MEDICAL TREATMENT OF CHRONIC HEART FAILURE

*L. Gates**
*M.J. MacLeod**
*J. McLay**

INTRODUCTION

Heart failure is a common and increasing clinical problem: the exact prevalence, morbidity, mortality and cost to the community within the UK are difficult to assess, but both its incidence and prevalence are increasing. Despite greater awareness among physicians and the introduction of angiotensin converting enzyme inhibitors, the prognosis has remained poor. Because of the chronic nature of heart failure and the need for frequent hospitalisations, the treatment of heart failure is costly to the community: within the UK, heart failure accounts for 4.9% of all acute admissions to general medical wards and that the cost burden to the Health Service is over 1% of total expenditure, and increasing as a result of new surgical and medical interventions.[1] Patients with heart failure are frequently admitted as inpatients with acute exacerbations of heart failure (on average 1.33 times per year.) The average inpatient stay has been reported to vary between 14.5 and 15.2 days for patients aged 65-74 years, which is longer than that for other medical causes.[2,3] Frequent admission and prolonged stay are major components of the high costs associated with the treatment of heart failure. It is clear that optimisation of medical therapy with diuretics, angiotensin converting enzyme (ACE) inhibitors, and beta-blockers can reduce admission frequency and length of hospital stay, however it is clear that less than 40% of patients receive optimal therapy.[4]

For most chronic conditions optimisation of therapy is attained through the use of specialist clinics, however although the value of such dedicated clinics in the treatment of other chronic diseases is well established, the value of dedicated heart failure clinics still remains unclear. Patients with heart failure are cared by general practitioners, hospital doctors and cardiologists, however heart failure is a syndrome which often requires relatively rapid intervention and complex decisions concerning multiple medications and pathologies, and such a disease may well be best managed in such dedicated heart failure clinics.

THE PHARMACOLOGICAL MANAGEMENT OF CHRONIC HEART FAILURE

To optimise the medical treatment of chronic heart failure (CHF) it is essential to understand the pathophysiology of the syndrome. The signs and symptoms of CHF are caused by either left ventricular systolic or diastolic dysfunction. Left ventricular diastolic dysfunction is typified by reduced ventricular compliance and increased ventricular filling pressures, most commonly due to ventricular hypertrophy secondary to hypertension. Typically patients with this type of disease process have a normal or high ejection fraction. Left ventricular systolic dysfunction, however, is frequently accompanied by a decreased ventricular ejection fraction <35%. This review will focus on the medical management of CHF caused by left ventricular systolic dysfunction.

**Department of Medicine and Therapeutics, The University of Aberdeen, Polwarth Buildings, Foresterhill, Aberdeen AB9 2ZD.*

MEDICAL MANAGEMENT

The short-term aims of medical treatment are to relieve symptoms and improve quality of life, while long-term aims revolve around slowing or possibly reversing progressive left ventricular dysfunction and improving life expectancy.

Despite the lack of controlled studies, the main treatment for symptomatic patients with CHF is the appropriate use of oral loop diuretics plus or minus thiazide diuretics or spironolactone. Diuretics relieve symptoms and are as effective as ACE inhibitors in improving exertional dyspnoea even in patients who are not clearly fluid-overloaded.[5,6,7] Withdrawal or reduction in diuretic dose or substitution with an ACE inhibitor has been associated with recurrence of symptoms in patients with overt fluid overload.[8]

Almost all patients with heart failure have a degree of sodium and fluid overload and are candidates for sodium restriction and diuretic therapy. In the small group of patients who present with fatigue and dyspnoea with no signs of fluid overload (dry failure), initiating therapy with an ACE inhibitor alone may be appropriate providing they have never experienced an episode of acute pulmonary oedema. Nevertheless, a diuretic should be added if symptoms persist.[9]

Some physicians initiate therapy with a thiazide diuretic, however the diuresis achieved is generally small, and if symptoms or if fluid overload persists, a loop diuretic such as frusemide should be substituted. A further advantage of loop diuretics is their ability to achieve a significant diuresis even in the presence of a reduced glomerular filtration rate (GFR <30-40 ml/min).

A loop diuretic is usually started at low dose (frusemide: 40 mg daily), however dosage should be determined by the condition of the patient and their response to treatment. The dose of diuretic is generally increased until obvious fluid retention is relieved, the JVP normalised and relief of symptoms optimised. Unless there is symptomatic hypotension or significant electrolyte or urea disturbance, the continuing presence of peripheral oedema, elevated JVP or hepato-jugular reflex indicates the need for increasing the diuretic therapy.[9,10]

Loop diuretics are effective when given once daily, and if the diuresis is inadequate it is better to double this once-daily dose than to introduce a twice-daily regimen. However, when large doses of diuretic are used (>frusemide 160 mg/day), a twice-daily regimen is more appropriate. In the most refractory cases a dose of frusemide of 240 mg twice-daily may be required.

However, before introducing such high doses of loop diuretic, additional efforts to improve diuresis such as the introduction of metolazone (2.5 mg/daily) or bendrofluazide

(5 mg) should be employed. Both metolazone and bendrofluazide act at the distal renal tubule while loop diuretics act at the ascending loop of Henle, therefore the effect of combining one of these agents with a loop diuretic is synergistic, and may lead to a profound and possibly life-threatening diuresis. For this reason it is recommended that if metolazone or bendrofluazide is added to a loop diuretic it should be pulsed, that is used once, twice or three times weekly rather than given continuously. Clearly, regular measurements of serum potassium, urea and creatinine should be made.

Excess diuresis is harmful, and such features as increasing fatigue, dizziness, hypotension or progressive renal impairment with normal JVP and no evidence of fluid retention indicate that diuretic therapy should be reduced.

Once an 'ideal' fluid state has been achieved, the patient's 'ideal' weight should be recorded and used as a reference point for further diuretic therapy. Because the need for diuretic therapy varies with diet and activity, patients should weigh themselves every one or two days and alter their diuretic dose to maintain body weight within a range in which they have few symptoms.[9,10] Most patients can be readily maintained on an outpatient basis by instructing them to take an extra 40 mg of frusemide in the morning if their weight increases by 1 kg or more, or if symptoms deteriorate, and to maintain this increased dose until weight or symptoms return to normal (for a maximum of three days).

Potassium depletion commonly occurs with chronic diuretic therapy, but the concurrent use of an ACE inhibitor tends to antagonise this effect. Despite ACE inhibitor therapy hypokalaemia may develop, and in such cases it may be appropriate to also use a potassium-sparing diuretic such as amiloride or spironolactone. However, the combination of an ACE inhibitor and a potassium-sparing diuretic may give rise to significant and dangerous hyperkalaemia.

ANGIOTENSIN CONVERTING ENZYME INHIBITORS

The evidence for the use of ACE inhibitors in the treatment of patients with mild and severe CHF is extensive. It is clear that the appropriate use of ACE inhibitor therapy improves exercise capacity, improves the symptoms of heart failure when these are moderate or severe, and significantly reduces total mortality and hospitalisations for congestive heart failure in all grades of patients.[11-14] The actual effect of ACE inhibitor therapy upon mortality appears to be variable. While the CONSENSUS trial[11] reported a reduction in one-year mortality from 52% (placebo) to 36% (enalapril) for patients with New York Heart Association (NYHA) grade 4 failure, the improvement in mortality for less severe grades of heart failure is less impressive, as demonstrated by the SOLVD treatment study[14] where one-year mortality fell from 40% to 35% for patients with NYHA class II heart failure. For these less severe grades of heart failure, the use of ACE inhibitors increases survival by only six months.[14]

ACE inhibitor therapy should be considered for all patients with heart failure due to LV systolic dysfunction unless there are clear contraindications, and when possible, the maximum recommended dose should be used.[15,16] For those patients who cannot tolerate high-dose ACE inhibitor, some comfort can be gained from the ATLAS trial which demonstrated that there was no significant difference in terms of mortality from the use of high or low-dose therapy.

Despite widespread use there are still several misconceptions about the prescribing of ACE inhibitors. They are **not** appropriate as the sole treatment for heart failure, except in those patients who do not demonstrate fluid retention. They do not allow, in general, a reduction in diuretic dose except in those patients who are overtreated with diuretic. Indeed, several studies have demonstrated a reduction in the diuretic actions of frusemide and a consequent acute fluid retention for the first month following introduction of ACE inhibitor therapy.[17]

Because of the risk of first-dose hypotension, ACE inhibitors are introduced at low-dose (captopril 6.25 mg, enalapril 2.5 mg) which is then gradually titrated up to the highest tolerated dose according to patient response. Many physicians use a low dose of a short-acting agent such as captopril to minimise the length of potential hypotensive episodes. This approach does not reduce the degree of hypotension; it possibly reduces the length of the hypotensive episode. Although hypotension is common, first-dose **symptomatic** hypotension is remarkably rare and, in reality, low-dose ACE inhibitor therapy with an agent such as captopril can be initiated in the outpatient setting providing the patient is observed for 2-3 hours following the first dose.[18]

The contraindications and side-effects associated with ACE inhibitors are well documented and will not be discussed further. ACE inhibitors and non-steroidal anti-inflammatory agents (NSAID) can precipitate acute renal failure in patients with pre-existing renal impairment and should be avoided.

ANGIOTENSIN-II ANTAGONISTS

Although as yet unproven in large controlled studies, there are several theoretical reasons why these agents should be of value in the treatment of heart failure, especially, in those 4% of patients who are intolerant of ACE inhibitor therapy due to cough. A further advantage is that unlike long-term ACE inhibitor therapy which is associated with angiotensin-II breakthrough, the selective angiotensin-II antagonists, such as losartan, directly block the detrimental effects of angiotensin-II at the AT_1 receptor and so have an obvious theoretical advantage over the ACE inhibitors. Although unproven the results of the ELITE study, which demonstrated a 46% reduction in mortality when compared to captopril, have added weight to the belief that these agents may be efficacious.[19]

Despite the lack of evidence, losartan started at a dose of 12.5 mg daily titrated up after seven days to 25 mg, and then 50 mg daily is recommended by the current SIGN Guidelines in ACE-intolerant patients.[15] Patients started on losartan should be monitored as for ACE inhibitor therapy.

BETA-BLOCKER THERAPY

Despite evidence that standard doses of beta-blockers may worsen or precipitate heart failure or prove fatal in patients with LV systolic dysfunction, it is now clear that the use of appropriate doses of a beta-blocker, such as carvedilol, bisoprolol (CIBIS II) or metoprolol, in selected patients is associated with a significant reduction in mortality and hospitalisation for patients with NYHA class II and III heart failure.[20-22] At present, the only beta-blocker to have a licence in the UK for the treatment of heart failure, is

carvedilol, but the results of the recently completed bisoprolol (CIBIS II) trial and an interim analysis of the metoprolol (MERIT) trials suggest that benefit is likely to be a 'class' effect.[21] The appropriate use of carvedilol, bisoprolol and metoprolol has been reported to reduce mortality by 60%, 31.7% and 35 % respectively, and hospitalisations for heart failure by 47%, 15.5% for carvedilol and bisoprolol respectively.

Traditionally the use of beta-blockers has been contraindicated in patients with heart failure and their injudicious use undoubtedly results in both increased morbidity and possibly mortality in patients with impaired ventricular function. It is therefore essential that, until the results of further morbidity/mortality studies become available, beta-blocker therapy be initiated in the younger patient (<65 years), those with mild to moderate heart failure (NYHA2/3), and those who are stable and have not had their medication changed or an acute hospital admission within the last two months.

Beta-blocker therapy should be initiated at a very low dose (carvedilol 3.125 mg, bisoprolol 1.25 mg, metoprolol 12.5mg CR) and up-titrated slowly, at no less than two-weekly intervals. Although current recommendations suggest that patients should be observed for two to three hours following initiation, or increase in the dose of beta-blocker, anecdotal evidence suggests that decompensation may occur several days after initiation of therapy. For this reason, it would seem reasonable to instruct patients started on beta-blocker to weigh themselves daily, and if weight increases or symptoms deteriorate to increase the dose of diuretic, and to report to their general practitioner or hospital physician at the earliest opportunity.

DIGOXIN

Despite wide usage elsewhere in the world, and the fact that digoxin when used with diuretic therapy reduces symptoms and signs of heart failure and improves exercise capacity,[23,24] it is not used routinely in the UK as standard therapy in the treatment of heart failure. Although the DIG trial reported that digoxin was safe at standard doses, and that its use was associated with a lower rate of hospital admissions for heart failure, the overall reduction in hospital admissions was only 6% with no reduction in mortality.[24] Currently digoxin is recommended for use in all patients with heart failure and atrial fibrillation, those with severe or symptomatic heart failure who have not responded to appropriate diuretic and ACE inhibitor therapy. It is also indicated in patients who have had more than one hospital admission for heart failure or have persistent cardiomegaly or in those who are unable to tolerate an ACE inhibitor or angiotensin-II antagonist.

If digoxin is to be used, the SIGN Guidelines recommend that dose should be adjusted to achieve a target plasma concentration of 0.9-2.0 ng/ml. As patients with severe heart failure tend to have highly variable renal function and digoxin has a narrow therapeutic index, frank digoxin toxicity is a potentially serious hazard. Aiming for a digoxin plasma concentration of 0.9 ng/ml, as reported in the DIG study, may allow a more pragmatic approach to treatment.

CALCIUM CHANNEL ANTAGONISTS

The use of short-acting dihydropyridine calcium channel blockers for the treatment of ischaemic heart disease, hypertension and heart failure has recently come under scrutiny.[26] Although the evidence for their usage in patients with heart failure is poor, recent studies with the newer calcium channel blockers, amlodipine and felodipine, have suggested that they are not harmful, and may be even beneficial in terms of improvement of symptoms and perhaps mortality.[27,28] The most beneficial effects were observed in patients with non-ischaemic heart failure, a group which tends to be small in the UK. At present the best that can be said for calcium channel blockers in the treatment of patients with heart failure is that they may be safe and appropriate therapy for the treatment of concurrent angina.

ANTICOAGULATION

Thromboembolism is believed to be a potential complication in patients with heart failure, however recent retrospective analyses of large-scale trials suggest that the incidence of thromboembolic events is in fact low (0.9-5.5 per 100 patient years).[29] The rationale for routine anticoagulation is therefore questionable.

Nevertheless, it is entirely appropriate for patients with co-existing atrial fibrillation or paroxysmal fibrillation, low ejection fraction (<20-25%) or mural thrombus to be fully anticoagulated with warfarin aiming at a target internationalised normalised ratio (INR) of 2.5 (2-3).

THIAMINE

Heart failure patients, especially the elderly, those who abuse alcohol (always more common than we believe), or those on high-dose loop-diuretic may be thiamine-deficient. Several studies have suggested that thiamine supplementation may improve left ventricular function in such patients.[30] Although the benefits of thiamine supplementation are unproven, the drug is cheap and generally safe, and a realistic approach may be to supplement a patient taking more than 80 mg of frusemide daily with thiamine, especially if alcohol abuse is suspected.

IMMUNISATION

Patients with heart failure are at a considerably increased risk of pneumonia and decompensation following influenza. Several studies have indicated that influenza and pulmonary infections are a significant cause of decompensation and hospital admissions for heart failure patients.[31,32] Influenza vaccination has been associated with a 37% reduction in hospital admissions in heart failure patients indicating that this is an appropriate therapeutic measure. The SIGN Guidelines currently recommend both a once only vaccination with pneumococcal vaccine and annual vaccination for influenza.

CLINIC FOLLOW UP

Unlike other chronic disease it is unusual to find patients attending a dedicated heart failure clinic, however initial results from a dedicated heart failure clinic operating in Aberdeen suggest that regular (3-6 monthly) follow-up by a consultant physician with an interest in heart failure can achieve results superior to aggressive drug therapy alone. Regular review at such a clinic (average 4.1 clinic visits/year) in which 98% of patients have NYHA class III or IV heart failure, are on an average dose of frusemide of 110 mg/day and have an average age of 69 years, significantly reduces hospitalisation rates for heart failure (0.7 per year), length of inpatient stay (11.8 and 10.5 days for females and males

respectively), and one- and five-year mortality rates to 3% and 26% respectively, when compared to national averages. Follow -up at such a clinic also facilitates implementation of medical guidelines and patient education.

CONCLUSIONS

- The treatment of patients with chronic heart failure should involve the appropriate and optimal use of a loop diuretic and an ACE inhibitor at full dose.
- In patients who are resistant or less responsive to a loop diuretic, additional pulsed metolazone or bendrofluazide should be considered.
- In those patients intolerant to ACE inhibitor, losartan may be a suitable alternative.
- Digoxin therapy may be of value in the more severe or symptomatic patients.
- The introduction of a beta-blocker should be considered in all stable patients with mild to moderate heart failure providing there are no contraindications.
- All patients should have a once-only pneumococcal immunisation and routine annual influenza immunisation.
- Patient education is pivotal and all patients should be educated about their disease, and possible lifestyle changes, and instructed on how to monitor their progress and modify their therapy on an outpatient basis.
- Where possible, patients should be reviewed regularly by a physician with an interest in the treatment of heart failure.

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