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Drug management of heart failure

Chronic heart failure is a serious, costly and increasingly common disorder. Management can be complex but there is increasing evidence supporting the effectiveness of drug therapies. In spite of this, chronic heart failure continues to be significantly undertreated,¹ and to be associated with high mortality rates and high healthcare costs.

Recent studies have addressed the use of angiotensin-converting enzyme (ACE) inhibitors, beta-blockers and spironolactone in patients with heart failure. The role of other diuretics and digoxin has also been re-evaluated, and guidelines provide advice on appropriate treatment regimens for individual patients with chronic heart failure.^{2,3}

This bulletin discusses the drug management of heart failure caused by left ventricular systolic dysfunction, with emphasis on the implications of new studies. Optimal drug therapy for patients with abnormal diastolic (rather than systolic) heart function has not been established.

Summary

- ♦ Appropriate pharmacological treatment of heart failure caused by left ventricular systolic dysfunction significantly **reduces mortality** and **improves clinical symptoms** cost-effectively.
- ♦ **ACE inhibitors** should be given to all patients except when contra-indicated. Giving adequate doses and monitoring renal function and serum potassium are important. **Angiotensin II receptor antagonists** are not licensed for heart failure and their place in therapy has not been established.
- ♦ **Diuretics** and **digoxin** improve symptoms and should be used when indicated.
- ♦ **Spironolactone** is recommended for all patients with class III or IV heart failure who are already being treated with a diuretic, with or without an ACE inhibitor or digoxin.
- ♦ **Beta-blockers** reduce mortality in heart failure and, unless contra-indicated, should be considered for all patients with class II to IV heart failure who are clinically stable on diuretics, with or without an ACE inhibitor or digoxin.

Initial measures

The diagnosis of heart failure is not always straightforward and should be confirmed before treatment is begun. The extent of heart failure is described using the New York Heart Association classification of symptoms (see the box on page 5).

Diagnosis of heart failure is best made with echocardiography (see the action plan for provision of services in Wales⁴). “Open-access” echocardiography is believed to be a cost-effective service when the costs of unnecessary or delayed treatment for heart failure are considered.⁵ However, such a service may not be available in all areas. The measurement of brain natriuretic peptide (BNP) in plasma as a screening test is currently being evaluated.

Initial measures for the management of heart failure include educating patients about lifestyle measures that can be beneficial, such as exercising, losing weight and reducing excessive salt or alcohol intake. Patients should also be made aware of the importance of taking the medicines prescribed for them. All patients with heart failure should receive an annual influenza immunisation and a once-only pneumococcal immunisation.

If possible, drugs that may aggravate heart failure should be stopped. These include nonsteroidal anti-inflammatory drugs (except aspirin) and some calcium-channel blockers that can worsen or precipitate heart failure² (see *Drugs for angina* on page 5).

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Angiotensin-converting enzyme (ACE) inhibitors

Large randomised controlled trials and meta-analyses have shown that ACE inhibitors (added to diuretic therapy) improve long-term survival in patients with all grades of heart failure, reduce the symptoms and slow the progression of heart failure.^{2,6-8} The use of ACE inhibitors in appropriate patients has been shown to be cost-effective.⁹ There is evidence that ACE inhibitors are not being prescribed when indicated or at adequate doses,¹ and that renal function is poorly monitored.¹⁰

Unless contra-indicated, an ACE inhibitor should be given to all patients with heart failure caused by left ventricular systolic dysfunction. This includes elderly and female patients,¹¹ those whose symptoms are being controlled by diuretics,² and patients with symptomatic or asymptomatic left ventricular dysfunction after myocardial infarction.¹² There is some evidence that an ACE inhibitor may be beneficial for all patients at high risk of cardiovascular disease regardless of left ventricular function.¹³

Meta-analyses have found no differences between the effects of different ACE inhibitors⁷ but enalapril has been the most studied in published trials. The target doses recommended are those used in the large clinical trials, for example:

- ◇ captopril 50 mg three times a day,
- ◇ enalapril 10 mg to 20 mg twice a day,
- ◇ lisinopril 32.5 mg to 35 mg once a day,
- ◇ ramipril 10 mg daily.

Doses used in practice tend to be too low.¹ A study of lisinopril¹⁴ has shown that patients given high doses (32.5 mg to 35 mg daily) had a lower risk of all-cause mortality or hospitalisation for any reason, or hospitalisation for heart failure, than patients given low doses (2.5 mg to 5 mg daily).

Patients should be considered for referral to hospital for initiation of treatment with an ACE

inhibitor if any of the following are present:^{2,3,7}

- ◆ serum sodium ≤ 130 mmol/l
- ◆ serum potassium > 5 mmol/l
- ◆ serum creatinine > 150 micromol/l
- ◆ serum urea > 12 mmol/l
- ◆ systolic blood pressure < 100 mm Hg
- ◆ daily diuretic dose > 80 mg furosemide (frusemide) or equivalents
- ◆ known or suspected renal artery stenosis
- ◆ symptoms of severe heart failure
- ◆ frail elderly patient.

Monitoring and dose adjustment

Renal function should be monitored before starting therapy with an ACE inhibitor, seven to ten days later, and one week after each dose increase. Therapy should be started with a small dose (for example, enalapril 2.5 mg twice a day) and the dose titrated upwards over the next few days or weeks. (The practice of initiating treatment with a captopril “test dose” has no advantage.) The dose should be increased to the maximum tolerated or the target dose (whichever is lower), not according to symptomatic response. Extra care should be used in the elderly.

It is not usually necessary to stop or reduce the dose of a diuretic when starting an ACE inhibitor² unless the patient is taking more than 40 mg of furosemide (frusemide) or is volume depleted (postural hypotension, dry tongue or skin, poor skin turgor, increased creatinine and urea).

Patients should be reviewed one month after initiating treatment. If adverse effects occur (such as serum potassium ≥ 5.5 mmol/l, symptomatic hypotension, renal dysfunction or intolerable cough) the patient should be referred to a specialist. It is important to note that cough may be a symptom of pulmonary congestion caused by heart failure and may not necessarily be an effect of the ACE inhibitor.

Angiotensin II receptor antagonists

Angiotensin II receptor antagonists have a different mechanism of action from ACE inhibitors and are used for the treatment of hypertension. There is little evidence supporting the use of these drugs for heart failure and none are currently licensed for this indication in the UK.

In a study in patients aged over 60 years with class II to IV heart failure, on standard treatment, no difference was found between captopril and losartan in the primary endpoint of death from any cause.¹⁵ However, fewer patients taking losartan discontinued treatment because of adverse effects.

A study of valsartan in patients with heart failure on standard therapy, including an ACE inhibitor, has recently been completed. An abstract of the results suggests that valsartan had a beneficial

effect on the time to mortality plus morbidity.¹⁶ However, because of the paucity of evidence, the place of angiotensin II receptor antagonists in the treatment of heart failure remains to be established.

Diuretics

Clinical experience and some controlled trials of loop diuretics have shown that diuretics improve symptoms of fluid retention in heart failure² such as breathlessness, peripheral oedema, elevated jugular venous pressure and exercise intolerance. A meta-analysis (to date published as an abstract only) found that mortality was lower in patients treated with diuretics.¹⁷

Because diuretics stimulate the renin-angiotensin system, it is preferable to start diuretic therapy after introducing an ACE inhibitor.

A loop diuretic is usually the first choice and may be more effective than a thiazide in moderate to severe heart failure. In patients with oedema that is resistant to either type of diuretic alone, a combination may be effective. A potassium-sparing diuretic should be added to a loop diuretic or a thiazide only if a patient cannot tolerate an ACE inhibitor.²

The dose of a diuretic should be altered according to response but most patients will not require more than 80 mg of furosemide (frusemide) daily or the equivalent. Close monitoring of serum potassium concentrations is required. Monitoring of electrolytes and renal function is especially important with combination therapy.

Spirolactone is a competitive antagonist of aldosterone and so, theoretically, might have an additional beneficial effect in patients on ACE inhibitors. A large randomised placebo-controlled trial showed that mortality from all causes was reduced significantly in patients with class III or IV heart failure when spironolactone 25 mg (in some cases increased to 50 mg) was added to their therapy.¹⁸ In patients receiving spironolactone the frequency of hospitalisation was lower and symptoms improved. Patients were already being treated with a loop diuretic and, in almost all cases, an ACE inhibitor with or without digoxin.

Spirolactone 25 mg daily is recommended for all patients with class III or IV heart failure already being treated with a diuretic, with or without an ACE inhibitor or digoxin, even if symptoms of water and sodium retention are controlled.² Patients with this degree of heart failure are usually seen by a specialist.

Although the incidence of serious hyperkalaemia (serum potassium ≥ 6 mmol/l) in the trial was not different in the spironolactone group compared with the placebo group,¹⁸ serum potassium concentrations and renal function should be carefully monitored as the risk may be greater in routine clinical practice. Abnormalities may occur some months after addition of spironolactone.

Digoxin

The use of digoxin to treat patients with atrial fibrillation and heart failure is well established. For patients with heart failure who are in sinus rhythm, most evidence for beneficial effects comes from studies in which digoxin was withdrawn, causing clinical worsening of heart failure and reduction of maximal exercise capacity.^{19,20} In the only placebo-controlled study of the effect of digoxin on morbidity and mortality in heart failure,²¹ there was no change in overall mortality but there was a significant reduction in hospitalisation for all causes and a reduction in the

number of patients hospitalised for worsening heart failure when digoxin was added to diuretic and ACE inhibitor therapy.

Digoxin should be given to patients with heart failure and atrial fibrillation for control of the ventricular rate. It is also recommended for patients in sinus rhythm with class III or IV heart failure who have symptoms in spite of treatment with ACE inhibitors and diuretics, patients who have had more than one hospital admission for heart failure, or those who have very poor

left ventricular systolic function or persisting cardiomegaly.² Such patients are likely to be under specialist care. Patients with heart failure being treated with a diuretic but intolerant of ACE inhibitors should also be given digoxin. However, digoxin is not a substitute for an ACE inhibitor as it is not as effective for controlling symptoms and does not reduce mortality.

Most patients in the trials mentioned above took 250 micrograms of digoxin daily, although doses ranged from 125 to 375 micrograms daily. Target serum concentrations of 0.8 to 0.9 micrograms/l are recommended.² However, serum levels should always be evaluated in conjunction with patients' symptoms. Lower doses may be required in patients with renal failure and the elderly.

Beta-blockers

There is good evidence that cautiously adding small doses of a beta-blocker (bisoprolol, carvedilol or sustained-release metoprolol) to standard treatment of patients with class II to IV heart failure reduces mortality, morbidity and the rate of hospitalisation for heart failure.²²⁻²⁷ The benefit may not apply to all beta-blockers. One recent trial of a beta-blocker not available in the UK, bucindolol, showed no effect on all-cause mortality in severe heart failure, although the risk of death from cardiovascular causes and the rate of hospitalisation from chronic heart failure were lower.²⁸ In a study of carvedilol in patients with heart failure after myocardial infarction, the primary endpoint (a combined outcome of death or hospitalisation for cardiovascular causes) was not affected by treatment, however, all-cause mortality was reduced.²⁹

Unless contra-indicated, beta-blockers should be considered for all patients with symptomatic classes of heart failure (class II to IV) who are clinically stable on diuretics, with or without an ACE inhibitor or digoxin. Treatment should be started under specialist supervision, such as in hospital or a specialised heart failure clinic where the patient can be observed for two to three hours. Thereafter the dose can be titrated by primary care professionals.

Beta-blockers currently licensed in the UK for heart failure are bisoprolol (only *Cardicor*,⁰ licensed for "moderate to severe" heart failure)

and carvedilol (licensed for class II and III heart failure). The dose is initially low (bisoprolol 1.25 mg daily or carvedilol 3.125 mg twice daily) and is gradually increased (every two weeks) up to a tolerable dose or the target dose (bisoprolol 10 mg daily or carvedilol 25 mg twice daily; patients weighing more than 85 kg may receive up to 50 mg of carvedilol twice daily). In practice, target doses may not always be achieved; for example, target doses were taken by 80% of patients in one trial²³ and approximately half of patients in two other trials.^{24,26}

Patients should be aware that for three to four weeks after starting treatment with a beta-blocker there may be some worsening of symptoms. Although doses of beta-blockers commonly used to treat hypertension have the potential to worsen heart failure, no serious problems with this (or bradyarrhythmias or hypotension) were seen in the heart failure trials. Discontinuation rates because of adverse drug reactions were similar in the beta-blocker groups compared with the placebo groups.^{23,25,27}

In elderly patients, use of beta-blockers may unmask existing heart conduction abnormalities and lower doses may be needed. Contra-indications to the use of beta-blockers in heart failure are the same as for their use in hypertension and include the concomitant use of beta-blocker eye drops. Extra caution should be used in patients also taking digoxin because of the increased risk of bradycardia with this combination.

Other drugs used in heart failure

Hydralazine plus nitrates

When an ACE inhibitor is contra-indicated or not tolerated, isosorbide dinitrate plus hydralazine is an alternative. However, in a comparison with enalapril the observed effect on survival was not as

great with this combination.³⁰ Initially isosorbide dinitrate 20 mg and hydralazine 37.5 mg are given four times a day.^{2,30} These doses are doubled after two weeks if they are tolerated by the patient.

Drugs for angina

Patients with angina and heart failure can be treated with nitrates or amlodipine^{2,31} in addition to the drugs already discussed (including the cautious use of beta-blockers). Some evidence suggests that felodipine may also be well tolerated.³²

Aspirin

Although the question of an interaction between aspirin and ACE inhibitors has been raised, no evidence for this was found in a systematic overview of over 96,000 patients in trials of ACE inhibitors.³³

Anticoagulants and anti-arrhythmic agents

Warfarin therapy is recommended for patients with heart failure and atrial fibrillation, aiming for a target INR of 2.5.² Digoxin should be used to control the ventricular rate. Amiodarone is the anti-arrhythmic drug of choice in patients with heart failure and severely symptomatic ventricular arrhythmias. (Beta-blockers may provide adequate control in less severe cases.) Amiodarone increases plasma concentrations of digoxin and warfarin, making close monitoring of digoxin concentrations and the INR essential in patients taking these combinations.

New York Heart Association (NYHA) classification for chronic heart failure symptoms²

- Class I** (asymptomatic left ventricular systolic dysfunction). Symptoms cause no limitation of physical activity. Ordinary physical activity does not lead to undue fatigue, palpitations or dyspnoea.
- Class II** ('mild' heart failure). Symptoms cause slight limitation of physical activity. Patient is comfortable at rest, but ordinary physical activity results in fatigue, palpitations or dyspnoea.
- Class III** ('moderate' heart failure). Symptoms cause marked limitation of physical activity. Patient is comfortable at rest, but even slight physical activity results in fatigue, palpitations or dyspnoea.
- Class IV** ('severe' heart failure). Symptoms of cardiac insufficiency are present at rest, and discomfort is increased with any physical activity.

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Manufacturers' data sheets and summaries of product characteristics should be consulted for full prescribing information.