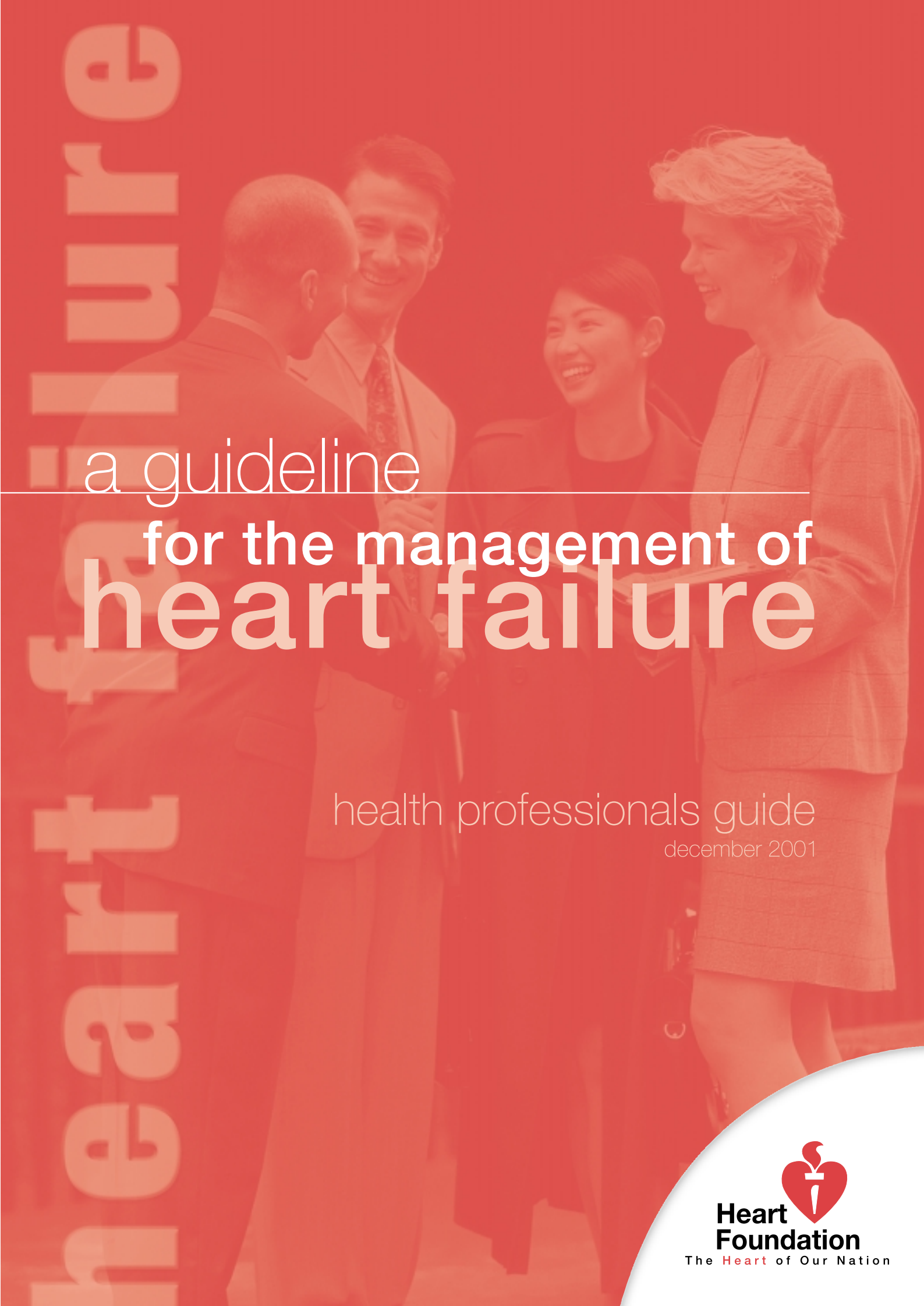

a guideline for the management of heart failure

health professionals guide

december 2001

Heart Foundation

The Heart of Our Nation

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the guideline process

scope

This guideline makes recommendations relating to the management of patients with an established diagnosis of congestive heart failure due to systolic ventricular dysfunction. Management of diastolic dysfunction is not included. There is commentary on diagnosis in order to define the population of patients to which this guideline refers.

objectives

The aim of this guideline is to reduce morbidity and mortality from congestive heart failure. It is also hoped that patients' understanding and satisfaction with their health care will be improved. Outcomes predicted are increased survival and reduced morbidity as represented by either functional scores or by hospital admission.

process

The first version of this guideline was published by the National Heart Foundation of New Zealand in 1996. The guideline team developed the guideline by adhering to the systematic approach developed by the Guidelines for Guidelines Trust.[1]

1. A systematic search of the external literature was undertaken to identify explicitly developed evidence based guidelines on the management of heart failure.

   The following guidelines were reviewed:
   - The New Zealand Guidelines for the Management of Chronic Heart Failure[2]
   - The American College of Cardiology/American Heart Association (1996)
   - The Canadian Cardiovascular Society (1994)
   - The Task Force on Heart Failure by the European Society of Cardiologists (1996)
   - The Anglia and Oxford Regional Health Authority (1995), and
   - The Agency for Health Care Policy and Research (AHCPR)[3]

   Of these the AHCPR guideline was determined to be systematically developed from a review of external evidence, and for which the strength of evidence could be ascertained for each recommendation. The Heart Foundation guideline[2] served as the key domestic resource.

2. Areas requiring further review and evaluation of the external evidence were identified on the basis of the strength of the evidence backing current recommendations (recommendations with less strong evidence were selected) or areas where there was identifiable new evidence.

   The following topics were selected for further review of the external evidence:
   - The management of atrial fibrillation
   - The role of anticoagulation in heart failure
   - The role of amiodarone in heart failure
   - The role of beta blockers in heart failure
   - The role of digoxin in heart failure
   - The effectiveness and role of patient education

- The effectiveness of interventions to improve patient compliance
- The effectiveness and role of exercise in heart failure.

3. Each review included a systematic Medline search of the literature by medical librarians.

4. Each paper was reviewed and critiqued by a member of the guideline team and strength of evidence assigned according to the following quality-rating scale. Final decisions regarding each paper and the recommendations of the guideline was established by consensus.

In April 2000 the guideline team selected topics for which there was consensus that significant new evidence was available. These were:

- The role of beta-blockers
- The optimal dose of ACE inhibitors
- The role of angiotenson II antagonists
- The role of spironolactone
- The effectiveness of patient held action plans

A systematic search of the literature to April 2000 was undertaken and evidence reviewed as the original guideline process. Two further large-scale randomised controlled trials (RCTs) of the effects of beta-blockers in patients with heart failure were published in 2001 and have been included because of the importance of these data.

the strength of evidence

The quality-rating scale, described by AHCPR was used.[3]

Seven levels were used:

I. Evidence from large, well conducted RCTs
II. Evidence from small, well conducted RCTs
III. Evidence from well-conducted cohort studies
IV. Evidence from well-conducted case-control studies
V. Evidence from uncontrolled or poorly controlled studies
VI. Conflicting evidence, but tending to favour the recommendation
VII. Expert opinion

The classification scheme for the guideline document was then simplified into a three-level system for strength of evidence:

A. Good evidence:
Evidence from well conducted RCTs or cohort studies (Levels I-III).
B. Fair evidence:
Evidence from other types of studies (Levels IV-VI).
C. Expert opinion:
(Level VII).

5. The draft guideline was written by the guideline team and subjected to peer review by the Goodfellow Unit, Division of General Practice and Primary Health Care, University of Auckland, the Royal New Zealand College of General Practitioners, and members of the Heart Foundation Heart Failure Guideline Committee.
The review confined itself to issues of format, presentation and utility, not issues of evidence.

review

A Heart Foundation committee will review these guidelines annually and decide whether updates are required.

funding

A one off grant by Merck Sharp and Dohme sponsored the initial guideline development process. Expenditure of the grant was at the discretion of the guideline team, such expenditure being for the purposes of developing the guideline. Any funds remaining at the end of the project were returned to the sponsor. No team member, except the MSD representative, received any remuneration from the sponsor. Printing of the revised guideline was supported by Merck Sharp & Dohme and Roche.

future research

The cost effectiveness of echocardiography in improving outcomes for patients with left ventricular failure and whether there are identifiable characteristics that will stratify patients that will most benefit from echocardiology.

the guideline team

- Dr Rob Doughty, Co-chair, Fellow of the New Zealand Guidelines Group, Heart Foundation BNZ Senior Fellow, University of Auckland.

- Dr Peter Didsbury, Co-chair, Director ProCare Health Limited, Member of the Advisory Group to the New Zealand Guidelines Group, GP, Manurewa, Auckland.

- Dr Arthur Coverdale, Cardiologist, Greenlane Hospital.

- Dr Peter Gow, Director Clinical Services, South Auckland Health.

- Dr James Kriechbaum, GP, Member of ProCare, Penrose.

- Dr Douglas Gillanders, GP, Glendowie, Director of ProCare Central.

- Dr David Woolner, Medical Director, Merck, Sharp and Dohme Ltd.

- Dr Jocelyn Tracey, GP and Professional Development Facilitator, South Med.

- Dr Andrew Kerr, Cardiologist, South Auckland Health.

- The Heart Foundation Heart Failure Guideline Committee: Professor Hamid Ikram (chair); Dr. Sandra Hicks; Professor Gary Nicholls; Professor Norman Sharpe; Dr. Larry Skiba; Professor Harvey White.

- Heart Foundation staff: Dr Diana North, Dr Boyd Swinburn, Mrs Pip Mason, Dr Mary Seddon.

These guidelines relate to the diagnosis and management of patients with congestive heart failure due to left ventricular systolic dysfunction.

diagnosis

Clinical Evaluation: Summary

- All patients, who complain of paroxysmal nocturnal dyspnoea, orthopnoea or new onset of shortness of breath on exertion, should undergo evaluation for heart failure unless history and physical examination clearly indicate a non-cardiac cause for their symptoms. *(Strength of evidence = B)*[3]

- The physical examination can provide important information about the aetiology of patients' symptoms and about appropriate initial treatment. However, physical signs are not highly sensitive for detecting heart failure.

- Elevated jugular venous pressure, a third heart sound, and a laterally displaced apical impulse are the most specific and are virtually diagnostic in a patient with compatible symptoms. *(Strength of evidence = B)*[3]

Symptoms of Heart Failure (see Box 1)

When clinical heart failure develops, dyspnoea on exertion is often the earliest symptom followed by paroxysmal nocturnal dyspnoea oedema, cough and orthopnoea.[4] Fatigue is an important symptom and may occur early in failure due to valvular disease. A history of hypertension, previous myocardial infarction, cardiac murmur or other heart disease in conjunction with the above symptoms points strongly toward a diagnosis of heart failure. It should be noted that many patients with impaired left ventricular function have no symptoms, eg 20% of patients with a left ventricular ejection fraction (LVEF) of less than 40% may have no clinical criteria for heart failure.[5] Furthermore, the symptoms listed above are not always due to heart failure.

Box 1. Symptoms suggestive of heart failure:

- Paroxysmal nocturnal dyspnoea
- Orthopnoea
- Dyspnoea on exertion
- Lower extremity oedema
- Decreased exercise tolerance
- Unexplained confusion or fatigue in elderly
- Nausea or abdominal pain (ascites or hepatic engorgement)

Physical Examination

Box 2. Abnormal physical findings in heart failure 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

In many patients with moderate-to-severe left ventricular systolic dysfunction or early symptoms of heart failure, there are few abnormal physical findings. A pathological third heart sound is the most sensitive physical sign, and is present in two-thirds of patients with ejection fractions below 30%.[6] Rales and/or a displaced apical impulse are present in about a third of patients. Jugular venous distension and peripheral oedema appear to be less sensitive signs.[4]

The specificity of physical findings are less well defined but an elevated jugular venous pressure and a third heart sound are probably the most specific clinical signs of heart failure. Lower extremity oedema is a relatively non-specific finding, common in older people, and usually due to chronic venous insufficiency.[3]

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 life-style (Box 3.) 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 heart failure on the basis of exercise intolerance examines only one facet of heart failure symptomatology. Many symptoms of heart failure (eg fatigue) are impossible to quantify with precision.

Box 3. New York Heart Association Functional Capacity:

Class 1.
Patients with cardiac disease but without resulting limitation in physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or anginal pain.

Class 2.
Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain.

Class 3.
Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnoea or anginal pain.

Class 4.
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.

aetiology of heart failure

Heart failure should never be the final diagnosis. The aetiology of heart failure and the presence of exacerbating factors or other diseases that have important influence on management should be carefully considered. The extent to which the cause of heart failure should be pursued by further investigation will depend on the life expectancy of the patient, the resources available, and the likelihood that diagnosis will influence management.

Chronic heart failure may be due to several different underlying aetiological factors (Table 1). Myocardial dysfunction as a result of coronary artery disease (most commonly from myocardial infarcts) is the most common cause of heart failure under the age of 75-years, and clear abnormalities of systolic function are usually present. In the elderly, accurate diagnosis is more difficult and obscured by multiple other diagnoses. Hypertension, hypertrophy, and myocardial fibrosis may be more important causes of heart failure in the elderly and may occur in the presence of preserved systolic function. Often there is uncertainty over which factor dominates.

A. Causative Factors:

- Coronary Artery Disease
- Hypertension
- Valvular Heart Disease
- Infections
- Cardiomyopathies (including alcoholic and idiopathic)
- Endocrine disorders (especially thyrotoxicosis)
- Genetic Conditions
- Congenital Heart Disease
- Inflammatory/immunological
- Chronic arrhythmias eg complete heart block or incessant tachycardia

B. Precipitating or Exacerbating Factors:

It is important to identify and treat any reversible factors, which may be exacerbating the symptoms of heart failure.

These factors include:

- Anaemia
- Infection
- Arrhythmias, especially atrial fibrillation
- Drugs, eg non-steroidal anti-inflammatory drugs, calcium channel blockers, corticosteroids and liquorice
- Renal dysfunction / renal artery stenosis
- Pulmonary embolism
- Silent myocardial infarction
- Excess salt intake

Table 1. Recommended Tests for Patients With Suspected Heart Failure:[7]

Test Recommendations	Finding	Suspected Diagnosis
Chest x-ray	Cardiomegaly Pulmonary venous congestion Interstitial fluid Pulmonary disease	Heart failure Lung conditions
Electrocardiogram	Acute ST-T wave changes Atrial fibrillation, other tachyarrhythmia Bradyarrhythmias Previous MI (eg Q waves) Left ventricular hypertrophy	Myocardial ischaemia or Thyroid disease or heart failure due to rapid ventricular rate Heart failure due to slow heart rate Heart failure due to reduced left ventricular performance Diastolic dysfunction
Echocardiogram*	LV systolic dysfunction LV hypertrophy LV diastolic dysfunction Valve disease	Severity of LV dysfunction and clues to potential aetiology of heart failure
Complete blood count	Anaemia	Heart failure due to or aggravated by decreased oxygen carrying capacity
Urinalysis	Proteinuria Red blood cells or cellular casts	Nephrotic syndrome Glomerulonephritis
Serum creatinine	Elevated	Volume overload due to renal failure
Serum albumin	Decreased	Increased extravascular volume due to hypoalbuminemia
T4 and TSH (obtain only if atrial fibrillation, evidence of thyroid disease, or patient age >65)	Abnormal T4 or TSH	Heart failure due to or aggravated by hypo/hyperthyroidism
Brain natriuretic peptide#	Elevated BNP	Heart failure likely if BNP elevated

TSH = Thyroid-stimulating hormone, MI = myocardial infarction

*** Note regarding echocardiography for assessment of suspected heart failure**

The guideline team recognise the important role of echocardiography for the assessment of patients with suspected heart failure. However, in many areas in New Zealand echocardiography is not widely available and there may be considerable delays in obtaining an echocardiogram. The guideline team have discussed this potential limitation in the assessment of suspected heart failure at length and the following points summarise the current position with regards to echocardiography:

- Imaging of the left ventricle is of paramount importance in the assessment of a patient with suspected heart failure (usually this will be with echocardiography)

- Open access echocardiography for primary care practitioners has been promoted in many areas. However, there is no randomised controlled evidence that the provision of this service alters outcome or is cost-effective.
- Open access echocardiography is generally not available in New Zealand.
- Despite these limitations echocardiography, where available, is still recommended as part of the assessment of patients with suspected heart failure.

Note regarding brain natriuretic peptide

Brain natriuretic peptide (BNP) is a protein released from the heart in response to changes in left ventricular wall stretch and is elevated in heart failure. BNP is a powerful neurohormonal predictor of left ventricular function and of prognosis in heart failure. BNP concentrations can help to discriminate between heart failure and other causes of breathlessness in patients admitted to hospital.[8] In particular, a normal BNP result in a symptomatic patient makes the diagnosis of heart failure very unlikely. BNP testing is available in some areas in New Zealand and, with the availability of point-of-care meters, is likely to increase over the next few years. However, the usefulness of BNP in unselected patients in the community is uncertain, and further studies will address this further.

management

A. Non-Pharmacological Management

Effective Patient Education

Educational interventions, including one to one patient counselling, improve patient compliance and outcomes. *(Strength of Evidence = B)*[9, 10]

General Counselling (see Table 2)

After a diagnosis of heart failure is established, patients and their families or caregivers should be counselled regarding the nature of heart failure, drug regimens, dietary restrictions, symptoms of worsening heart failure, what to do if these symptoms occur, and prognosis (see Table 2). The impact of heart failure on a patient's life may be related as much to psychological adaptation to the disease as to impairment in physical functioning.[11] Nursing interventions, family involvement, and support groups may all help patients cope with heart failure.

Smoking

Practitioners should emphasise the importance of not smoking or chewing tobacco.

Vaccination

Practitioners should recommend that patients receive vaccination against influenza and pneumococcal disease. (Strength of Evidence = C)

Discussion of Prognosis

Patient counselling with respect to prognosis should be guided by evidence from recent trials and the Framingham experience[12], which indicate that the average annual mortality rate for patients with heart failure is approximately 10% per year. Mortality increases with age, severity of disease, and the presence of angina. The one-year mortality for patients with severe heart failure (NYHA IV) is approximately 30-50%.

It is vital that patients receive accurate information concerning prognosis in order to make decisions and plan for the future. Practioners should discuss patients' desires regarding resuscitation. All patients should be encouraged to complete advance directives regarding their health care preferences.

Table 2. Suggested Topics for Counselling and Education:

1. General Counselling
   - Explanation of heart failure and reasons for symptoms
   - Cause of heart failure
   - Expected symptoms
   - Symptoms of worsening heart failure
   - What to do if symptoms worsen
   - Self-monitoring with daily weights
   - Explanation of treatment/care plan
   - Clarification of patient's responsibilities

2. Prognosis
   - Life expectancy
   - Advance directives regarding resuscitation
   - Advice for family members in the event of sudden death

3. Activity Recommendations
   - Recreation, leisure, and work activity
   - Exercise
   - Sex, sexual difficulties, and coping strategies

4. Dietary Recommendations
   - Sodium restriction
   - Avoidance of excessive fluid intake
   - Fluid restriction (if required)
   - Alcohol restriction

5. Medications
   - Effects of medications on quality of life and survival
   - Dosing
   - Likely side effects and what to do if they occur
   - Coping mechanisms for complicated medical regimens
   - Availability of lower cost medications or financial assistance

6. Importance of compliance with the Treatment / Care Plan

Activity Recommendations

Rehabilitative exercise training in patients with heart failure and moderate-to-severe left ventricular systolic dysfunction improves functional capacity and symptoms. *(Strength of evidence = A)*

Comments

There have been a number of randomised controlled trials regarding the role of exercise training in patients with heart failure. These have shown significant improvements in functional capacity and symptoms.[13-15] One RCT demonstrated that a combination of ACE inhibitor treatment and exercise training produced greater symptomatic improvement than ACE inhibitor therapy alone.[16] It appears that this improvement is mediated through adaptations in the peripheral circulation and skeletal musculature rather than adaptations in cardiac musculature. Elderly patients are able to participate in exercise training programs and should be strongly encouraged to participate. A non-randomised controlled trial showed that patients older and younger than 70 years of age had comparable responses to exercise training, which was similar in men and women.[17]

Dietary Recommendations

Dietary sodium should be restricted to as close to 2 grams per day as possible. In no case should sodium intake exceed 3 grams daily. *(Strength of Evidence = C)*

In simple terms the advice to patients should be to avoid adding salt to cooking, not to add extra salt at the table and to avoid foods which are very high in salt (2 gms of salt is equal to approximately half teaspoon).

Patients with heart failure should be advised to avoid excessive fluid intake. However, fluid restriction is not advisable unless patients develop hyponatremia. *(Strength of Evidence = C)*

Alcohol

Alcohol use should be discouraged. Patients who drink alcohol should be advised to consume no more than one drink per day or, if suffering from alcohol related cardiomyopathy, abstain altogether. *(Strength of Evidence = C)*

The Problem of Non-compliance

Non-compliance is a major cause of morbidity and unnecessary hospital admissions in heart failure.

Practitioners should be attuned to the problem of non-compliance and its causes. They should discuss the importance of compliance at follow-up visits and assist patients in removing barriers to compliance (eg cost, side effects, or complexity of the medical treatment regimen). *(Strength of Evidence = B)*

Other risk factors for admission or early readmission to hospital include:

- previous admissions in the last 12 months
- uncontrolled hypertension
- myocardial infarction, and
- low socio-economic status and low life satisfaction score.

Patient held action plans. No data was found on the effectiveness of patient held (self-management) plans.

B. Pharmacological Treatment Guidelines

Angiotensin-converting enzyme (ACE) inhibitors

All patients with heart failure due to systolic dysfunction should be considered for treatment with an angiotensin converting enzyme inhibitor in appropriate doses. ***(Strength of evidence = A)***[18,19]

Key Points

- ACE inhibitors improve symptoms of heart failure, improve left ventricular function, decrease hospital admissions and improve survival.
- ACE inhibitor therapy can also prevent the progression to heart failure in patients with asymptomatic LV dysfunction and should thus be used early in the course of the disease.
- It is likely that the effects of ACE inhibitors in heart failure are a class effect and thus no specific ACE inhibitor is recommended.
- Consider low starting dose (eg captopril 6.25mg, enalapril 2.5mg) and titrate up to the doses used in the RCTs, ie recommended dose captopril 50mg tds, enalapril 10mg bd, cilazapril 5mg daily, quinapril 10 mg bd. Higher doses may be indicated for some patients (eg if coexisting hypertension).
- Hypotension may occur after the first dose especially if there is pre-existing hypotension, hyponatraemia, or over-diuresis.
- Monitor blood pressure, K+ and renal function (at least weekly initially).
- Contraindications to ACE inhibitors: prior ACE inhibitor intolerance; symptomatic hypotension; angioedema; K+>5.5mmol/l; creatinine >0.25mmol/l (some patients with renal failure may tolerate an ACE inhibitor but specialist referral is recommended).
- Concomitant use of diuretics is usually required for management of fluid overload.

Comments

The ACE inhibitor enalapril has been shown to reduce mortality in patients with moderate and severe heart failure in the SOLVD[19] and CONSENSUS[18] trials respectively (see Evidence Tables 1 & 2). The relative risk reduction was 31% (absolute risk reduction of 16%) for those with severe heart failure over 12 months. While in those with mild heart failure the overall relative risk reduction 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 overt heart failure has not been studied.

Both enalapril and captopril have been shown to improve functional status, in 40-80% of patients.[18,20] The average improvement has been 0.5-1 NYHA functional class.[3] The SOLVD trial showed a modest reduction (RRR = 9.5%) in hospitalisation for those with mild to moderate congestive failure.[19]

Side-effects with ACE inhibitors are common - experienced by 87% in the SOLVD trial (note, 82% taking placebo also reported side-effects). The most common side-effect is dizziness due to hypotension, and cough. The actual average changes in blood pressure were modest, a decrease of 5mmHg systolic blood pressure. Symptomatic hypotension is more common in those who have been over-diuresed, or are hypotensive to begin with. In the CONSENSUS trial[18] (severe heart failure), 5.5% were withdrawn because of symptomatic hypotension. In general, systolic blood pressure of > 90mmHg, without postural hypotension, is acceptable.[21]

Cough is common with ACE inhibitors, but is also common in patients with heart failure. It was reported in 37% of those taking enalapril in the SOLVD trial, and in 31% 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 the treatment if the cough is not severe and the benefits are explained.

Initiating ACE inhibitor therapy

ACE inhibitors can be added after volume overload has been controlled with diuretics. Patients who are at high risk of hypotension ie those with severe left ventricular systolic dysfunction, systolic blood pressure <100mmHg, or serum sodium <135mmol/l, should be given a small dose of a short acting agent (eg captopril 6.25mg), and monitored closely for 2-hours.[3,22]

Initial dose of ACE inhibitor should be low and dose titrated over 2-3 weeks with monitoring of BP and renal function. It is recommended that for those who are not at risk of hypotension, low doses should be started (eg enalapril 2.5mg bid), and patients reviewed after a week to monitor blood pressure, renal function and serum potassium.[3] Doses should be titrated up over 2-3 weeks aiming for the doses used in the large-scale trials, ie enalapril 10mg bd and captopril 50mg tid, cilazapril 5mg per day, quinapril 10mg bid.

Diuretics

Patients with heart failure and clinical signs of fluid overload should be started on a diuretic. *(Strength of evidence = B)*

Key Points

- Diuretics provide relief of symptoms of pulmonary and systemic venous congestion in patients with heart failure
- There are no data regarding the effects of loop or thiazide diuretics on mortality in patients with heart failure
- Target doses of diuretics depend on the identification of a "dry" (or target) body weight
- 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 to counteract this neuro-hormonal activation

Comments

There are few studies of the optimal diuretic therapy for heart failure, and the dose requirements may vary depending on the patients' needs. In mild heart failure a thiazide may be sufficient (eg bendrofluazide 2.5 - 5mg daily initially).[23]

In general a loop diuretic will be required in moderate or severe heart failure or if the patient has failed to respond to thiazide diuretics (eg frusemide 40mg daily initially). If the initial dose proves inadequate, greater diuresis will usually be achieved by doubling the dose rather than by giving the same dose twice daily.[3] Diuretic use should be combined with careful clinical monitoring, usually with patients monitoring their own weight.

A thiazide may be used in combination with loop diuretics for resistant oedema but only with extreme caution as a profound diuresis may ensue.

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

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 usually potassium replacement will 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).

Beta-Blockers

Beta-blockers should be considered for all patients with heart failure due to systolic dysfunction (low ejection fraction) who have mild to moderate symptoms and are clinically stable. The aim of treatment is to improve survival and reduce hospitalisations. (Strength of Evidence = A).[24-28]

Key Points

- To date, 14,776 patients with chronic heart failure have been entered into 28 randomised clinical trials of beta-blocker therapy[24-28] (these clinical trial data are approximately double that which is available for ACE inhibitors in patients with heart failure).
- The trials have now shown conclusively that beta-blockers improve survival, decrease hospitalisations and improve left ventricular function in patients with chronic heart failure (see over page).
- Effects on patients symptoms and exercise tolerance are less consistent, and probably should not be considered a main aim of therapy (at least in the short-term).
- The benefits of beta–blockers are *in addition* to the benefits gained with ACE inhibitor therapy.

- There is a potential for adverse effects of beta-blockers particularly during initiation of therapy. Patient selection, timing of starting therapy and careful dose titration are of key importance (see below).
- The role of beta-blockers is in the treatment of patients with chronic heart failure and there is no place for the use of beta-blockers in the treatment of acute pulmonary oedema.

Benefits

The following data for survival benefits are from the total dataset combined in a meta-analysis:[24-28]

Absolute risk reduction	4.5% (approx. annual mortality rate 17.4% in placebo treated patients vs 12.9% in beta-blocker treated patients)
Relative risk reduction	28% (SD 4%)
Number needed to treat	22 (to prevent one death during approximately 1 year of treatment)

Practical Points for Use of Beta-blockers in Heart Failure

Patients considered for beta-blocker therapy should be similar to those represented in the clinical trials. Patients should:

- have chronic stable heart failure
- have left ventricular systolic dysfunction (LVEF< approximately 45%)
- have mild to moderate symptoms (NYHA functional class II-III)
- be clinically stable on adequate doses of ACE inhibitor and diuretic
- in general, be stable for about 2 weeks (without major changes in diuretic regime)

Starting Patients with Heart Failure on Beta-blockers

Patients with heart failure should be started on beta-blockers by clinicians experienced with their use in heart failure or in specialist clinics. Contraindications to beta-blockade, such as asthma or heart block (in the absence of a permanent pacemaker) should be checked for prior to starting treatment.

Initiation of beta-blockers in patients with heart failure:

- Start at low dose, eg metoprolol CR 47.5 mg $^{1}/_{4}$ tablet, or carvedilol 3.125-6.25mg
- Give under supervision in out-patient setting
- Some patients may need observation of heart rate and BP for 2 hours
- In some case, beta-blockers may be initiated prior to hospital discharge provided that the patient does not have signs of overt congestion[27]

Dose titration:

- Fortnightly visits to titrate dose of beta-blocker. Check specifically for signs of worsening congestion, hypotension or bradycardia at each visit
- Withhold the morning dose on the day of the visit
- Some patients may need observing for 2 hours after each dose increment (eg if relative hypotension)
- Doubling of the dose every two weeks is a reasonable titration regime. However, titration can occur slowly and sometimes may take several months to achieve the desired maintenance dose

Potential adverse effects of beta-blockers in heart failure patients:

- Dizziness (common with the vasodilating beta-blockers such as carvedilol, often decreases if persist with treatment)
- Hypotension – usually a sign of intolerance (decrease dose or stop)
- Worsening heart failure – mainly increasing congestion. Manage by increasing diuretics and continuing beta-blocker if possible
- Heart block

Target doses:

- Aim for metoprolol 150-200mg daily (exact dose depends on preparation of metoprolol used) or carvedilol 25mg bid

Spironolactone

Patients with severe heart failure (NYHA classification III or IV, and who have been class IV within the last 6 months) should be considered for the addition of spironolactone 25mg daily to existing therapy (including ACE Inhibitors). (Strength of evidence = A)[29]

Until recently it has been assumed that the suppression of the renin-angiotensin system by an ACE inhibitor alone would suppress the formation of aldosterone. In addition, there has been concern that the concurrent use of an aldosterone-receptor blocker and an ACE inhibitor could lead to dangerous hyperkalaemia. The RALES trial[29], a single yet large and well designed trial, found that the use of spironolactone in people with severe heart failure was not only safe but conferred substantial survival benefits.

In the RALES trial[29] patients with severe heart failure (NYHA classification III or IV and LVEF< 35%) who had spironolactone 25mg daily added to usual therapy (including ACE inhibitors) had reduced mortality, improved quality of life and reduced hospital admissions.

- Survival benefit –

Absolute risk reduction	11% (two year mortality rate 46% in placebo treated patients vs 35% spironolactone treated patients)
Relative risk reduction	30%
Number needed to treat	9 (to prevent one death during average 2 years treatment)

- Reduction of number of patients requiring hospital admission for cardiac causes: NNT=11 (2 years)
- Improved symptoms of heart failure
- 10% of patients experienced gynaecomastia or breast pain (NNT =11, 2 years)

Dose: Spironolactone 25mg od
Creatinine and electrolytes should be checked 3-4 days, one week and one month after initiation and then as indicated by renal function (6 monthly in stable patients).

Contraindications
Serum creatinine > 0.25mmol/l, potassium >5.0 mmol/l.

Digoxin

(a) *Digoxin in patients with atrial fibrillation*

Digoxin should be considered for all patients with heart failure who are in atrial fibrillation. ***(Strength of evidence = B)***

Key Points

- Digoxin is useful for control of the 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 with exercise
- Additional agents such as low dose diltiazem or amiodarone may be required to control the exercise heart rate. If a beta-blocker is to be used for the treatment of heart failure then this may provide additional rate control.

(b) *Digoxin in patients with heart failure and sinus rhythm*

Digoxin should be considered for patients with heart failure who remain symptomatic despite treatment with ACE inhibitor and diuretics, with the aim of improving symptoms and preventing further clinical deterioration. (Strength of evidence = A)[30, 31]

Key Points

- Digoxin can improve symptoms of heart failure, reduce hospitalisation for worsening heart failure but has no overall effect on total mortality in patients with heart failure who are in sinus rhythm.[31]
- The lack of effect on total mortality means that digoxin need not be used if patients are asymptomatic with diuretics and ACE inhibitors.
- Generally, digoxin should be considered if a patient has failed to respond to ACE inhibitors and diuretics.

Comments

The DIG Trial[31] examined the role of digoxin in patients with heart failure who are in sinus rhythm (see evidence Table 3). While this trial showed that overall mortality was not affected in those taking digoxin, both hospitalisation due to worsening heart failure, and the combined end-point of death or hospitalisations due to worsening heart failure were decreased. The absolute risk reduction (ARR) was approximately 7%. It had been previously shown that when digoxin was withdrawn from patients, that exercise tolerance, NYHA class and quality-of-life scores deteriorated.[32] However, given that digoxin does not reduce mortality, patients who are asymptomatic after treatment with ACE inhibitors and diuretics, are unlikely to gain a benefit from the addition of digoxin.

Loading doses of digoxin are generally not required. In the presence of normal renal function a dose of 0.25mg daily may suffice. In the elderly or in those with renal impairment a reduced dose such as 0.125 or 0.0625mg daily is necessary. Digoxin levels should be checked after about 1 week in those with normal renal function, although steady state may take longer to be achieved in those with renal impairment.

Signs of digoxin toxicity include: confusion, nausea, anorexia, visual disturbance and either tachy- or bradyarrhythmias. Digoxin toxicity should be suspected in any patient presenting with any of the above symptoms or unusual symptoms, particularly in the elderly. Some drugs may increase plasma digoxin levels, for example: amiodarone, diltiazem, verapamil, antibiotics, quinidine.

Angiotensin II (AII) Antagonists

All antagonists should be considered for patients intolerant of ACE inhibitors. *(Strength of evidence = C)*

Evidence summary

These drugs (eg losartan) block the angiotensin II type 1 receptors and thus block the renin-angiotensin-aldosterone system at a point beyond the angiotensin converting enzyme. The potential advantages include more complete renin-angiotensin-aldosterone blockade and reduced side-effects such as cough and angio-oedema. An initial pilot study in patients with heart failure (ELITE I)[33] suggested that losartan may reduce mortality relative to captopril. However, a large-scale mortality trial (ELITE II[34]) has not shown a superiority of losartan over captopril. Currently AII Antagonists should be considered for patients intolerant of ACE inhibitors.

Anticoagulation

Routine anticoagulation is not recommended for all patients with heart failure.

Long-term anticoagulation with warfarin should be considered in patients with concurrent atrial fibrillation (INR 2.0 – 3.0). *(Strength of evidence = A)*[35,36]

Anticoagulation with warfarin should be considered in patients with a history of systemic or pulmonary emboli, documented left ventricular thrombus (optimal range for anticoagulation in these groups has not been ascertained, consider using INR 2.0 – 3.0). *(Strength of evidence = C)*

Key Points

- There are no controlled trials of the effects of routine anticoagulation in all patients with heart failure
- Left ventricular systolic dysfunction is a significant risk factor for stroke in patients with atrial fibrillation
- Consider referral to specialist with aim to restore sinus rhythm

Comments

Atrial fibrillation occurs in 15% to 30% of patients with heart failure.[37] Furthermore, the risk of stroke is greater in patients with atrial fibrillation and concomitant heart failure, than those with isolated lone atrial fibrillation (annual risk of stroke 5-8% versus 1.3%).[35,36]

An analysis of pooled data from five randomised controlled trials, concluded that warfarin consistently decreased the risk of stroke in patients with atrial fibrillation (RRR of 68%), with virtually no increase in the frequency of major bleeding.[35]

The Stroke Prevention in Atrial Fibrillation (SPAF) III trial[38] which compared conventional warfarin dosage (aiming for an INR of 2.0-3.0) with low dose warfarin (INR of 1.2 to 1.5) combined with aspirin, was terminated early, because of an excess of strokes in the low dose warfarin arm. It was concluded that conventional dose warfarin should be regarded as optimal treatment for the majority of patients with atrial fibrillation. An INR of 2.0-3.0 provides a reasonable balance between reducing the risk of thromboembolism and minimising potential for bleeding complications. Patients who are at higher risk of serious bleeding include those susceptible to falls, those with a previous history of gastro-intestinal haemorrhage, those with impaired liver function, and those who are unable to participate in the monitoring required. Monitoring will be required for the duration of the anticoagulation with regular INRs.

Aspirin

Patients with underlying coronary artery disease or concomitant peripheral vascular or cerebrovascular disease should be treated with low-dose aspirin (eg 75-150mg daily) to prevent further vascular events. *(Strength of evidence = A)*

Key Points

- Aspirin reduces vascular events when used as secondary prevention in patients with coronary artery, peripheral vascular or cerebrovascular disease
- There is some concern that aspirin reduces the survival benefit of ACE inhibitors in patients with heart failure. However, this is still unclear and further clinical trials are awaited to clarify this situation.

Co-prescribing

Certain drugs interact adversely with the primary therapeutic agents for congestive heart failure or are poorly tolerated. Vigilance should be exercised in all prescribing.

The following groups of drugs should be used cautiously or avoided altogether:

- NSAIDS
- Calcium channel blockers (with the exception of amlodipine and felodipine)
- Corticosteroids
- Tricyclic Antidepressants
- Carbenoxolone
- Urinary alkalinisers (high sodium content)

Concomitant conditions

Atrial fibrillation

The following points should be considered when managing a patient with heart failure who is in atrial fibrillation (AF):

- Should restoration of sinus rhythm be attempted?
- Is AF the cause or consequence of heart failure?
- Does the patient have underlying mitral valve disease?
- Does the patient have thyrotoxicosis?
- Are there contraindications to warfarin therapy?

Consideration of these points helps to identify those in whom intervention may be required, rather than just aiming for rate control.

Recommendation:

In patients with AF anticoagulate with warfarin to prevent thromboembolism (INR 2.0-3.0). *(Strength of evidence = A)*

Consider the need for cardioversion (will require specialist referral for cardioversion).

Medical cardioversion may be achieved by amiodarone: 200mg tds for 2 weeks, 200mg bid for 2 weeks then 200mg daily (Strength of evidence = B).[39] Anticoagulation with warfarin is required whether cardioversion is undertaken electrically or chemically. Cardioversion is recommended after 4 weeks if still in AF (success is much higher if the history of AF is less than 1 year or the left atrial diameter is less than 50mm) (Strength of evidence = C).

Continue anticoagulation for a further 6-12 months while monitoring for recurrence. If AF persists consider long-term therapy with amiodarone. (Strength of evidence = C)

Clinical Notes

Digoxin alone will usually not adequately control the ventricular rate in atrial fibrillation. The increasing use of beta-blockers in patients with heart failure will allow these agents to be used for rate control. Diltiazem or amiodarone may be required in some cases to achieve adequate rate control.

Ischaemic heart disease

Patients with congestive heart failure and ischaemic heart disease, and who do not have contraindications to bypass surgery, should have the risks and benefits of coronary artery surgery considered. This will usually require a specialist cardiology assessment.

Coronary artery bypass grafting (CABG) improves survival in patients with moderate (LVEF 35 to 50%) heart failure due to ischaemic heart disease. *(Level of evidence = A)*[40]

CABG surgery improves survival, NYHA class and angina in selected patients with severe (LVEF < 30%) heart failure. *(Level of evidence = B)*

Comments

Ischaemic heart disease (or coronary heart disease) is a common cause of heart failure.

There are several ways in which ischaemia may present as heart failure, including one or more myocardial infarctions culminating in heart failure, primary presentation as congestive heart failure without clinically overt antecedent infarction ("ischaemic cardiomyopathy" which is most commonly a diffuse fibrosis), a large full thickness infarct resulting in a left ventricular aneurysm, or transient global ischaemia resulting in acute pulmonary oedema.

The aim of CABG surgery is to prevent further ischaemic myocardial damage and to reverse myocardial hibernation. Hibernating myocardium occurs in some patients with congestive heart failure due to underlying chronic ischaemia. It is characterised by areas of hypocontractile myocardium that are potentially reversible if adequate coronary perfusion is restored by revascularisation.[41]

Hibernating myocardium may be identified using radionucleotide ventriculography or dobutamine stress echocardiography.

Most of the large randomised controlled trials of medical versus CABG surgery excluded patients with heart failure and severe left ventricular impairment. The Coronary Artery Surgery Study (CASS) did examine a subset of 160 patients with LVEF between 35 and 50%. After seven years follow-up, survival in the surgical group was 84% compared with 70% in the medical group.[40] The CASS Registry data on patients with LVEF <26%, showed a 5-year survival of 63% in those undergoing CABG surgery, compared with 43% in the medical cohort.[42] The benefits of CABG surgery have not been confined to improved survival. Several cohort studies[43,44] have shown improved LV function after surgery (in patients with baseline LVEF < 30%), and corresponding improvement in functional status. Most report that patients improve by 1 to 1.5 NYHA classes. This together with improvements in angina class could reasonably be expected to improve patients' quality of life.

criteria for specialist referral

Many patients with heart failure are elderly and have multiple concomitant medical conditions in whom extensive investigation may not be appropriate. Recommendations regarding the criteria for specialist referral cannot be based on evidence from randomised controlled trials as the interventions evaluated in such trials are usually refer to subsets of patients with established diagnoses. Consequently, the recommendations for referral outlined below are based on consensus from this guidelines group (with outside consultation). Clinicians should rely on their clinical judgement and when in doubt should err on the side of referral.

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

- The onset of heart failure in younger patients (in whom transplantation may be considered)
- Those whose history suggests severe ischaemia or significant valvular disease where further investigation and intervention (such as angioplasty or surgery) 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 (either supra-ventricular, ventricular or at times atrial fibrillation) are apparent
- In those with sudden onset of heart failure
- When beta-blocker treatment is being considered
- Those who have an inadequate response to treatment
- When the indication for anticoagulation is uncertain

Clinical Notes

The recommendations for specialist referral should not delay initiation of appropriate treatment for patients with symptomatic heart failure.

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appendix I evidence tables

Evidence table 1: Clinical Area: ACE inhibitor treatment of severe CHF.

Reference: The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. N Eng J Med 1987;316 (23): 1429-35.

Study type/grade	**Randomised-controlled trial. Grade 1**
Outcomes	• primary - 6-month mortality; cause of death • secondary -12-month mortality
Design	• n= 253; 127 enalapril, 126 placebo; with severe CHF (NYHA class IV) • Mean age 70 years; 29.5% female; mean ejection fraction not stated. • exclusion criteria: Acute pulmonary oedema, haemodynamically important aortic or mitral valve stenosis; myocardial infarction within the previous 2 months; unstable angina, planned cardiac surgery; right heart failure due to pulmonary disease; serum creatinine >300mmol/L. • method of randomisation: Computer-generated allocation, stratified with regard to treatment with vasodilators. • intervention: Enalapril titrated to a maximum of 20mg/day. (mean dose 18.4mg) • blinding: Double-blinded for randomisation and end-point ascertainment. • length of follow-up: 12-months. • completeness of follow-up: 100%
Validity	• is the study type appropriate for the questions being asked? - Yes
	• was the study population typical of patients with this disease? - Yes • were the treatment/control groups comparable at baseline? - Yes • was the intervention compared to placebo and/or best accepted intervention? - Yes • was there compliance with the intervention? - Withdrawals were not significantly different in the two groups (14% placebo, 17% enalapril group). No specific mention of compliance in the remaining subjects. • was there equal intensity of observation of study and control subjects? - Yes • was the process of observation likely to effect the outcome? - No • intention to treat analysis? - Yes • did conclusions about safety take into account the limited size of the study? - Yes

	• Is effectiveness proven? - Yes • **Summary** - Excellent study. Enrolment and follow-up terminated ahead of schedule because of consistent difference in favour enalapril.					
Results	**Outcome**	**Relative risk reduction**	**p-value**	**Absolute risk reduction**	**Numbers needed to treat**	
	• Mortality at 6 months • Mortality at 12 months • Mortality in those not taking vasodilators at time of randomisation • Mortality due to progression of CHF	40% 31% 38% 50%	0.002 0.001 <0.02 p<0.001	18% (6-mths) 16% (12-mths) 23% 17.6%	5.5 (6-mths) 6.25 (12-mths) 4.3 5.7	
Note:	Improvement in NYHA class occurred in 22% of placebo group and 42% of enalapril group. Heart size reduced by 3.2% in placebo group and 9.6% in enalapril group (p=0.02). Most common adverse effects were hypotension necessitating withdrawal of 7 cases in treatment group (notably when starting dose was 5mg,) and raised creatinine, 6 withdrawals.					
Authors' conclusions	That treatment with enalapril improves survival in those with severe CHF. Also noted improvement in NYHA class, heart size, and concomitant use in those in the enalapril group. The entire treatment effect was due to a reduction in mortality from the progression of heart failure, with no differences in rate of sudden death between the groups.					
Reviewers' conclusions	Agree with authors' conclusions.					

Evidence table 2: Clinical Area: ACE inhibitor treatment of CHF

Reference: The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Eng J Med 1991;325(5):293-302

Design	• n=2569 (39 924 screened): 1285 enalapril, 1284 placebo; with clinically stable CHF. • Mean age 60 years; 20% female; 90% NYHA Classes II - III; mean ejection fraction 24.85%. Groups comparable at baseline. • exclusion criteria: Age > 80-years; Haemodynamically serious valvular disease requiring surgery; unstable angina; myocardial infarction in the previous month; severe pulmonary disease; serum creatinine> 0.177mmol/L. • method of randomisation: Computer-generated allocation schedule, stratified by site. • intervention: Enalapril titrated to a maximum of 10mg twice daily. • blinding: Double-blind for randomisation and end-point ascertainment. If patient remained symptomatic despite maximal therapy, open-label treatment with an ACE-inhibitor was allowed, and blinded medication discontinued. • length of follow-up: Range 22 to 55 months, average 41,4. • completeness of follow-up: Almost complete: the vital status of one patient in each group was not known.
Validity	• is the study type appropriate for the questions being asked? - Yes • was the study population typical of patients with this disease? - Yes, except those over 80-years old. • were the treatment/control groups comparable at baseline? - Yes • was the intervention compared to placebo and/or best accepted intervention? - Yes • was there compliance with the intervention? - Proportion of patients taking at least 75% of prescribed dose at: 1-year = 80% in treatment group, 77% in placebo; 2-years = 74% and 67%; 3-years = 69% and 60%. At the final visit 49.3% in the treatment group were taking 10mg/day, 49.1% of the placebo group were taking equivalent amount. Mean daily dose of enalapril was 11.2 mg. • was there equal intensity of observation of study and control subjects? - Yes • was the process of observation likely to effect the outcome? - No • intention to treat analysis? – Yes • did conclusions about safety take into account the limited size of the study? - Yes • is effectiveness proven? – Yes • **Summary** - Very good study.

Results	Outcome	Relative Risk reduction % (95% CI)	One-sided p-value	Absolute risk reduction (over 48 mths)	Number needed to treat (over 48-months)	
	• Death #	16 (5 to 26)	<0.0036	4.5	22	
	- cardiovascular deaths	18 (6 to 28)	<0.002	4.8	21	
	- progressive heart failure	22 (6 to 35)	<0.0045	3.2	31	
	- myocardial infarction	28 (-8 to 52)	>0.07	not statistically significant	not statistically significant	
	• Hospitalisation for cardiovascular reasons	9.5	<0.001	6	16	
	• Deaths or hospitalisation for CHF	26 (18 to 34)	<0.0001	9.6	10	
	* risk reduction calculated by the authors using a log-rank analysis, reflecting the risk over the entire follow-up period. # Greatest reduction in mortality seen in the first 24 months (23% RRR)					
Authors' conclusions	That ACE inhibitor therapy in the form of enalapril reduced overall mortality by 16%, and this was both clinically and statistically significant. Treating 1000 patients for 3-years, would prevent 50 premature deaths, and 350 hospitalisations. The greatest benefit of treatment was the decrease in mortality from progressive heart failure.					
Reviewers' conclusions	Good evidence of survival benefit in patients with mild to moderate heart failure, when given enalapril in addition to usual management.					

Evidence table 3 : Clinical Area: Management of heart failure: the role of digoxin.

Reference: The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure.
N Eng J Med. 1997;336(8): 525-33

Study type/grade	Randomised-controlled trial. Grade 1
Outcomes	• Primary - All cause mortality. • Secondary - Mortality from cardiovascular causes; mortality from worsening heart failure; hospitalisation from worsening heart failure.
Design	• n= 6800; 3397 digoxin: 3403 placebo. • Patients with left ventricular ejection fraction (LVEF) £0.45. Predominantly mild to moderate heart failure, with only 2% in NYHA functional class IV. Mean age 63.5, 22.3% women. 98.4% taking either ACE-inhibitors or diuretics. (94.4% on ACE-inhibitors). • exclusion criteria: myocardial infarction, cardiac surgery or PTCA within previous 4 weeks; atrial fibrillation/flutter; II°-III° AV block without pacemaker; unstable or refractory angina; hypertrophic cardiomyopathy. • method of randomisation: Telephone, stratified by site. • intervention: Digoxin, initial dose titrated according to an algorithm based on age, sex, weight and renal function. • blinding: Double-blinded. • length of follow-up: Average 37-months. • completeness of follow-up: 98.6%
Validity	• is the study type appropriate for the questions being asked? - Yes • was the study population typical of patients with this disease? - Yes, with the exception that their were few with severe heart failure. • were the treatment/control groups comparable at baseline? - Yes • was the intervention compared to placebo and/or best accepted intervention? - Yes • was there compliance with the intervention? - Yes: at 1-year 85.6% of those in the digoxin group were compliant, 82.9% in the placebo group; at final visit the figures were 70.8% and 67.9% respectively. • was there equal intensity of observation of study and control subjects? - Yes • was the process of observation likely to effect the outcome? - No

	• intention to treat analysis? - Yes • did conclusions about safety take into account the limited size of the study? - Yes • is effectiveness proven? - Yes • **Summary** - Valid study.			
Results	**Outcome**	**Relative risk reduction** (95% CI)	**Absolute risk reduction**	**Numbers needed to treat**
	• Death (all cause)	1% (-0.07 to 9, p=0.80)	-0.3% (not significant)	
	• Death from cardiovascular causes	-0.01% (-0.10 to + 0.07, p=0.78)	+0.4% (not significant)	
	• Death from worsening heart failure	12% (-0.01 to 33%, p=0.06)	not significant	
	• Hospitalisation due to worsening heart failure	28% (21 to 34, p<0.001)	-7.9%	12.7
	• Death or hospitalisation due to worsening heart failure	25% (18 to 31)	-7.3%	13.7
Authors' conclusions	Digoxin had no effect on overall mortality, though there were fewer deaths and hospitalisations due to worsening heart failure. This reduction was greatest in those that had LVEFs < 0.25, or NYHA functional class III/IV.			
Reviewers' conclusions	Adding digoxin to ACE inhibitors and diuretics for the management of patients with heart failure who are in sinus rhythm, has no effect on overall mortality. Further the effect on death and hospitalisation due to worsening heart failure would appear to be confined to those with moderate to severe heart failure.			

The National Heart Foundation of New Zealand
PO Box 17-160, Greenlane, Auckland, New Zealand
Tel: 0064 9 571 9191
Fax: 0064 9 571 9190
Web: www.heartfoundation.org.nz