REVIEW ARTICLE

Pharmacotherapy For Chronic Heart Failure

[1]**DR J.A.SALEH,** *MBBS, DM,* [2]**DR B.M.AJI,** *MBBS, MPharm,* [3]**DR H.YUSUPH,** *MBBS, FMCP*

[1]Dept. Of Medicine, Imperial College, Hammersmith Hospital, London. [2]Dept. Of Medicine, Hull Royal Infirmary, Kingston Upon Hull, U.K. [3]Dept. Of Medicine, University Of Maiduguri Teaching Hospital, Nigeria.

Abstract:

Background: *Heart failure is a chronic and progressive disorder which results due to inability of the heart to pump adequate blood to meet up the metabolic demands of the body.*

Detecting patients with heart failure could be simple but rather complex of clinical decisions as presentation could be classical or non-specific with minimal symptoms and or signs.

Management is aimed at relieving symptoms, improving quality of life, preventing hospitalisation and arresting disease progression thus prolonging survival. In addition to pharmacologic measures, non-pharmacologic ones are also employed.

Method: *Relevant literature was reviewed using medical journals and also via internet. The key words employed were: Heart failure, Chronic heart failure, Diuretics, Vasodilators, Angiotensin receptor blockers (ARBS) and Angiotensin converting enzyme inhibitors (ACEI). The National Heart, Lung and Blood Institute, Canadian Cardiovascular Society, American College of Cardiology websites were also used in the course of this review.*

Results: *This review was able to support the use of beta-blockers, ACEI, ARBS, digitalis, diuretics, vasodilators and aldosterone antagonists in the management of chronic heart failure.*

Conclusion: *The objectives of drug therapy in heart failure includes the short-term goals of stabilising the patient, improving haemodynamic function and conferring symptomatic improvement, as well as the long-term goal of limiting disease progression, decreasing hospital re-admission rates and improving survival. The cause needs to be established and aggravating factors identified (and where possible treated). Most of the drugs, if not all, are used in combination with one another to achieve maximal therapeutic goal. Use of some drugs could be entertained as an add-on therapy depending on any co-existing medical condition.*

KEY WORDS- *Chronic Heart Failure, Diuretics, Angiotensin Converting Enzymes Inhibitors, Angiotensin Receptor Blockers, Beta Blockers, Vasodilators.*

Paper accepted for publication 3rd March 2007

INTRODUCTION:

Heart failure, which is the resultant effect of inability of the heart to pump adequate blood to meet up with the metabolic demands of the body, is on the increase in both incidence and prevalence the world over. It is a leading cause of death and hospitalisation in the developed world[1].

In the United Kingdom the incidence of heart failure is about 20-30:1000 per year and the prevalence is about 1%; this increases with age reaching about 30% in those over 80 years[2]. The prevalence increases with an ageing population[3] and could be as a result of improvements in the management of myocardial infarction with more people surviving to develop the condition in later life.

In developing countries, epidemiological data on heart failure is generally lacking except from local studies carried out in some centres. However, in a study conducted by Adedoyin et al to assess a five year incidence and patterns of cardiovascular disease in a Nigerian teaching hospital involving a total number of 1104 subjects, heart failure was found to be the most prevalent (35%) followed by hypertension (25%)[4].

In old age, there is stiffening of the arteries which alters the afterload and left ventricular geometry. The resting left ventricular systolic function is spared but there is a substantial change in the left ventricular diastolic function. This adversely lowers the threshold at which cardiovascular diseases become apparent[5,6].

CLINICAL MANIFESTATIONS:

This could be classical or non-specific with minimal symptoms and or signs. Presentation could be just exertional dyspnoea or shortness of breath. Other symptoms may include orthopnoea, paroxysmal nocturnal dyspnoea, dependent oedema and productive cough. Clinical review may reveal bibasal crepitations, third heart sound and in some cases fourth heart sounds, murmurs, gallop rhythm, cold peripheries, peripheral cyanosis, low systolic blood pressure, raised JVP, pleural effusions and hepatomegaly[5].

Correspondence: **Dr. J. A. Saleh,** *drjalals@yahoo.com*

In the elderly, presentation is often subtle and bizarre hence the delay in diagnosis thus presenting in a decompensated stage. Acute confusion, generalised weakness, fatigue/impaired exercise tolerance, daytime oliguria and nocturia may be the presentation; acute dyspnoea or resting tachycardia may not be there[5].

INVESTIGATIONS:

Although chronic heart failure is a clinical diagnosis, investigations help in establishing the cause, risk of complications and worsening of clinical picture. This may include:

- Chest X-ray
- Electrocardiography
- Full blood count
- Echocardiography
- Cardiac catheterisation for pressure recordings or to rule out pulmonary disease as a cause of left sided heart failure
- Holter monitoring
- Doppler Echo (differentiates ventricular systolic or diastolic dysfunction)
- Radio-nucleotide ventriculography (differentiates segmental and global wall motion abnormality)
- Stress testing (often assess the response of elderly patients to therapy) [5].
- Serum urea, electrolytes should form part of the routine investigations in all patients
- In obscure cases, thyroid function test, iron studies, serum-calcium, electrophoresis (e.g. amyloidosis), ACE (e.g. sarcoidosis) blood culture, heavy metal poisons; Ventricular biopsy, CT-scan and MRI could also be used.

PHARMACOTHERAPY:

The drugs employed acts not only on the heart alone but other organs and or endocrine systems as well. They are often used in combination with one another for enhanced therapeutic goal.

DIURETICS:

Its use reduces the risk of death and worsening of heart failure as evidenced by some studies[7]. They reduce pre-load thus improving pulmonary congestion and oedema. Although several studies have indicated its use to treat fluid overload[8,9], it should not be used alone to manage heart failure. The potassium sparing type confers additional benefit than the non-potassium sparing type[10] in great number of patients as in addition to improving the functional status of patients, there is a substantial reduction in the rate of hospitalizations as well as mortality of patients[11-13]. The use of diuretics generally, should be tailored to individual need and sometimes stopped[14] especially in patients who are not fluid overloaded.

ANGIOTENSIN CONVERTING ENZYMES INHIBITORS (ACEI):

In chronic heart failure, the renin-angiotensin-aldosterone mechanism is activated[15]. This leads to increase in the preload and afterload with angiotensin II adversely affecting the cardiac muscles. These drugs have been shown to reduce both morbidity and mortality in patients with symptomatic chronic heart failure and asymptomatic left ventricular dysfunction[16,17]. They reduce systemic vascular resistance and venous pressure, and further lower the levels of circulating catecholamines thus improving myocardial activity.

ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs):

These drugs (e.g. Losartan, valsartan and ibersartan) have similar effects to ACEI but do not affect bradykinin metabolism thus do not produce cough as an unwanted side effect. They specifically block angiotensin II type 1 receptors, which presumably mediate most of the adverse effect of angiotensin II in heart failure[18.] Angiotensin-receptor blockers are a safe and effective alternative; they are often employed when ACEI are contraindicated, as they do not primarily show superiority over the ACEI but rather a more favourable effect of the ACEI[14]. Its use, as the ACEI, requires careful monitoring as may produce hypotension, hyperkalaemia and renal dysfunction.

ALDOSTERONE ANTAGONISTS:

Aldosterone regulates urinary retention of sodium, excretion of potassium, and tissue inflammatory response and stimulates cytokine secretion, fibroblast growth, and collagen turnover[19]. There is increase level of aldosterone seen in heart failure which is due to increased production by the adrenals and decreased hepatic clearance as a result of hepatic hypoperfusion[19]. It may equally be secreted independent of angiotensin II concentrations hence the need to block it[20]. Inhibition of ACE suppresses aldosterone temporarily ('the aldosterone escape') hence the need for direct blockade of aldosterone to give salutary effect[20].

Spironolactone reduces mortality significantly when added to conventional treatment. However, the dosage of spironolactone and eplerenone should be from a low dose. Recent studies have shown incidence of hyperkalaemia in patients receiving spironolactone hence the need for close monitoring[21].

VASODILATORS:
this class of drug lowers systemic vascular resistance thus improving arterial haemodynamics. In the first V-HeFT study they were shown to reduce mortality in chronic heart failure, though not so in the long-term trials[14]. Some studies have showed that the use of Enalapril[22] or hydrallazine-isosorbide dinitrate combination improves survival and left ventricular ejection fraction[23].

BETA-ADRENERGIC RECEPTOR BLOCKERS:
Multiple clinical trials have shown that this class of drugs have significant role to play in the management of patients with chronic stable heart failure as they reduce all-cause mortality rate significantly, regardless of the cause[24-26]. They should be used with caution, at a low dose and under close supervision. In addition to reducing hospitalisations, they improve functional status and left ventricular function[27]. The commonly employed drugs are Carvedilol, Bisoprolol and Metoprolol; they both reduce mortality and morbidity irrespective of the severity of the heart failure[28]. Contraindications to its use include severe bronchospasm, advanced heart block, bradycardia, and hypotension.

DIGITALIS GLYCOSIDES:
are often used to support myocardial function in patients with left ventricular dysfunction as the inotropic state of the failing myocardium is impaired. They have neurohormonal effect rather than just being weak inotropes as supported by recent studies; it suggests that they sensitizes baroreceptors, decrease sympathetic outflow and inhibit renin release[29]. A study showed that use of digoxin reduces hospitalisation and improves clinical status of patients[30].In a study conducted by Digoxin Investigation Group, it showed that digoxin combined with ACEI and diuretics, reduced death and hospitalisation resulting from progressive heart failure in patients in sinus rhythm[31].

INOTROPIC AGENTS:
Timewell et al[32] have shown that use of beta agonists (xamoterol) as monotherapy in heart failure is associated with favourable outcome; however, other studies have shown that mortality was unfavourably influenced by its long term use especially in patients with moderate-to-severe heart failure[33,34]. Although use of dopamine agonist (ibopamine) as an additive improves symptoms in heart failure, this class of drugs increases the risk of death in advanced heart failure[35,36]. Phosphodiesterase inhibitors (sildenafil) in heart failure increases intracellular cAMP concentrations and augments excitation-contraction coupling; however, its long term use is associated with severe cardiac side effects and increase in mortality[37].

- ANTITHROMBOTIC AGENTS:
at present has no supporting evidence for their routine use in heart failure due to non-ischaemic cause and in sinus rhythm; it is equally uncertain whether they reduce the incidence of thrombo-embolism in patients with heart failure[38].

- CACIUM CHANNEL BLOCKERS:
The dihydropyridines worsens heart failure hence contraindicated in such patients; this is because of their negative inotropic effect[39,40]. Studies showed amlodipine and felodipine to be the only members that prove safe in patients with heart failure but without coronary heart disease[41-43.]

ENDOTHELIN RECEPTOR BLOCKERS:
Endothelin-1, synthesized by the endothelial linings of the blood vessels, greatly plays an important role in the pathophysiology of heart failure[44] because of its vasodilator effect and, salt and water retention properties. Studies have shown that blocking these receptors with Bosentan, an oral endothelin receptor blocker, significantly influence the outcome of heart failure[45]. However, its role slowing the progression of the disease and improving survival remains to be established[46].

VASOPEPTIDASE INHIBITORS:
This class of drugs inhibits neutral endopeptidase and ACE[47]. They improve haemodynamic effects and clinical status in patients with decompensated congestive heart failure through its vasodilatory actions, hence BNP-guided treatment has been shown to reduce the cardiovascular adverse event rate, and delay the time to first event in patients with symptomatic heart failure (NYHA class IIIV)[15,48]. A study on omapatrilat, a vasopeptidase inhibitor, showed its superiority over ACEi[49] and is reserved for use in refractory heart failure patients[50.]

ANTI-ARRYTHMIC AGENTS:
are not routinely employed in the management of heart failure because of their negative inotropic effect. This is not withstanding the fact that heart failure patients are at high risk of sudden death most likely from arrythmias[51]. Amiodarone may be employed, if the need arises, in heart failure patients due its proven safety compared to other members of the group[52].

OTHER AGENTS:

clinical trials of some newer drugs like arginine vasopressin antagonists[54], anti-TNF[53], and the use of oestrogen in elderly patients[55], are yielding positive results.

CONCLUSION:

Drug therapy has greatly improved the management of heart failure unlike in the past when prognosis was of dismal nature. This review was able to discuss the different drugs employed in the management of heart failure. However, side effects of these drugs should be closely observed and be part of the management.

REFERENCES:

1. Haldeman GA, Croft JB, Giles WH et al. Hospitalization of patients with heart failure: National Hospital Discharge survey, 1985 to 1995. *Am Heart J*. 199;137:352-360
2. Andrew J. S. Coats (1998). Initiating therapy in heart failure, Magister Consulting Ltd, pp2-29.
3. Steward S, MacIntyre K, Capewell S et al. Heart failure and the aging population: an increasing burden in the 21st century? *Heart* 2003;89:49-53.
4. Adedoyin RA, Adesoye A. Incidence and pattern of cardiovascular disease in a Nigerian teaching hospital. *Trop Doct*. 2005;35(2):104-106.
5. Tresch DD. Clinical manifestations, diagnostic assessment, and etiology of heart failure in elderly patients. *Clinics in Geriatric Medicine* 2000; 16: 445-456.
6. Helen Oxenham and Norman Sharpe. Cardiovascular aging and heart failure. *Eur J Heart Fail.* 2003 Aug; 5(4), 427-434.
7. Faris R, Flather M, Purcell H et al. Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials. *Int J Cardiol.* 2002;82:149-158.
8. Hunt SA, Baker DW, Chin MH et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2001. Accessed at www.acc.org/clinical/guidelines/failure/hf_index.htm
9. The 2002/3 Canadian Cardiovascular Society Consensus Conference Update for the Diagnosis and Management of Heart Failure. Accessed at www.ccs.ca/download/CCSHFConsUpdateDraft0103EMail.pdf
10. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J.* 2001;22:1527-1560.
11. Foody JM, Farrell MH, Krumholz HM. Beta-blocker therapy in heart failure: scientific review. *JAMA* 2002;287:883-889.
12. McAlister FA, Lawson FM, Teo KK, Armstrong PW. A systematic review of randomized trials of disease management programs in heart failure. *Am J Med* 2001;110:378-384.
13. Shah NB, Der E, Ruggerio C, Heidenreich PA, Massie BM. Prevention of hospitalizations for heart failure with an interactive home monitoring program. *Am Heart J* 1998;135:373-378.
14. Dirk J.van Veldhuisen and Wiek H. van Gilst; The pharmacological management of heart failure: too many treatments. Barry Greenberg, Claudio Borghi and Sergio Perrone; Alternative therapeutic approaches. *Eur J Heart Fail.* 2003 Jan; 5(1), 5-21.
15. Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. *N Engl J Med.* 1999;341:577-585.
16. Torp-Pedersen C, Køber L. Effect of ACE inhibitor trandolapril on life expectancy of patients with reduced left-ventricular function after acute myocardial infarction. TRACE Study Group. Trandolapril Cardiac Evaluation. *Lancet.* 1999;354:9-12.
17. Hall AS, Murray GD, Ball SG. Follow-up study of patients randomly allocated ramipril or placebo for heart failure after acute myocardial infarction: AIRE Extension (AIREX) Study. Acute Infarction Ramipril Efficacy. *Lancet*. 1997;349:1493-1497.
18. Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. *N Engl J Med.* 1999;341:577-585.
19. Weber KT. Aldosterone in congestive heart failure. *N Engl J Med*. 2001; 345:1689-1697.
20. Cicoira M, Zanolla L, Franceschini L, et al. Relation of aldosterone "escape" despite angiotensin-converting enzyme inhibitor administration to impaired exercise capacity in chronic congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol*. 2002; 89:403-407.
21. Bozkurt B, Agoston I, Knowlton AA. Complications of inappropriate use of spironolactone in heart failure: when an old medicine spirals out of new guidelines. *J Am Coll Cardiol.* 2003;41:211-214.
22. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med.* 1991;325:303-310.
23. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. *N Engl J Med*. 1986;314:1547-1552.
24. Doughty RN, Rodgers A, Sharpe N, et al. Effects of beta-blocker therapy on mortality in patients with heart failure. A systematic overview of randomized controlled trials. *Eur Heart J.* 1997;18:560-565.
25. Heidenreich PA, Lee TT, Massie BM. Effect of beta-blockade on mortality in patients with heart failure: a meta-analysis of randomized clinical trials. *J Am Coll Cardiol.* 1997;30:27-34.
26. Lechat P, Packer M, Chalon S, et al. Clinical effects of beta-adrenergic blockade in chronic heart failure: a meta-analysis of double-blind, placebo-controlled, randomized trials. *Circulation.* 1998;98:1184-1191.
27. A randomized trial of beta-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS). CIBIS Investigators and Committees. *Circulation.*1994;90:1765-1773.
28. Anissa Bouzamondon et al. Beta blocker benefit according to severity of heart failure. *Eur J Heart Fail.* 2003 June; 5(3), 281-289.
29. Gheorghiade M, Ferguson D. Digoxin. A neurohormonal modulator in heart failure? *Circulation.* 1991;84:2181-2186.
30. Hood WB Jr, Dans AL, Guyatt GH, et al. Digitalis for treatment of congestive heart failure in patients in sinus rhythm: a systematic review and meta-analysis. *J Card Fail.* 2004;10:155-164.

31. Parveen K, Michael C (eds). Kumar & Clarke Clinical Medicine, 5th edition 2002. W.B. Saunders Company. 754-763.
32. Timewell RM, Stark RD, Marlow HF. Xamoterol monotherapy in heart failure. The European 'Corwin' Group. *Eur Heart J.* 1990;11Suppl A:62-64
33. Ikram H, Crozier IG. Xamoterol in severe heart failure. The Xamoterol in Severe Heart Failure Study Group. *Lancet.* 1990;336:1-6.
34. Cruickshank JM. The xamoterol experience in the treatment of heart failure. *Am J Cardiol.* 1993;71(9):61C-64C.
35. Hampton JR, van Veldhuisen DJ, Kleber FX, et al. Randomised study of effect of ibopamine on survival in patients with advanced severe heart failure. Second Prospective Randomised Study of Ibopamine on Mortality and Efficacy (PRIME II) Investigators. *Lancet.* 1997;349:971-977
36. Metra M, Dei Cas L. Clinical efficacy of ibipomine in patients with chronic heart failure. *Clin Cardiol.* 1995;18(3 Suppl I):122-131
37. Lehnart SE, Marks AR. Phosphodiesterase 4D and heart failure: a cautionary tale. *Expert Opin Ther Targets.* 2006;10(5):677-688
38. Lip GY, Gibbs CR. Antiplatelet agents versus control or anticoagulation for heart failure in sinus rhythm. Cochrane Database Syst Rev. 2001;(4):CD003333.
39. Littler WA, Sheridan DJ. Placebo controlled trial of felodipine in patients with mild to moderate heart failure. UK Study Group. *Br Heart J.* 1995;73:428-433.
40. De Vries RJ, van Veldhuisen DJ, Dunselman PH. Efficacy and safety of calcium channel blockers in heart failure: focus on recent trials with second generation dihydropyridines. *Am Heart J.* 2000;139:185-194.
41. Cohn JN, Ziesche S, Smith R, et al. Effect of the calcium antagonist felodipine as supplementary vasodilator therapy in patients with chronic heart failure treated with enalapril: V-HeFT III. Vasodilator-Heart Failure Trial (V-HeFT) Study Group. *Circulation.* 1997;96:856-863.
42. Packer M, O'Connor CM, Ghali JK, et al. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. Prospective Randomized Amlodipine Survival Evaluation Study Group. *N Engl J Med.* 1996;335:1107-1114.
43. Packer M. Prospective Randomized Amlodipine Survival Evaluation (PRAISE 2). Presented at the American College of Cardiology 49th Annual Scientific Session. Late Breaking Clinical Trials. Accessed at www.theheart.org/viewEntityDispatcherAction.do?primaryKey_172902
44. Spieker LE, Noll G, Ruschitzka FT, et al. Endothelin receptor antagonists in congestive heart failure: a new therapeutic principle for the future? *J Am Coll Cardiol.* 2001;37:1493-1505.
45. Ellahham SH, Charlon V, Abassi Z, et al. Bosentan and the endothelin system in congestive heart failure. *Clinical Cardiol.* 2000;23(11):1493-1505.
46. Su¨tsch G, Kiowski W, Yan XW, et al. Short-term oral endothelin-receptor antagonist therapy in conventionally treated patients with symptomatic severe chronic heart failure. *Circulation.* 1998;98: 2262-2268.
47. Weber MA. Vasopeptidase inhibitors. *Lancet.* 2001;358:1525-1532.
48. Packer M, Califf RM, Konstam MA, et al. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). *Circulation*. 2002;106:920-926.
49. Rouleau JL, Pfeffer MA, Stewart DJ, et al. Comparison of vasopeptidase inhibitor, omapatrilat, and lisinopril on exercise tolerance and morbidity in patients with heart failure: IMPRESS randomized trial. *Lancet.* 2000;356:615-620.
50. Felker GM, O'Connor CM. Inotropic therapy for heart failure: an evidence-based approach. *Am Heart J.* 2001;142:393-401.
51. Stevenson WG, Stevenson LW, Saxon LA. Sudden death prevention in patients with advanced ventricular dysfunction. *Circulation.* 1993;88:2953-2961.
52. Singh SN, Fletcher RD, Fisher SG, et al. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. *N Engl J Med.* 1995;333:77-82.
53. Bozkurt B, Torre-Amione G, Warren MS, et al. Results of targeted anti-tumor necrosis factor therapy with etanercept (ENBREL) in patients with advanced heart failure. *Circulation.* 2001;103:1044-1047.
54. Gheorghiade M, Niazi I, Ouyang J, et al. Vasopressin V2-receptor blockade with tolvaptan in patients with chronic heart failure: results from a double-blind, randomized trial. *Circulation.* 2003;107:2690-2696.
55. Steven E. Reis, et al. Estrogen is associated with improved survival in aging women with congestive cardiac failure: analysis of vesnarinone studies. *J Am Coll Cardiol.* 2000 Aug.1; 36(2), 529-533.