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CONGESTIVE HEART FAILURE

-  Congestive heart failure is a complex clinical syndrome affecting 6-10% of people aged >65 years
-  Early diagnosis and treatment reduces mortality and morbidity
-  Standard treatment involves use of a diuretic, ACE inhibitor and β -blocker
-  Treatment of concomitant / underlying diseases improves outcome

INTRODUCTION

Congestive heart failure (heart failure) constitutes a major public health problem¹. It is estimated that 1-2% of the adult population have heart failure however, this rises to 6-10% of people aged > 65 years². Heart failure is a major cause of mortality, with rates of up to 30% recorded at one year and 60-70% at five years³. Heart failure also negatively impacts on quality of life, in terms of the physical aspects of day-to-day life⁴. It is the leading cause of acute medical hospital admissions, accounting for at least 20% of admissions among people aged > 65 years⁵. Moreover, one third of hospitalized patients are readmitted 3-6 months after discharge⁶. This places a huge cost burden on the health service, accounting for about 2% of all health-care spending in some countries². This bulletin will focus on the causes, diagnosis and contemporary management of heart failure, with particular reference to primary care.

PATHOPHYSIOLOGY OF HEART FAILURE

Heart failure comprises a complex clinical syndrome that arises as a consequence of an abnormality in cardiac structure, function, rhythm or conduction. Table 1 outlines the classification of heart failure according to clinical presentation³. In the early stages, following an insult to the myocardium, a series of compensatory changes take place to counteract any reduction in cardiac output. These include the activation of several neurohumoral systems, including the renin-angiotensin-aldosterone system (RAS), stimulation of the sympathetic nervous system and release of several natriuretic peptides (including B-type natriuretic peptide, BNP) in response to atrial and ventricular stretching⁷. In addition, the myocytes undergo structural change and this, together with the persisting influence of the neurohumoral hormones, results in remodeling of the damaged cardiac muscle. If these changes (which precede symptoms) are not reversed they cause considerable damage to heart function, leading to reduced performance and the development of symptoms⁵. This represents an opportunity to delay the onset of heart failure by early management of risk factors, including hypertension, diabetes and coronary artery disease⁷.

In the Western world, underlying hypertension and coronary artery disease / prior myocardial infarction (MI) are the commonest causes of heart failure⁸. Among Framingham Heart Study subjects who were free of heart failure at baseline, lifetime risk for developing heart failure was doubled for both men and women with blood pressure > 160/100 versus < 140/90 mmHg⁹. Valvular heart disease, dilated cardiomyopathy (which may be genetic in up to 30% of cases) and thyroid dysfunction are also common causes of heart failure⁷. In fact almost any insult to the heart (e.g. infections, alcohol misuse, drugs) can result in heart failure³.

Table 1: New York Heart Association (NYHA) classification of heart failure³

| Class I | Class II | Class III | Class IV |
|---|--|---------------------------------------|--------------------|
| No limitation during normal physical activity | Slight limitation on moderate exertion | Marked limitation on minimal exertion | Breathless at rest |

DIAGNOSIS OF HEART FAILURE

Diagnosis is primarily clinical, with confirmation from objective tests. Patients usually present with the symptoms of breathlessness, exercise intolerance and fatigue with/without oedema³. Chest X-ray will indicate the size of the heart and the degree, if any, of pulmonary congestion. A 12-lead electrocardiogram (ECG) is useful to identify ischaemic changes, prior MI, atrial fibrillation and left ventricular hypertrophy^{3,8}. Echocardiography is an invaluable tool to determine the type and severity (in terms of ejection fraction) of heart failure.

Heart failure is divided into 2 main types: systolic dysfunction and diastolic dysfunction. **Systolic dysfunction** occurs in up to 70% of patients; it is characterized by left ventricular dilatation, decreased ejection fraction and cardiac output and is the result of volume overload⁸. In addition to the classical symptoms, patients may also have mitral regurgitation. On echocardiography, the heart typically shows an ejection fraction of <40%, myocardial hypertrophy and dilated chambers.

Diastolic dysfunction is estimated to occur in 20-50% of heart failure patients. Patients have the classical symptoms of heart failure; however, the heart shows a normal ejection fraction on echocardiography and although there may be evidence of ventricular hypertrophy, there is usually no evidence of ventricular dilatation. The reduced cardiac output is due to abnormal relaxation (diastole), resulting in inadequate filling of the ventricles, especially during exercise⁵. Diastolic heart failure should be considered if a patient presents with classical symptoms, in the presence of a normal ejection fraction on echocardiography². The following types of patients are at increased risk of diastolic heart failure: older females, patients with hypertension, obesity, diabetes or sleep

apnoea⁵. The differential diagnosis is important, since it has been shown that treating concomitant diseases such as hypertension aggressively improves prognosis significantly in diastolic heart failure¹⁰. If in doubt, the patient should be referred for specialist review¹¹.

Several studies¹² have shown that B-type natriuretic peptide (BNP) can be a useful tool in the differential diagnosis of patients with breathlessness; the primary role of BNP measurement in clinical practice is as a “rule out” test to exclude significant cardiac disease as normal BNP levels make a diagnosis of heart failure unlikely¹³.

MANAGEMENT OF HEART FAILURE

The aims of treating heart failure are to improve the patient’s symptoms, to avoid hospitalisation and to prolong life². This involves non-pharmacologic and pharmacologic management options.

NON-PHARMACOLOGIC MANAGEMENT

Heart failure is a chronic condition that requires lifelong management. Patients and their families should be advised on the following since these are common causes of hospitalization and/or a worse prognosis in heart failure patients¹⁴:

Lifestyle modifications: these include smoking cessation, diet (including salt restriction to < 4g/day and weight reduction if overweight), monitoring of fluid intake (to balance intake and output with diuretic therapy) and the importance of regular exercise (especially in stable patients). Recommendations for exercise training programmes in patients with NYHA II-III heart failure have been published by the European Society of Cardiology¹⁵.

Weight monitoring: patients should be advised to weigh themselves on a regular basis and in the case of any sudden unexpected weight gain of > 2kg in 3 days to either report it or increase their dose of diuretic as agreed with their physician¹³.

Adherence to medication regimen: this is especially important when patients become asymptomatic.

Avoidance of certain medications: these include non-steroidal anti-inflammatory drugs (negative effect on renal function leading to fluid retention), tricyclic anti-depressants (cardio-toxic), lithium (risk of toxicity with sodium depletion) and corticosteroids (fluid retention, hypertension)¹³.

In addition, patients should be advised to seek **early treatment of acute chest infections** and receive **regular immunization against influenza and pneumococcal infections** in order to prevent respiratory infection-related hospitalization¹⁶.

PHARMACOLOGIC MANAGEMENT

The aims of pharmacologic management are to improve the patient’s symptoms and to delay or prevent the structural damage, as described previously. **The recommended standard drug treatments are diuretics, angiotensin-converting enzyme inhibitors (ACEIs) and β-blockers.** It is important to note that nearly all the evidence base for use of these drugs comes from studies undertaken in patients with heart failure due to systolic dysfunction¹⁰.

DIURETICS – Background: Diuretic treatment results in rapid improvement in symptoms and increased exercise tolerance in more than two-thirds of patients with congestive heart failure¹⁷. **However, no studies on their effect on mortality have been undertaken (with the exception of spironolactone), therefore they are not recommended for monotherapy in heart failure but rather should be used in association with an ACEI and β-blocker¹⁸.** Loop diuretics are usually the diuretic of first choice as they result in urinary excretion of up to 25% of the filtered load of sodium¹⁹; there are no apparent differences in efficacy between the various loop diuretics¹⁷. Restriction of fluid to < 1 litre per day may be recommended in refractory patients to relieve fluid retention¹⁸. Thiazides are less potent diuretics (excretion of approximately 5% of the filtered sodium load), but they may be useful as initial therapy in patients with mild heart failure and concomitant hypertension¹⁷. Thiazides may also be added to loop diuretic therapy, under careful supervision, to improve symptomatic relief.

SPIRONOLACTONE is a diuretic that acts via aldosterone antagonism²⁰. It was reported to reduce mortality in patients with severe heart failure from 46% to 35% over a 2-year period of review, when used as “add-on” therapy to existing diuretic, ACEI and β-blocker therapy²¹. Monitoring of plasma potassium is especially important due to the risk of hyperkalaemia, especially when administered with ACEI or angiotensin receptor blocker (ARB), or in patients with renal dysfunction. Spironolactone is also known to cause gynaecomastia in male patients. The newer aldosterone antagonist eplerenone has also shown benefit in patients with severe heart failure when used in combination therapy²², and has a better safety profile than spironolactone.

Practical Advice: Table 2 lists the commonly used diuretics and their recommended doses. In general, treatment should be initiated at low dosage and up-titrated according to response. **It is important to remember that the dose of diuretic may need to be reduced once the patient is on optimum ACEI therapy.**

Hypokalaemia is uncommon as it is usually counteracted by the co-administration of an ACEI. However, **it is recommended that plasma potassium monitoring be undertaken in heart failure patients in the initial stages of treatment, when increasing the dose and in those patients also taking digoxin, due to the risk of toxicity in the presence of hypokalaemia¹⁷.** The concomitant use of NSAIDs with loop diuretics should be avoided as they may counteract the effects of the diuretic and worsen renal function. These effects are especially likely in the older patient, where heart failure is more prevalent.

As use of **aldosterone antagonists** is reserved for NYHA class III or IV with severe symptoms, these patients will usually be under specialist care. However, it is important to ensure that plasma potassium and creatinine levels are regularly checked.

Table 2: Commonly prescribed diuretic agents in Ireland*

| Drug Name | Drug type | Recommended Initial Dose ^{7,13,23} | Maximum Daily Dose ^{7,13,23} |
|---------------------|------------------------|---|---------------------------------------|
| Furosemide | Loop diuretic | 20-40mg once-twice daily | 600mg** |
| Bumetanide | Loop diuretic | 0.5-1mg once-twice daily | 5-10mg*** |
| Bendroflumethiazide | Thiazide | 2.5mg daily | 10mg |
| Spironolactone**** | Aldosterone antagonist | 12.5-25mg (50mg if no ACEI) | 50mg (100-200mg if no ACEI) |

*Data from GMS diuretic prescribing figures for April 2006 from Eastern Regional Area.

** doses > 80mg with specialist supervision only *** doses > 2mg with specialist supervision only **** specialist supervision drug

ACEIs – Background: Several large studies have shown that ACEIs decrease the rate of hospitalizations, improve symptoms and increase survival in heart failure patients¹³. A summary of the types and doses of ACEIs used in the main studies in heart failure is contained in Table 3. They are thought to exert their effect in heart failure by inhibiting the multiple pathophysiological effects of angiotensin II and decreasing the breakdown of bradykinin (which promotes vasodilatation in the vascular endothelium and causes natriuresis in the kidneys)⁵. They are recommended for use in all stages of heart failure, including asymptomatic patients, but their

effect is more marked in patients with more severe symptoms¹¹.

Practical Advice: Treatment should be initiated with the lowest recommended dose and gradually titrated at one to two weekly intervals to the recommended maintenance dose (see Table 3 and the Summary of Product Characteristics for individual drugs²³). Excessive diuresis should be avoided before treatment. After the initial dose, the patient may suffer hypotension, therefore blood pressure should be monitored, especially if he/she is known to have renal dysfunction or low blood pressure. In addition, renal function, plasma electrolytes and blood pressure should be evaluated after each increase of dose until the target dose is reached. Thereafter, they should be checked at 3-6 monthly intervals. If renal function deteriorates, the ACEI should be stopped and the patient referred for specialist advice¹³. ACEIs may also cause angioedema (at any time during treatment) and dry cough occurs frequently; these adverse effects may also necessitate discontinuation of treatment and switch to ARBs¹³ (see below).

Table 3: Summary of ACEIs evaluated in the main heart failure studies^{13,23}

| Drug Name | Recommended* Initial Dose | Recommended* Maintenance Dose |
|--------------|---------------------------|-------------------------------|
| Enalapril | 2.5mg daily | 10mg twice daily |
| Lisinopril | 2.5mg daily | 5-20mg daily |
| Captopril | 6.25mg three times daily | 25-50mg three times daily |
| Ramipril | 1.25-2.5mg daily | 2.5-5mg twice daily |
| Trandolapril | 1mg daily | 4mg daily |

Note: Other ACEIs may be authorised for heart failure in Ireland. Check individual Summaries of Product Characteristics for recommended doses.

* as per Summary of Product Characteristics

β-BLOCKERS – Background: β-blockers have been evaluated in more than 20,000 patients with heart failure who participated in over 20 placebo-controlled clinical trials⁷. Results have shown that long-term treatment with β-blockers can lessen the symptoms of heart failure, improve clinical status and enhance the patient’s overall sense of well-being, as well as reducing the combined risk of death or hospitalization. β-blockers may not all have the same efficacy¹¹; Table 4 outlines the β-blockers for whom the most clinical evidence of efficacy is available, together with the recommended dosage regimen.

Practical Advice: β-blockers should be suitable for most patients with heart failure, provided their symptoms are stable and they don’t have substantial fluid retention⁵. They should be started at a low dose and since symptoms may be exacerbated initially, heart rate, blood pressure and overall clinical status, including weight, should be closely monitored. Patients should be advised that exacerbations of heart failure symptoms may occur but are likely to be temporary. They should be told not to stop taking their medication without first consulting their physician as the symptoms can usually be managed in the short-term by adjustment of other medications such as diuretics. The dose should be slowly increased (no greater than a doubling of the previous dose, at intervals of no less than 2 weeks apart) until the recommended maximum dose/highest tolerated dose is achieved¹¹. During up-titration, if patients develop worsening of symptoms, the existing dose should be halved or the dose of diuretic increased and the situation reviewed in 2 weeks. If no improvement occurs, specialist advice should be sought. β-blockers are known to cause bradycardia and to lower blood pressure. If the patient develops bradycardia (<50 bpm) or symptomatic hypotension, the dose should be halved and the patient reviewed for the possibility of heart block. In general, it is important NOT to discontinue the β-blocker suddenly unless absolutely necessary as there is a risk of a “rebound” increase in myocardial ischaemia¹¹. If in doubt, specialist advice should be sought. Lethargy and fatigue have also been reported with use of β-blockers and may result in a reduction of dose or prevent titration to the maximum recommended dose²⁰.

β-blockers should not be used or should be used only with extreme caution⁵ in the following groups of patients: patients with reactive airways disease, those with diabetes in association with frequent episodes of hypoglycaemia and those with bradyarrhythmias or heart block who do not have a pacemaker. It is likely that these patients will be under specialist care already.

Table 4: Summary of β-blockers evaluated in the main heart failure studies^{7,23}

| Drug name | Recommended* Initial Dose | Recommended* Maximum Dose |
|---------------------------|---------------------------|---------------------------|
| Bisoprolol | 1.25mg once daily | 10mg once daily |
| Carvedilol | 3.125mg twice daily | 25mg twice daily |
| Metoprolol succinate CR** | 12.5-25mg once daily | 200mg once daily |
| Nebivolol | 1.25mg | 10mg once daily |

Other β-blockers may be authorised for heart failure in Ireland. Check Summary of Product Characteristics for recommended doses. * as per Summary of Product Characteristics

** not authorized in Ireland; dosage based on clinical trials data

OTHER DRUGS

ANGIOTENSIN RECEPTOR BLOCKERS (ARBs): Like ACEIs, these drugs act by inhibiting the renin-angiotensin system. They are used in the management of hypertension and more recently some ARBs have shown efficacy in terms of improved mortality and morbidity in the management of heart failure in clinical trials. Table 5 lists the ARBs authorised for heart failure treatment in Ireland. Overall, there is considerably less experience with use of ARBs in heart failure compared with ACEIs⁷. There is a difference between expert guidelines as to the current role of ARBs in the management of heart failure²⁴. All guidelines agree that ARBs should be used in patients intolerant of ACEIs (e.g. due to cough, angioedema). In addition, studies have shown a modest decrease in hospitalization with ARBs used in combination with ACEIs⁷. Previously, uncertainty existed regarding the safety of combination of an ARB and a β-blocker, but these concerns have been addressed in recent studies¹³. However, it is recommended that such combination use should be under specialist supervision²⁰. The practical advice regarding initiation of dosage and monitoring of ARB usage is similar to the guidance given for ACEIs (see above).

Table 5: Angiotensin Receptors Blockers (ARBs) licensed for heart failure treatment in Ireland²³

| Drug name | Recommended* Initial Dose | Recommended* Maintenance Dose |
|-------------|---------------------------|-------------------------------|
| Losartan | 12.5mg once daily | 50mg once daily |
| Candesartan | 4mg once daily | 32mg once daily |
| Valsartan | 40mg twice daily | 160mg twice daily |

DIGOXIN: Atrial fibrillation occurs frequently in patients with heart failure, therefore many patients may receive digoxin for rhythm control²⁰. The role of digoxin, which has positive inotropic activity, in the contemporary management of heart failure in patients with sinus rhythm is more controversial²⁴. The DIG study²⁵, involving more than 6,000 patients with normal sinus rhythm heart failure, with an average follow-up of 37 months, showed no significant benefit in terms of mortality for digoxin over placebo. However, there was a significant reduction in hospitalizations both overall and for worsening heart failure. Current guidelines give conflicting advice regarding the role of digoxin in heart failure patients with normal sinus rhythm^{7,13}. However, it does appear to have a potential role in patients in normal sinus rhythm who have worsening or severe heart failure due to left ventricular systolic dysfunction, despite treatment with ACEI, β -blocker and diuretic therapy¹¹. Such usage should be under specialist supervision²⁰ and plasma potassium levels must be monitored regularly to avoid toxicity due to hypokalaemia.

OTHER PHARMACOLOGIC AGENTS¹³: Vasodilator agents (e.g. hydralazine, isosorbide dinitrate) have no specific role in the management of heart failure although they may be used as adjunctive therapy for concomitant angina. However, studies have shown that a combination of hydralazine and isosorbide dinitrate may be beneficial when added to standard therapy in African-American patients with moderate to severe heart failure²⁶. In general, calcium antagonists are not recommended in heart failure. In particular, diltiazem and verapamil-type calcium antagonists are not recommended in the presence of systolic dysfunction and are contraindicated with the use of β -blockers. Felodipine and amlodipine may offer a safe alternative for the treatment of concomitant hypertension or angina not controlled by nitrates and β -blockers. Amiodarone may be used for the prevention of ventricular arrhythmias in high-risk patients with heart failure⁷, but only under specialist supervision²⁷.

IMPLANTABLE DEVICES may be used for the management of specific types of heart failure, including refractory patients or those at high risk of sudden death. In addition to standard pacemakers, **cardiac resynchronisation therapy (CRT)** is a specific pacemaker-based approach used to improve ventricular synchrony and overcome conduction defects in patients with a wide QRS complex on ECG and severe systolic dysfunction. Although symptomatic improvements have been reported, CRT has not been shown to enhance survival⁵. **Implantable cardioverter defibrillators (ICD)** may be used for patients who have survived cardiac arrest and/or have sustained ventricular tachycardia, which is either poorly tolerated or is worsening ventricular function¹³.

THE MANAGEMENT OF DIASTOLIC HEART FAILURE

There are little objective data to guide the therapy of patients with diastolic heart failure¹⁰. These patients often present with breathlessness but with none of the other signs and symptoms of heart disease. It is recommended that where this type of heart failure is suspected the patient should be referred for specialist diagnosis and treatment¹¹. In the absence of controlled clinical trials, management is based on control of physiological factors (blood pressure, heart rate, blood volume and myocardial ischaemia) that are known to exert important effects on ventricular relaxation (i.e. diastole)⁷. As mentioned previously, these patients are frequently older females with concomitant illnesses such as hypertension and diabetes mellitus, therefore optimal management of these underlying conditions results in symptomatic improvement and improved survival prospects¹⁰.

MANAGEMENT OF HEART FAILURE IN GENERAL PRACTICE

Table 6 outlines the steps to be taken in the management of patients with heart failure in general practice.

Table 6. Management Outline of Heart Failure Patients in General Practice¹³

- Identify symptoms and signs of heart failure; confirm diagnosis with appropriate tests (as above)
- Assess the severity of symptoms
- Determine underlying causes and precipitating factors
- Counsel patient and relatives on non-pharmacological / lifestyle management programme and need for, and importance of adherence to, his/her therapeutic regimen
- Initiate standard therapy of diuretic, ACEI and β -blocker (using dosing schedules outlined above)
- Identify concomitant diseases and include their treatment in the overall management programme for the individual patient
- Monitor patient's progress in terms of response to individualized drug and lifestyle management programme on a regular basis
- Seek specialist advice if patient cannot tolerate standard therapy/deteriorates while on maximum standard therapy or if uncertain about the diagnosis

SUMMARY

Heart failure is one of the commonest diseases encountered in general practice. Current guidelines recommend the use of diuretics, ACEIs, and β -blockers (in addition to lifestyle management and control of concomitant diseases) as standard therapy for heart failure patients^{7,11,13}. However, studies have shown that patients in general practice do not routinely receive these therapies²⁸. This may be because the patients encountered in everyday practice are more difficult to treat than patients enrolled in clinical trials. A recent multinational EU study²⁹ showed that only about 56% of prescribing for heart failure management in primary care was appropriate, taking patient characteristics into account. Age, gender and co-morbidities such as chronic obstructive lung disease appeared to influence the type and combination of therapies prescribed in the patients. The authors suggest that prescribers may be unwilling to disturb the therapeutic status quo in a patient with co-morbidities, despite the evidence base supporting the benefit of the above standard therapies. Moreover, under-utilisation of the so-called standard therapies has been identified in patients with no obvious contraindications to their use³⁰. This included sub-optimal dosage of ACEIs and under-prescribing of β -blockers. While use of lower doses or monotherapy may be better than none at all³¹, the evidence base for efficacy in terms of improved outcome for the patient is based on the optimum drugs and dosages used in the landmark trials.

A heart failure management programme that includes multidrug therapy allows symptomatic relief of the patient's symptoms and avoids hospitalizations; in addition, it addresses the pathophysiological process underlying the development of heart failure³², thereby improving survival prospects.

References available on request. Date prepared: July 2006

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue. Prescribers are recommended to refer to the drug data sheet or summary of product characteristics (SPC), also available on www.medicines.ie for specific information on drug use.

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