is not associated with increased mortality,<sup>186</sup> and this makes it a suitable agent for patients with HF requiring antiarrhythmic therapy. However, the use of amiodarone is frequently associated with serious non-cardiac side effects and requires careful monitoring.

Dronedarone, a multichannel blocker with electrophysiological properties similar to those of amiodarone, has been developed for the treatment of AF. It does not cause iodine-related adverse events, and proarrhythmia has not been observed. Dronedarone has been evaluated in patients hospitalised with HF and who had significant LV systolic dysfunction.<sup>187</sup> The study was stopped prematurely due to excess mortality in the group treated with dronedarone compared with placebo. While the absolute numbers were small, it appeared that the excess in mortality was due to worsening HF. Interestingly, while amiodarone has not been associated with increased mortality in patients with HF, subgroup analysis of the Sudden Cardiac Death in HF Trial suggested that amiodarone was associated with excess mortality compared with placebo in patients with NYHA class III HF, but not in those with less severe symptoms.<sup>142</sup>

Non-antiarrhythmic drug therapy may decrease the incidence of AF in patients with HF. It has been postulated that ACE inhibitors and ARBs may, by unloading the left atrium, prevent fibrosis and the development of the substrate for AF. There have been few prospectively-designed trials to test this hypothesis, and evidence comes primarily from secondary analysis of large clinical trials. A meta-analysis has reported a 28% reduction in the relative risk of AF with these drugs, with the greatest benefit in patients with HF (relative risk reduction 44%).<sup>188</sup> A recent large, prospective trial of valsartan for the secondary prevention of AF, showed no reduction in recurrence of the arrhythmia.<sup>189</sup> However, only 8% of subjects had HF or systolic dysfunction at enrollment and follow-up was only for a year.

The role of curative catheter ablation of AF in this patient group is yet to be defined. A recent trial randomised 81 patients with HF and drug-refractory AF to either pulmonary vein isolation or AV node ablation with biventricular pacing.<sup>190</sup> At follow-up the pulmonary vein isolation group had a higher LVEF and longer 6-minute walk test, suggesting that there may be a future role for this evolving therapy.

## **2. Prevention of thromboembolism**

HF is associated with an increased risk of thromboembolism. However the optimal prevention strategy remains unclear except in patients with specific risk factors such as AF or demonstrated intracardiac thrombus. As patients with HF are often elderly and frequently have comorbid conditions that increase the risk of bleeding with anticoagulation, careful individual assessment of risks and benefits is required.

For a detailed advice regarding initiation and monitoring of warfarin therapy, including management during intercurrent surgery and of International Normalised Ratio (INR) values outside the therapeutic range, refer to the NZGG Guideline for The Management of People with Atrial Fibrillation and Flutter<sup>178</sup> ([www.nzgg.org.nz](http://www.nzgg.org.nz)).

### **Recommendations**

**Anticoagulation with warfarin (target INR 2.0-3.0) is recommended for the prevention of thromboembolism in patients with heart failure and atrial fibrillation, or a history of atrial fibrillation, unless contraindicated.**

*Level of evidence I: Grade of recommendation A*

**Anticoagulation is recommended in patients with intracardiac thrombus detected on cardiac imaging, or where there is evidence of systemic embolism.**

**There is no evidence for the routine anticoagulation of other patients with heart failure except in the presence of a prosthetic heart valve.**

*Level of evidence I: Grade of recommendation B*

### **Clinical Practice Points**

- The risk of bleeding needs to be assessed in all patients with atrial fibrillation or flutter being considered for anticoagulant treatment, and reassessed periodically.
- Anticoagulation should be maintained in patients with a history of atrial fibrillation because of the high rate of silent recurrence of atrial arrhythmias and the associated risk of thromboembolism.
- Warfarin interacts with numerous drugs, and care needs to be taken when prescribing new medications.
- Given the narrow therapeutic range of INRs, barriers that prevent access to medication and INR testing need to be addressed on an individual basis.

### **Supporting Evidence**

Patients with chronic HF are at increased risk of thromboembolic events due to stasis of blood and perhaps due to increased activity of procoagulant factors. However, retrospective studies have demonstrated a relatively low risk of clinically apparent thromboembolism of 1-3% per year.<sup>191</sup> The routine use of warfarin in patients with HF has therefore been controversial.

Two recent randomised prospective trials attempted to determine the optimal antithrombotic therapeutic approach for patients with HF in sinus rhythm. The WASH trial<sup>192</sup> was a pilot study which randomised 279 patients with systolic dysfunction and diuretic requirement to aspirin 300mg daily, warfarin with a target INR of 2.5, or no antithrombotic therapy. The primary outcome was death, non-fatal myocardial infarction or nonfatal stroke. There was no difference between groups in the primary outcome, but there was a nominally significant excess of hospitalisations in the aspirin group. The WATCH trial<sup>193</sup> randomised patients with symptomatic HF (NYHA class II-IV), sinus rhythm, and LVEF ≤35% to aspirin 162mg daily, clopidogrel 75mg daily, or warfarin with a target INR of 2.5-3.0. The trial was stopped early due to slow

recruitment. A total of 1,587 patients were randomised with a mean follow-up of 1.9 years. The primary outcome was time to first occurrence of death, non-fatal myocardial infarction or non-fatal stroke. There was no difference between groups in the primary composite endpoint or all-cause mortality. There were fewer non-fatal strokes in the warfarin arm, although absolute numbers were small, and the difference did not persist when central nervous system bleeding was added to all strokes. As in the WASH trial, more patients in the aspirin group were hospitalised for HF than in the warfarin group. There was no significant difference in HF admissions between the warfarin and clopidogrel arms. The combined results of these two trials do not suggest a clinically significant benefit of routine anticoagulation in patients with HF and systolic dysfunction.

AF is a common comorbidity in HF, and HF is an independent risk factor for stroke in patients with AF in some, but not all, studies.<sup>194</sup> HF is a component of the CHADS<sub>2</sub> score, which has been validated as highly predictive of stroke risk in patients with AF.<sup>195</sup> In addition, HF frequently is associated with other components of the CHADS<sub>2</sub> score, namely hypertension, older age, and diabetes. Warfarin therapy is associated with a 68% reduction in stroke risk in patients with AF.<sup>196</sup> A systematic review of the literature concluded that in patients with AF, an INR <2 is associated with a significant increase in stroke risk compared with an INR ≥2. Patients with an INR >3 are at a significantly higher risk of bleeding than patients maintained in a range of 2-3.<sup>197</sup>

Anticoagulation should also be considered in other subgroups of HF patients who are at increased risk of thromboembolism. These include those with a prior thromboembolic event, underlying conditions such as amyloidosis and LV non compaction, familial dilated cardiomyopathy, and/or a history of thromboembolism in first degree relatives.<sup>198</sup> Anticoagulation is also recommended in patients with intracardiac thrombus detected on imaging,<sup>199</sup> although many cardiac thrombi detected on echocardiography do not embolise.<sup>200</sup>

## **Summary**

Currently available evidence does not support routine anticoagulation with warfarin for patients with HF. Specific groups at increased risk of thromboembolism should be considered for anticoagulation.

## Palliative Care in Patients with Heart Failure

Patients with advanced HF may have frequent symptoms and poor QOL. Traditionally, palliative care services have been available for patients with malignancy. However, it is now recognised that palliative care is appropriate for all individuals affected by a life-limiting disease, including those with HF.<sup>201</sup>

### Recommendations

All patients with end-stage heart failure resistant to optimal heart failure therapy should be offered a palliative approach.

*Level of evidence IV: Grade of recommendation D*

### Clinical Practice Points

- A palliative care plan does not replace the multidisciplinary programmes of care used for optimal heart failure management, but rather builds on and adds to such strategies.
- Management of symptoms associated with heart failure at the end of life is an important aspect of palliative care:
  - *breathlessness*: diuretics will generally still be required to optimise management of fluid overload. Opioids such as morphine can also be effective in managing shortness of breath;
  - *fatigue*: look for potentially reversible causes such as infection, anaemia and drug side effects. Measures such as gentle exercise, relaxation, visualisation techniques and pacing of activities may be helpful;
  - *thirst*: sucking on frozen juice cubes, using mouth washes or artificial salivas/ saliva stimulants (such as chewing gum) may be effective in managing xerostomia;
  - *angina*: some patients with end-stage heart failure may have ongoing debilitating angina. Continuation of long-acting nitrate therapy and morphine may be required;
  - *anorexia/cachexia*: look for potentially reversible causes such as oral candidiasis, untreated nausea, constipation and ill-fitting dentures.
- The indications for ongoing medical heart failure therapies should be reviewed regularly. Some therapies may assist with symptom management at end of life and should be continued, whilst others may not be required. Therapeutic decisions should be individualised for each patient.
- Patients with an ICD may require specific counselling regarding switching off the ICD during end-of-life care.

### Supporting Evidence

Palliative care refers to a holistic approach to relieving symptoms for those with a life-limiting illness, while also achieving the best QOL for the patient and providing support for their families and caregivers. An important aspect of palliative care is that it looks beyond the disease to the person and their needs. This is achieved through the prevention and relief of suffering by means of early identification, and impeccable assessment and treatment, of pain and other problems (physical, psychosocial and spiritual).<sup>202</sup> Historically, the concept of palliative care has been most often applied in the setting of cancer.

Patients with severe HF who fail to respond to available pharmacological and non-pharmacological interventions have been shown to have poor QOL; in some cases QOL is as severely impaired as in patients with cancer.<sup>203-205</sup> Furthermore, cardiac patients receive less health, social and palliative care services than those with inoperable lung cancer, and these services are not well co-ordinated.<sup>204</sup> In patients with severe HF, survival rates are also as low as for the most common form of cancer, with an overall 5-year case-fatality rate of 75%.<sup>16</sup> The symptoms of NYHA Class IV congestive HF include anorexia, cachexia, fatigue, depression and sleep disturbance, and prognosis in these patients is very poor.<sup>206</sup>

The number of patients living with HF has increased, due to the survival gains achieved through advances in therapy.<sup>207</sup> In addition, the increasing rate of survival after acute MI and the aging population demographic contribute to an increased number of people who potentially will have to deal with end-stage HF.

There are therefore a variety of reasons why a palliative care approach is clearly indicated in patients with end-stage HF, and it is important for healthcare professionals to be aware of this. The main aim of intervention should be effective control of symptoms to optimise QOL, along with facilitation of end-of-life decision making for the patient and their family. This sentiment was echoed by the National Institute for Clinical Excellence (NICE) in the UK which stated that “there is substantial evidence for considerable unmet palliative needs of patients with HF and their informal carers. The main areas of need include symptom control, psychological and social support, planning for future, and end of life care”.<sup>208</sup>

A palliative care plan does not replace the multidisciplinary programmes of care used for optimal HF management, but rather builds on and adds to such strategies. In addition, a good palliative care approach can reduce the amount of time patients spend in acute care settings.<sup>209</sup> According to the European Society of Cardiology (ESC) position statement, “palliative care should be integrated as part of a team approach to comprehensive [HF] care and should not be reserved for those who are expected to die within days or weeks. Rather, this should be considered for the general clinical cohort as part of a comprehensive care provision over the whole disease trajectory”.<sup>201</sup>

### **Definitions**

Generalist palliative care is provided to those affected by life-limiting illness as part of standard clinical practice by any healthcare worker. This is delivered in the community by a variety of groups, including general practice teams, Maori health providers, allied health teams, district nurses and residential care staff. In hospitals, generalist palliative care is provided by ward staff and disease-specific teams (e.g. the cardiac team). Generalist palliative care should be available throughout the course of a life-limiting illness.

Specialist palliative care is provided by healthcare professionals who have undergone specific training and/or accreditation in palliative care or medicine, working as part of an expert interdisciplinary team. These teams have a higher level of expertise in complex symptom management, psychosocial support, grief and bereavement. Providers of such care are usually associated with a hospice or hospital. Specialist palliative care should be provided on the basis of assessed need, rather than simply diagnosis or prognosis.

Both of these levels of palliative care are important. However, it has been suggested that the majority of patients with end-stage HF are likely to have complex medical and other issues that may not be able to be adequately managed by generalists, without consulting specialist palliative care services.<sup>210</sup> In addition, specialists have an important role to play in educating generalists about the provision of palliative care.<sup>210</sup>

### **General considerations**

Palliative care should be available wherever the patient is – be that home, hospital, residential care or hospice. It should be centred on the patient and their family/caregivers. The level of palliative care support required in any individual situation is dynamic and will vary during the course of illness (and into bereavement). A programme of care individualised to the needs of the patient and their family is extremely important.

### **Special considerations in New Zealand**

In applying palliative care in New Zealand<sup>211</sup> some additional points need to be taken into account, including:

- The holistic Maori philosophy/model, such as Te Whare Tapa Wha (four-sided house) towards health/wellbeing: Te Taha Tinana (physical health), Te Taha Hinengaro

(psychological health), Te Taha Wairua (spiritual health) and Te Taha Whanau (family health).

- The diverse range of cultural beliefs, values and practices of patients and their families.
- Advanced directives: these have been defined in the Code of Health and Disability Services Consumers' Rights as "a written or oral directive – a) by which a consumer makes a choice about a possible future health care procedure; and b) that is intended to be effective only when he or she is not competent". The NZ Medical Association has produced information about advanced directives in line with the code including sample forms that can be used by patients.<sup>39</sup>

### **Palliative care in heart failure**

In patients with HF, palliative care needs to be integrated into optimal medical management plans. It should include discussion of prognosis, management of symptoms and comorbidities, and hospice care, along with end-of-life directives. Palliative care discussion and implementation does not need to be left until the patient is seriously ill. In fact, it is preferable to have discussions about end-of-life decisions and advance directives during the process of treating a patient with HF because it can be difficult to know when a patient with HF has reached the "end-of-life" criteria.<sup>212</sup> Furthermore, sudden death does occur in patients with HF and this can happen at any time in the disease process, which can be distressing for family and friends if not anticipated.<sup>213</sup>

Aside from sudden death, strong markers of impending mortality in patients with HF are:<sup>214-217</sup>

- advanced age;
- recurrent hospitalisation for decompensated HF and/or a related diagnosis;
- NYHA class IV symptoms;
- advanced renal dysfunction;
- cardiac cachexia;
- hyponatraemia;
- refractory hypotension necessitating withdrawal of medical therapy.

It has been shown that the best predictor of survival in patients with HF is the severity of symptoms after treatment rather than during a disease exacerbation.<sup>218, 219</sup> However, it is recognised that accurate prediction of outcome among individual patients with end-stage HF is difficult and clinical course can be variable even at the end of life.

### *Goals of therapy*

Important goals in the management of all patients with end-stage HF include reducing the number of symptom exacerbations that necessitate hospitalisation and keeping the patient comfortable.<sup>220</sup>

Patients and their families may require support in adjusting to the change in goals of care from life-prolonging therapies to management that aims to improve the patient's overall QOL. Healthcare professionals should discuss with patients the level of intervention appropriate and/or desirable during this phase, so that unwanted interventions are avoided.

### *Symptom control*

Optimal use of HF therapies, including ACE inhibitors, ARBs, beta-blockers, diuretics, spironolactone and digoxin, has the potential to relieve symptoms, and therefore improve QOL. These treatments should be continued and dosages adjusted as long as the patient continues to tolerate them. As disease progression continues, such treatments may not fully relieve symptoms, and this is where more palliative therapies can be introduced.<sup>221</sup>

### *Shortness of breath (dyspnoea)*

Shortness of breath is common, and is one of the most limiting and distressing symptoms of HF for both patients and their families/caregivers. Significant shortness of breath has been reported in 60% of patients with advanced HF.<sup>222, 223</sup> Opioids such as morphine are useful for relieving shortness of breath in this setting.<sup>224</sup> Mechanisms of benefit include the ability to

decrease preload and afterload, and potential action in the midbrain centres.<sup>225</sup> A morphine dose of 2mg given orally every 2-3 hours appears to offer significant relief.<sup>225, 226</sup>

#### *Anorexia/cachexia*

Anorexia and cachexia are common symptoms in patients with end-stage HF. Consider potentially reversible causes such as untreated nausea, constipation and oral candidiasis. Simple measures such as offering several small snacks throughout the day and assistance with meal preparation can be helpful. Consider referral to a dietitian for those with clinically stable HF who are thought to be in negative calorie balance.<sup>227</sup>

#### *Pain*

Pain is common, particularly in the terminal stages of HF. It may be of cardiac or noncardiac origin and should be managed palliatively. As well as improving shortness of breath, opioids can be useful for the control of pain, regardless of its cause. Nonsteroidal anti-inflammatory agents (NSAIDS) should not be used to treat pain in patients with HF because they directly antagonise the effects of diuretics and ACE inhibitors resulting in fluid retention and deteriorating renal function, which in turn could exacerbate HF.<sup>228-230</sup>

#### *Fatigue*

Patients with end-stage HF often report fatigue, which is most likely related to their high level of functional impairment. Fatigue may therefore respond to optimisation of HF medications. Identification and management of potentially reversible causes of fatigue should be considered such as anaemia, sleep disorders, medication side effects and depression. Psychological and situational factors could also play a role in fatigue, making management a challenge that is likely to require multidimensional strategies. Simple measures such as pacing of activities, gentle exercise, relaxation and visualisation techniques may be helpful.

#### *Depression*

Depression is a symptom that is under-recognised and under-reported in patients with end-stage HF. Symptoms of depression have been reported to be associated with an adverse prognosis in patients with HF, irrespective of disease severity.<sup>231</sup> It is therefore important that patients with HF are screened for depression and treated appropriately. Tricyclic antidepressants should be avoided because of their potential to induce hypotension and arrhythmias in HF patients; selective serotonin reuptake inhibitors (SSRIs) are the preferred option.

#### *Implantable cardioverter defibrillators (ICD)*

In some instances, palliative management may include the deactivation of an ICD. It is recommended that all patients with such a device receive information about the option to deactivate defibrillation.<sup>3</sup> Deactivation may be appropriate when the extent of deterioration of HF symptoms is such that there is a potential for the device to increase distress without having a meaningful impact on prognosis.<sup>232</sup> This is a complex ethical decision that requires careful attention,<sup>233</sup> and discussions should involve the patient, their family, and their general practitioner with an appropriate level of emotional support. The latter could be provided by specialist palliative care workers in partnership with the cardiology team. Any decision made, and its rationale, should be clearly documented.

#### **Conclusion**

Palliative care, with the goal of relieving suffering, improving patient QOL and supporting families/caregivers, is an important part of disease management in HF. In fact, palliative care should be offered in parallel with optimal treatment strategies.<sup>212</sup> Palliative care is best delivered through an integrated approach to care that recognises the roles and responsibilities of both cardiac and palliative care specialists. Such integration is essential for effective palliative care provision. Palliative care needs to be provided according to an individual's need, and may be suitable whether death is days, weeks, months or occasionally even years away.

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## Appendix 1

**Table A1. Key Characteristics of Meta-analyses and Systematic Reviews of the Efficacy of Exercise Training in Patients with Heart Failure**

	Spruit et al (2009) <sup>1</sup>	Chien et al (2008) <sup>2</sup>	Haykowsky et al (2007) <sup>3</sup>	Van Tol et al (2006) <sup>4</sup>	Rees et al (2004) <sup>5</sup>	ExtraMATCH (2004) <sup>6</sup>	Smart & Marwick (2004) <sup>7</sup>	Lloyds-Williams et al (2002) <sup>8</sup>
Type of analysis	Systematic review	Meta-analysis	Meta-analysis	Meta-analysis	Meta-analysis	Individual pt meta-analysis	Meta-analysis (of RCT only)	Systematic review
Objective	Resistance training	Home-based exercise training vs usual care	Type of exercise training vs usual care	Exercise training vs usual care	Exercise training vs usual medical care	Exercise training vs usual care	Exercise training	Exercise training
2 reviewers	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes
Identification/selection of studies:								
Search terms	Present	Present	Present	Present	Present	Not reported	Present	Present
Databases	Present	Present	Present	Present	Present	Present	Present	Present
Hand searches	Completed	Completed	Completed	Completed	Completed	Completed	Completed	Completed
Expert advice	Not reported	Yes	Not reported	Not reported	Yes	Yes	Not reported	Not reported
Inc & exc criteria	Present	Present	Present	Present	Present	Present	Not reported	Present
English only	Yes	Yes	Yes	Plus 3 others	No language restrictions	Not reported	Not reported	Yes
RCT parallel crossover Other designs	Yes ? ?	Yes No No	Yes No No	Yes Yes No	Yes Yes No	Yes No No	Yes Yes Yes	Yes Yes Yes
Search completed	Aug 2008	July 2006	2006	Oct 2004	2001	Unclear	Aug 2003	Dec 2000
No of studies/participants	resist 5/130 comb 5/145	10/648	aerobic 9/538 resist 1/88 comb 4/168	35/1486	29/1126	9 studies (data sets)/801 pts	81/2387	31 studies
Identification of quality of studies	Delphi Score	PEDro Scale	Jadad Scale	Delphi Score	Jadad Scale	Not reported	Not reported	Jadad Scale (RCTs only)
Identified exercise parameters	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Data analysis discussed/described including heterogeneity	Authors deemed inappropriate to conduct a meta-analysis	Yes	Yes	Yes	Yes	Yes	Unclear	Author deemed inappropriate to conduct a meta-analysis

RCT = randomised controlled trial, pt = patient, resist = resistance, comb = combination, vs = versus.

**Table A2. Efficacy of Exercise Training on Exercise Capacity and HRQOL in Patients with Heart Failure: Results of Meta-analyses**

	<b>Peak Oxygen Uptake (peak VO<sub>2</sub> or Maximum Oxygen Uptake (VO<sub>2max</sub>)</b>	<b>Six Minute Walk Test (6MWT)</b>	<b>Health Related Quality of Life (HRQOL)</b>
Chien et al (2008) <sup>2</sup>  Home-based exercise training vs usual care/activity	Peak VO <sub>2</sub> WMD = 2.71 mL/kg/min; 95% CI 0.67, 4.74 (7/10 studies; 355 pts) *Summary interpretation Significantly favoured exercise training	WMD = 41m; 95% CI 19, 63 (5/10 studies; 320 pts) Summary interpretation Significantly favoured exercise training	WMD = 0.5 out of 105, 95% CI -4.4, 5.4 (MLwHF; 3/10 studies; 198 pts) Summary interpretation Inconclusive
Haykowsky et al (2007) <sup>3</sup>  Exercise training & type of training vs usual care	Peak VO <sub>2</sub> WMD = 2.98 mL/kg/min; 95% CI 2.47, 3.49 (9/14 studies; 538 pts) Summary interpretation Significantly favoured aerobic exercise training	Not assessed	Not assessed
Van Tol et al (2006) <sup>4</sup>  Exercise training vs usual care	Peak VO <sub>2</sub> 2.06 mL/kg/min; SES = 0.6, 95% CI 0.42, 0.79 (31/35 studies; 1240 pts) Summary interpretation Significantly favoured exercise training	+46.2m; SES = 0.52, 95% CI 0.36, 0.69 (15/35 studies; 599 pts) Summary interpretation Significantly favoured exercise training	-9.7 points; SES = -0.41 95% CI -0.60, -0.22 (MLwHF; 9/35 studies; 463 pts) Summary interpretation Significantly favoured exercise training
Rees et al (2004) <sup>5</sup>  Exercise training vs usual medical care	VO <sub>2max</sub> WMD = 2.16 mL/kg/min; 95% CI 2.82, 1.49 (24/29 studies; 848 pts) Summary interpretation Significantly favoured exercise training	WMD = 40.9m; 95% CI 64.7, 17.1 (8/29 studies; 282 pts) Summary interpretation Significantly favoured exercise training	7/9 studies (467 pts) that reported HRQoL found improvement Summary interpretation Favoured exercise training

\*Two reviewers, one of which was a statistician with expertise in meta-analysis, extracted data from the literature and then a consensus was agreed upon, providing a summary interpretation. Significantly favours = significant statistical difference, Favours = not a statistical difference, Inconclusive = small number of studies and not statistically significant. Not significant = Not statistically significant and magnitude of change was negligible. WMD = weighted mean differences, SES = summary effect size, MLwHF = Minnesota Living with Heart Failure Questionnaire, vs = versus; CI = confidence interval.

**Table A3. Efficacy of Exercise Training on Hospitalisation, Mortality, and Combined Endpoints: Results of Meta-analyses**

	Hospitalisation	Mortality	Combined Endpoints
Chien et al (2008) <sup>2</sup>  Home-based exercise training vs usual care/activity	OR = 0.75; 95% CI 0.19, 2.92 (2/10 studies; 143 pts) *Summary interpretation Inconclusive	Not assessed	Not assessed
Rees et al (2004) <sup>5</sup>  Exercise training vs usual medical care	OR = 0.28; 95% CI 0.09, 0.85 (1/29 studies; 99 pts) Summary interpretation Significantly favoured exercise training	OR = 0.32; 95% CI 0.13, 0.8 (1/29 studies; 99 pts) Summary interpretation Significantly favoured exercise training	Not assessed
ExtraMATCH (2004) <sup>6</sup>  Exercise training vs usual care	Not assessed	HR = 0.65; 95% CI 0.46, 0.92 (9/9 studies; 801 pts) Summary interpretation Significantly favoured exercise training	<u>Death or time to hospitalisation</u> HR = 0.7; 95% CI 0.56, 0.93 (8/9 studies; 721 pts) Summary interpretation Significantly favoured exercise
Smart & Marwick (2004) <sup>7</sup>  Exercise training	Not assessed	OR = 0.71; 95% CI 0.37, 1.02 (11 RCT; 737 pts) Summary interpretation Favoured exercise training	<u>Death and adverse events</u> OR = 0.98; 95% CI 0.61, 1.32 (17 RCT; 870 pts) Summary interpretation Non significant  <u>Hospitalisation and withdrawal from programme</u> OR = 0.83; 95% CI 0.50, 1.39 (14 RCT; 1197 pts) Summary interpretation Favoured exercise training

\*Two reviewers, one of which was a statistician with expertise in meta-analysis, extracted data from the literature and then a consensus was agreed upon providing a summary interpretation. Significantly favours = significant statistical difference, Favours = not a statistical difference, Inconclusive = small number of studies and not statistically significant. Not significant = Not statistically significant and magnitude of change was negligible. OR = odds ratio, HR = hazard ratio, CI = confidence interval, vs = versus.

**Table A4. Effects of Exercise Training on Cardiac Performance in Patients with Heart Failure: Results of Meta-Analyses**

	LVEF	End-diastolic volume	End-systolic volume
Haykowsky et al (2007) <sup>3</sup> Type of training vs usual care			
<b>Aerobic only</b>	WMD = 2.59%; 95% CI 1.44%, 3.74% (9/14 studies; 538 pts) *Summary interpretation Significantly favoured aerobic training	WMD = -11.49mL; 95% CI -19.95, -3.02 (5/14 studies; 371 pts) Summary interpretation Significantly favoured aerobic training	WMD = -12.87mL; 95% CI -17.80, -7.93 (5/14 studies; 371 pts) Summary interpretation Significantly favoured aerobic training
<b>Aerobic + Resistance</b>	WMD = 0.37%; 95% CI -2.23%, 2.97% (4/14 studies; 249 pts) Summary interpretation Inconclusive	WMD = 0.39mL; 95% CI -25.84, 26.62 (2/14 studies; 198 pts) Summary interpretation Inconclusive	WMD = -0.73mL; 95% CI -23.19, 21.72 (2/14 studies; 198 pts) Summary interpretation Inconclusive
<b>Resistance only</b>	WMD = -4.5%; 95% CI -13.14%, 4.14% (1/14 studies ; 25 pts) Summary interpretation Inconclusive	Not assessed	Not assessed
Van Tol et al (2006) <sup>4</sup>			
<b>Exercise training vs usual care</b>	+0.8%; SES = 0.16 95% CI -0.12, 0.45 (14/35 studies; 683 patients) Summary interpretation Favoured exercise training	-3.13mL; SES = -0.21 95% CI -0.39, -0.04 (9/35 studies; 527 pts) Summary interpretation Significantly favoured exercise training	-0.96mL; SES = -0.21 95% CI -0.58, 0.07 (7/35 studies; 485 pts) Summary interpretation Non significant

\*Two reviewers, one of which was a statistician with expertise in meta-analysis, extracted data from the literature and then a consensus was agreed upon providing a summary interpretation. Significantly favours = significant statistical difference, Favours = not a statistical difference, Inconclusive = small number of studies and not statistically significant. Not significant = Not statistically significant and magnitude of change was negligible. WMD = weighted mean difference, SES = summary effect size, CI = confidence interval, pt = patients, vs = versus.

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Heart disease is the single biggest killer of men and women in New Zealand.

The Heart Foundation is the charity that works to stop New Zealanders dying prematurely from heart disease. It does this through funding vital heart research, continuing the education of cardiologists, improving heart disease risk assessment and cardiac care, and promoting heart healthy lifestyles.

Without the generosity of the New Zealand public, the Heart Foundation could not continue its lifesaving work. Any help you can give is greatly appreciated.

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