

HEART FAILURE

SUMMARY

- + **Heart Failure is a condition affecting a large number of Irish people and is associated with significant morbidity and mortality.**
- + **ACE inhibitors, in combination with diuretics, are the cornerstone of heart failure treatment.**
ACE inhibitors should be titrated to the target dose or the maximum tolerated dose if lower.
- + **Recent studies have shown that beta-blockers and spironolactone have a beneficial role to play in the management of heart failure.**

Heart failure is a complex clinical syndrome where the ability of the ventricle to eject blood is compromised.¹ The principal manifestations of heart failure are non-specific symptoms such as fatigue, shortness of breath and fluid retention/oedema.^{2,3} It is a progressive disorder which carries a grave prognosis and is associated with significant morbidity.^{3,4} The prevalence of heart failure is 3 to 20 per 1,000 population but exceeds 100 per 1,000 in the over 65 age group.⁵ Morbidity and mortality for all grades of symptomatic heart failure are high with 20-30% one year mortality in mild to moderate heart failure and over 50% one year mortality in severe heart failure.⁶

Heart failure can occur with both normal systolic function and reduced systolic function. There is no proven effective strategy for the management of heart failure associated with normal systolic function. Diuretics may relieve symptoms but the value of ACE inhibitors, beta-blockers and other agents discussed below are as yet unproven. Ongoing trials may help to clarify this.

Aetiology and Pathophysiology

Coronary artery disease is the commonest cause of heart failure in Western countries followed by hypertension and other cardiomyopathies.^{4,7,8} A greater understanding of the pathophysiology of heart failure has resulted in therapeutic advances. Heart failure is characterised by activation of the renin-angiotensin aldosterone system (RAAS) and the sympathetic nervous system, which while beneficial in the short-term, may be detrimental in the long-term.

Clinical Features

Patients with heart failure frequently present with dyspnoea, fatigue, swollen ankles and exercise intolerance. In some patients drugs may exacerbate this condition.(Table 1)

Table 1: Drugs That May Exacerbate Heart Failure⁸

NSAIDs
Class I anti-arrhythmics e.g. quinidine, flecainide
Beta-blockers (See text)
Calcium antagonists (verapamil and diltiazem)
Tricyclic antidepressants
Corticosteroids

Lithium Products with a high sodium content (e.g. antacids, effervescent formulations)

Investigations for patients with suspected heart failure include full blood count, blood biochemistry including electrolytes, creatinine, liver enzymes, cholesterol and glucose, 12 lead ECG, chest X-ray and echocardiogram.³

Non-Pharmacological Treatment Options

Aims of treatment of heart failure are to decrease symptoms, limit progression and prolong survival. Related aims include improving the potential for activity and quality of life.^{3,9} There are several general measures that can be taken in the heart failure patient including control of hypertension, weight reduction in obese patients, smoking cessation and maintenance of fluid balance e.g. salt restriction.^{1,3,9} Chest infections and poor drug compliance are common factors precipitating admission to hospital. Immunization against pneumococcal infection and influenza are recommended and close follow-up, especially in relation to compliance with diet and medications is required.

Pharmacological Treatment Options

Angiotensin Converting Enzyme (ACE) Inhibitors

ACE inhibitors can alleviate the symptoms and reduce the risk of hospitalisation and mortality in all grades of heart failure associated with left ventricular systolic dysfunction i.e. reduced ejection fraction. They are now recommended as first-line therapy for virtually all patients with congestive heart failure unless there are specific contraindications to their use.¹⁰ Studies have shown that a substantial proportion of patients who should be treated with an ACE inhibitor are not receiving them or are receiving them at doses lower than those used in clinical trials.²⁷ ACE inhibitors reduce the conversion of angiotensin I to angiotensin II. Angiotensin II is a powerful vasoconstrictor. ACE inhibitors also increase the production of bradykinin and reduce the activity of the sympathetic nervous system.¹¹

Although efficacy data may favour enalapril, the available evidence suggests no significant difference between ACE inhibitors in their clinical effects.⁴ There has also been debate over high dose vs low dose therapy. The ATLAS study randomised patients to low dose lisinopril (2-5mg OD) vs high dose lisinopril (32.5-35mg OD) and demonstrated that high dose therapy led to better outcomes, predominantly reduced morbidity.¹² ACE inhibitors are generally added to treatment with diuretics and may be used together with digoxin or beta-blockers. They should be initiated at very low doses to avoid hypotension and titrated to the target dose or to the maximum tolerated dose if lower (Table 2).^{4,10,13} Asymptomatic hypotension is not a concern in patients started on ACE inhibitors and may indeed be a goal of therapy in patients with heart failure. Low dose initiation and titration means the vast majority of patients can be started in the community and it is not usually necessary to discontinue or reduce the dose of diuretic.¹³ Hospital admission and/or specialist advice may be appropriate for a minority of patients starting ACE inhibitors e.g. the frail, elderly, etc.^{13,14}

Table 2: Target Doses for ACE inhibitors.¹⁰

Drug	Starting Dose	Target Maintenance Dose
Benazapril	2.5mg daily	20mg daily

Captopril	6.25mg twice daily	50mg three times daily
Cilazapril	0.5mg daily	1-2.5mg daily
Enalapril	2.5mg daily	10-20mg twice daily
Lisinopril	2.5mg daily	20-40mg daily
Perindopril	2mg daily	4mg daily
Quinapril	2.5mg daily	20-40mg daily
Ramipril	1.25mg daily	5-10mg daily
Trandolapril	0.4mg daily	4mg daily

Most of the adverse effects associated with ACE inhibitors can be attributed to two of their principle pharmacological actions i.e. those related to the effects of angiotensin suppression e.g. hypotension, potassium retention and those related to the production of kinin e.g. cough and angioedema. Renal function and serum potassium should be assessed within 1-2 weeks of initiating therapy and periodically thereafter.¹ Cough, which is a class effect, occurs in about 5-50% of patients on an ACE inhibitor and is the most common reason for patients to be withdrawn from long-term treatment with these drugs. It is characteristically non-productive, usually appears within the first few months of therapy, disappears within 1-2 weeks of discontinuing therapy and recurs within days of rechallenge. It is important to exclude lingering congestion as a cause of cough. Many patients may consider continuing therapy, despite the occurrence of a cough, if the importance of this therapy is explained to them. In situations where the cough is intractable or intolerable an angiotensin II receptor antagonist e.g. losartan might be a suitable alternative.^{1,11,26}

Beta-Blockers

Beta-blockers act by interfering with the actions of the sympathetic nervous system. In the past beta-blockers, because of their negative inotropic effects, were contraindicated in patients with heart failure. Recently though several large clinical trials (CIBIS, CIBIS-II, MERIT-HF, COPERNICUS) have demonstrated their benefit and there is now considerable evidence available to support their use in symptomatic chronic stable heart failure.^{2,11,15,16} Therefore like ACE inhibitors, long-term treatment with beta-blockers can lessen the symptoms of heart failure and improve the clinical status of patients with chronic heart failure. In addition, they reduce the risk of death as well as the combined risk of death or hospitalisation. These benefits were seen in patients already receiving ACE inhibitors suggesting that combined inhibition of two neurohormonal systems can produce additive effects.¹ Patients who are already treated with diuretics and/or digoxin and an ACE inhibitor, who are clinically stable with symptomatic heart failure, due to left ventricular systolic dysfunction, should be considered for treatment with a beta-blocker. Such treatment should be undertaken only under the supervision of a hospital physician and in the absence of contraindications such as bronchospasm, symptomatic bradycardia or heart block.^{1,4,13}

Carvedilol and bisoprolol are licensed in Ireland for the management of heart failure.^{17,18} Treatment should be commenced at very low doses and titrated carefully under specialist supervision at two weekly intervals.¹⁰ To avoid complications such as severe hypotension, a “start low, go slow” policy should be employed. Patients should be advised that symptoms may worsen initially and that the beta-blocker may reduce the risk of disease progression even if symptoms do not respond to treatment.⁴

The major side effects such as hypotension, fluid retention and worsening heart failure are often avoided by careful patient selection, dose titration and monitoring.²

Patients should be advised that clinical responses to the drug may be delayed and may require 2-3 months to become apparent.

Diuretics

Diuretics have been the mainstay of therapy and play an important role in the control of fluid balance, pulmonary and other organ congestion.¹⁰ They have been shown to improve cardiac function, symptoms (breathlessness and oedema) and exercise tolerance.¹⁹

Diuretics antagonize sodium retention that occurs in heart failure by inhibition of sodium reabsorption at specific sites in the renal tubules. All patients with signs and symptoms of sodium and water retention should be considered for treatment with diuretics.¹³ There have been no long-term trials of diuretic therapy in heart failure and so the effects on morbidity and mortality are not known. Short-term trials have shown that the use of diuretics led to a reduction in jugular venous pressures, pulmonary congestion, peripheral oedema and body weight within days of initiating therapy.¹ Diuretics should not be used as monotherapy even when symptoms are well-controlled and should generally be combined with an ACE inhibitor or a beta blocker if appropriate.^{2,8,10} Underdosing can lead to fluid retention which in turn can diminish the response to ACE inhibitors. Alternatively overdosing can lead to volume contraction and resultant increased risk of hypotension with ACE inhibitors.¹

In general, diuretics should be introduced at a low dose and the dose increased according to clinical response.²⁰ Loop diuretics e.g. frusemide, bumetanide are first choice in the elderly or renally impaired and in those with more severe heart failure.^{4,10,13,20} Loop diuretics have a rapid onset of action. Oral absorption of frusemide may be reduced in heart failure, however the pharmacokinetics of bumetanide may allow improved bioavailability.²⁰ Thiazides are often ineffective in elderly people owing to age-related and heart failure mediated reduction in GFR. In advanced or severe heart failure the combination a loop diuretic and thiazide or thiazide-like diuretic should be considered. In some patients a large diuretic effect may occur soon after the combination regimen has been started and therefore it is advisable to consider combination therapy on a twice weekly basis, at least initially.²⁰

The risks associated with diuretic therapy include electrolyte depletion. Monitoring of renal function and serum electrolytes is advised for all diuretic therapy and combination therapy.¹³ Combination therapy should only be used where careful monitoring of urea and electrolyte levels can be undertaken as significant falls in sodium and potassium and elevation in urea may occur. Concomitant administration of ACE inhibitors alone or in combination with potassium-sparing agents e.g. spironolactone can prevent electrolyte depletion in most patients.^{1,4}

Spironolactone

Persistently elevated aldosterone concentrations are thought to cause or contribute to many of the adverse changes in heart failure including water retention and electrolyte abnormalities.^{21,22} While aldosterone is indirectly suppressed by ACE inhibitors and angiotensin II antagonists there is evidence that this is transient and incomplete and may not be sustained during long-term treatment.¹³

The addition of low-dose spironolactone (25mg daily) to traditional heart failure medications (ACE inhibitors, loop diuretics, digoxin) reduced the number of hospitalisations, improved the symptoms of heart failure and increased survival in patients with severe heart failure (RALES study).²¹

Treatment with spironolactone is generally well tolerated with adverse effects such as gynaecomastia and hyperkalaemia reported. The risk of developing hyperkalaemia is increased at spironolactone doses greater than 50mg/day, concomitant high doses of ACE inhibitor therapy or evidence of renal impairment.^{4,11,20,22} It is recommended that patients receiving spironolactone especially in conjunction with an ACE inhibitor should have their serum potassium and creatinine concentrations monitored after seven days therapy and then frequently (weekly-monthly) for the first few months and routinely (3-6 monthly) thereafter.²²

Digoxin

Although it has no benefit on overall mortality, the primary benefit of digoxin in heart failure is to alleviate symptoms, improve clinical status and thereby decrease the risk of hospitalisation for heart failure when added to diuretics and an ACE inhibitor.^{1,4,15,23}

Digoxin is generally well tolerated, however caution is needed when selecting a maintenance dose. Plasma levels should be checked in all patients in whom toxicity is suspected and dose adjusted to achieve therapeutic levels. Drug interactions are known to occur with diuretics, amiodarone and NSAIDs.^{11,14}

Other Agents

Angiotensin II receptor antagonists offer an alternative method of blocking the renin-angiotensin system. Losartan has been compared with captopril in the ELITE and ELITE-II studies and it was not shown to be superior although improved tolerability was reported.^{24,25} Currently, there are a number of ongoing trials involving other angiotensin II receptor antagonists e.g. CHARM. The ValHeFT (valsartan) study recently showed that the addition of an angiotensin II receptor antagonist in patients already treated with an ACE inhibitor can further reduce morbidity. However there is lingering concern regarding the use of this combination therapy in patients on a beta-blocker. Treatment with an angiotensin II receptor antagonists remains an appropriate alternative in patients who are intolerant of ACE inhibitors.^{4,20} Losartan is currently the only angiotensin II receptor antagonist licensed for heart failure in Ireland.

Conclusion

Heart failure is a condition affecting a large number of Irish patients and is associated with significant morbidity and mortality. ACE inhibitors, which significantly reduce mortality and are underused in practice in combination with diuretics, are the cornerstones of current therapy. Studies in recent years have shown that spironolactone and beta-blockers have an important role to play in the management of this condition.

Table 3: Daily Costs of Heart Failure Therapies (GMS August 2001)

ACE Inhibitors	Daily Dose Range	Cost (£)
Benazepril	2.5mg-20mg	0.16-0.82
Captopril	12.5mg-150mg	0.13-0.78
Cilazapril	0.5mg-2.5mg	0.17-0.31
Enalapril	2.5mg-20mg	0.13-0.39

Lisnopril	2.5mg-40mg	0.27-1.10
Perindopril	2mg-4mg	0.24-0.48
Quinapril	2.5mg-40mg	0.17-0.42
Ramipril	1.25mg-10mg	0.21-0.50
Angiotensin II Inhibitors		
Losartan	12.5mg-50mg	0.15-0.61
Beta-blockers		
Carvedilol	6.25mg-50mg	0.37-0.48
Bisoprolol	1.25mg-10mg	0.25-0.38
Diuretics		
Digoxin	62.5mcg-250mcg	0.02
Diuretics		
Spiroonolactone	25mg-50mg	0.09-0.19
Frusamide	20mg-40mg	0.02-0.03
Bumetanide	0.5mg-2mg	0.030.13

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Correction: New Drugs For Epilepsy

In our bulletin on New Drugs For Epilepsy the dose section of topiramate should have read: " Therapy should be initiated at a dose of 25mg at night for one week and increased by 25-50mg at weekly intervals according to response."