

Medical Management of Heart Failure

Manish M Juneja¹

ABSTRACT

Heart failure is a clinical condition where heart is unable to provide sufficient blood flow to meet metabolic requirements of the body. This clinical syndrome is characterized either by restricted filling of ventricles (diastolic heart failure) or by ejection abnormalities (systolic heart failure). Heart failure associated mortality is higher than in most malignancies. This article aims at discussing the available pharmacotherapy in patients with reduced ejection fraction and preventive therapies that can be used to limit progression of structural and functional changes that worsens heart failure.

Heart failure is a clinical condition where heart is unable to provide sufficient blood flow to meet metabolic requirements of the body. This clinical syndrome is characterized either by restricted filling of ventricles or by ejection abnormalities. Heart failure patients will manifest with symptoms such as dyspnoea because of pulmonary congestion, peripheral edema and ascites due to impaired venous return. General symptoms such as nausea, lack of appetite, and fatigue may also be seen. Conditions those are responsible for developing heart failure includes ischemic heart disorders, hypertension, valvular disease, post infectious myocarditis, connective tissue diseases (e.g. systemic lupus erythematosus), cardiomyopathy, metabolic disorders, systemic toxins, and cardiotoxic drug and idiopathic.¹ Knowledge of structural pathologies and hemodynamic changes is essential for managing a patient of heart failure. Hence management of heart failure includes treatment of causative pathology. Besides this the major goal of therapy is to relieve symptoms, avoid hospital admissions, prolong life and also improve quality of life.²

Pharmacotherapy has found to be beneficial mainly in patients with reduced ejection fraction. Alternatively preventive therapies can be used to reduce progression of structural and functional

changes that worsens heart failure. Heart failure patients have a poor prognosis due to limited treatment options. Heart failure associated mortality is higher than in most malignancies.² Though new treatment options have been introduced and CHF mortality has decreased considerably over the past, yet still very high rates of 5-year mortality and chances of frequent re-hospitalisations has been observed in patients of heart failure.²

Broadly management of heart failure is divided into : Symptomatic treatment & Long term prophylaxis.

Symptomatic treatment comprises of Diuretics to relieve the symptoms of congestion and Inotropes to improve cardiac output. Long term prophylaxis is given to retard progress of heart failure and improve survival rate. Nowadays major focus is shifted towards prophylaxis so as to retard pathological changes and improve outcome. Drugs used for Prophylaxis include Drugs acting on Renin Angiotensin Aldosterone System (RAAS), Beta blockers, Mineralocorticoid Receptor Antagonists and some newer drugs.

General Measures advised include Life style changes, fluid and salt restriction, alcohol restriction, weight control, and graded supervised exercise program. Treatment strategies have been based upon the understanding of the compensatory mechanisms which are activated during heart failure. The Renin angiotensin aldosterone system and sympathetic system get activated to bring compensatory pathological changes. And treatment aims at reducing activation of these systems.

¹Interventional Cardiologist,
Shree Krishna Hrudayalaya, Nagpur

Address for Correspondence -

Dr. Manish M. Juneja

E-mail : drmanishjuneja@gmail.com

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Pharmacotherapy

Diuretics

Digoxin

ACE Inhibitors and ARB

Beta Blockers

Mineralocorticoid receptor antagonist

Newer Therapies^{3,4}

- Angiotensin ReceptorNeprilysin Inhibitor (ARNI) (e.g. Valsartan / Sacubitril)
- Sinoatrial node modulator (ivabradine).
- BNP Analogues : Nesiritide
- Vasopressin antagonist : Tolvaptan
- Iron Therapy
- Inodilator : Levosimendan
- Endothelin Receptor Antagonists

ACE INHIBITORS (ACEI) AND ANGIOTENSIN-II BLOCKERS (ARB):

Use of ACE inhibitors in various cardiovascular diseases has led to the substantial improvement in outcome and it has significantly reduced mortality as well as morbidity. Initially ACE inhibitors were got approval for management of hypertension. But after better understanding of the pathophysiology of Congestive heart failure it is well established that Renin Angiotensin Aldosterone system has a major role to play in the progression of disease. ACE inhibitors work by inhibiting Angiotensin converting enzyme which is responsible for producing more potent form of angiotensin i.e. Angiotensin II. This angiotensin II is implicated for production of pathological changes of activation of RAAS. Several trials have demonstrated the positive effect of ACE inhibitors in patients of heart failure with systolic dysfunction. ACE inhibitor reduces mortality and frequency of hospitalizations and improves overall prognosis. The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial established that the addition of enalapril to conventional therapy in patients with severe congestive heart failure can reduce mortality and improve symptoms.⁵ The Studies of Left Ventricular Dysfunction (SOLVD) extended these

benefits of ACE inhibitor therapy to symptomatic and asymptomatic patients.⁶

Although Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF), study found some beneficial effect of perindopril among patients with Heart Failure and diastolic dysfunction, drug therapy in diastolic dysfunction has not got desired success.⁷

In the Assessment of Treatment with Lisinopril and Survival (ATLAS trial) a low-dose of Lisinopril was compared to a high-dose lisinopril therapy in over 3,000 patients of heart failure. Patients in the high-dose group had significantly lower risk for hospitalization and mortality without increasing chances of drug discontinuation. Maximum tolerated dose of ACE inhibitor is recommended to achieve adequate inhibition of the renin-angiotensin system.⁸

ACE inhibitors decreases the formation of Angiotensin II and also inhibits the degradation of Bradykinin. This effect of ACE inhibitors on the Bradykinin pathway differentiate ACE inhibitors from other agents modulating Renin Angiotensin System (like angiotensin receptor blockers (ARBs) and renin inhibitors) and probably contribute to the clinical benefits of ACE inhibitor. All ACE inhibitors do not have same pharmacological profile. Captopril (Captopril, Lisinopril) like active drugs and Enalapril like Prodrugs drugs (enalapril, perindopril, ramipril, andtrandolapril) are the two major groups.⁹

Unless contra indicated, all patients of heart failure with systolic dysfunction shall receive ACE inhibitor therapy. Symptomatic as well as Asymptomatic patients shall receive the therapy. Although the precise level of ventricular dysfunction at which treatment should be initiated remains to be clarified. The side effects limiting the use of ACE inhibitors are cough and angioedema.

ARBs are recommended in patients who cannot tolerate an ACE inhibitor due to cough or angioedema. The combination of ACEIs and ARBs is only recommended in exceptional cases and is contraindicated in patients with concomitant

Mineralocorticoid receptor antagonist treatment. The ARB produces its effect through receptor blockade and hence considered to be superior as it blocks all actions of Angiotensin through receptors. But ACEI has distinct advantage that it also acts on Bradykinin pathway and produce beneficial effects.

In Valsartan Heart Failure Trial (Val-HeFT)¹⁰, the combination of valsartan and an ACE inhibitor decreased hospitalizations but did not improve mortality but in fact mortality was increased when such a combination was used along with beta blockers.

Valsartan in Acute Myocardial Infarction Trial (VALIANT)¹¹ and the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTAR-GET)¹² showed that ARBs are not superior to an ACE inhibitor, and that the addition of an ARB to a full dose of an ACE inhibitor was associated with additional adverse effects, including hypotension and renal dysfunction

BETA-BLOCKERS

Along with RAAS activation neurohumoral changes in heart failure include sympathetic activation. Beta blockers have been proved to be beneficial in reducing sympathetic changes.

the beneficial effects of beta-blocker therapy has been established in multiple trials.

the Cardiac Insufficiency Bisoprolol Study II (CIBIS II),¹³ Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS),¹⁴ Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF),¹⁵ and the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS),¹⁶ COMET,¹⁷ OPTIMISE HF¹⁸, B CONVINCED¹⁹ all these studies equivocally proved that beta blockers reduce mortality and morbidity associated with heart failure.

Like ACE inhibitors, beta-blockers should be started at a low-dose, and doses shall be titrated upward. Contraindications for beta blocker therapy includes are bradycardia HR < 55 beats/ min, second- or

third-degree heart block, marked hypotension < 80 mmHg and bronchial asthma. Diabetes, Peripheral vascular diseases, Chronic obstructive lung disease are no more considered as strict contraindication for beta-blocker therapy. According to the various guidelines, ACEIs and beta-blockers should be started immediately after diagnosis heart failure. Sudden withdrawal of Beta blocker therapy shall be avoided.

Mineralocorticoid Receptor Antagonists and Renin inhibitors

Regulation of aldosterone synthesis is regulated by angiotensin-II and by plasma potassium. Randomized Aldactone Evaluation Study (RALES)²⁰ and Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS)²¹ has evaluated role of mineralocorticoid receptor antagonist in the management of heart failure, Mineralocorticoid Receptor Antagonists therapy is found to be useful mainly in severe heart failure.

Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF)²² showed that patients with Mild heart failure will also get benefited by MRA. most common side effect seen with Mineralocorticoid Receptor Antagonists is Hyperkalemia.

ATMOSPHERE trial²³ observed that the use of aliskiren in combination with enalapril was not associated with a decrease in heart failure hospitalization or cardiovascular death.

Ivabradine

Treatment of heart failure with beta blocker reduces heart rate. But while optimising beta blocker therapy with larger dose adverse effects may appear. If channel inhibitor (Ivabradine) acts on sinus node and reduces heart rate without affecting myocardial contractility. Thus it reduces heart rate like beta blockers but unlike them ivabradine do not have significant effect on cardiac contractility and conduction.

Systolic Heart Failure Treatment with If Inhibitor Ivabradine Trial (SHIFT)²⁴ noted that addition of ivabrdine to concomitant heart failure therapy

resulted in a significant decrease in HF hospital admissions and cardiovascular mortality. BEAUTIFUL²⁵ trial has demonstrated that ivabradine has beneficial effect in heart failure patients with heart rate more than 70 per min. Thus in a patient with sinus rhythm and heart rate more than 70, Ivabradine can be used as add on therapy to other heart failure medications.

ANGIOTENSIN RECEPTOR-NEPRILYSIN INHIBITOR (ARNI)

The FDA approved sacubitril / valsartan in patients who have chronic and stable but symptomatic HF. ARNI is a novel treatment concept in HF. Neprilysin plays a crucial role in the degradation of natriuretic peptides. ARNI inhibit RAAS and also prevent degradation of natriuretic peptide. Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF)²⁶ trial was a large randomized phase III study which demonstrated the role of ARNI in heart failure. ARNI can be used as an alternative to ACEI or ARB. While changing from an ACEI to sacubitril / valsartan, intake of the ACEI has to be stopped at least 36 hours before the first intake of sacubitril / valsartan in order to prevent angioedema. The major side effect noted with ARNI was significantly higher incidence of symptomatic hypotension.

Diuretics

Diuretics are added during initial part of the therapy to get rid of symptoms of congestion and edema. These drugs have to be used at lowest possible dose and afford symptom relief without major effect on long term mortality.

Digitalis

As observed in Digitalis Investigation Group [DIG] trial²⁷, Digitalis reduces morbidity and hospital admissions but no effect on long term survival. Besides it has narrow therapeutic index.

Iron

Iron deficiency causes dysfunction of important proteins in the cardiac muscle and leads to anemia. Iron deficiency impairs prognosis in heart failure patients.

In the Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency study,²⁸ intravenous administration of (ferric carboxymaltose) leads to improved exercise capacity and positive effect on quality of life in patients with HF.

In addition to above therapies new drugs like levosimendan, tolvaptan, nesiritide are being investigated in the management of heart failure. Role of B natriuretic peptide is investigated in the management of heart failure. Endothelin antagonist, Vasopeptidase inhibitor and many new therapies are being tried. Device based therapies is also an option of management. The emphasis of all these therapies is to prolong life and improve quality of life.

The choice of initial treatment depends on signs and symptoms along with severity of the disease. Stevenson et al has developed an algorithm depending on the presence of congestion and perfusion status of the patient. Presence of congestion will be labeled “wet” and absence as “dry”. Similarly inadequate perfusion is termed as “cold” and those with good perfusion as “warm”. Thus four clinical hemodynamic profiles can be formed by combining this. The most common type ‘wet-warm’ (i.e. congested but well perfused), group with worst prognosis ‘wet-cold’ (i.e. congested and hypoperfused), less common ‘dry-cold’ (not congested and hypoperfused), and lastly fourth group ‘dry-warm’ representing the compensated heart failure (decongested, well-perfused). This classification may help to guide initial therapy and gives prognostic information.^{29,30}

References :

1. The pathophysiology of heart failure : Clinton D. Kemp John V. Conte : Cardiovascular Pathology, Volume 21, Issue 5, September October 2012, Pages 365-371.
2. Berliner D, Bauersachs J. Current Drug Therapy in Chronic Heart Failure: the New Guidelines of the European Society of Cardiology (ESC). Korean Circ J. 2017;47(5):543-554.
3. Pitchai Balakumar and Manjeet Singh , 2007. Recent Advances in Pharmacotherapy for Heart Failure: Future Directions. Trends in Medical Research, 2: 61-71.
4. Ayan R. Patel, MD; Marvin A. Konstam, MD : Recent Advances in the Treatment of Heart Failure: Circ J 2002; 66:117-121.
5. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987; 316:1429-1435.

6. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991; 325:293-302.
7. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J; PEP-CHF Investigators. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J* 2006; 27:2338-2345.
8. J Butler et al: Dose of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers and Outcomes in Heart Failure A Meta-Analysis : *Circulation: Heart Failure*. 2017;10
9. Angiotensin-converting enzyme inhibition: a landmark advance in treatment for cardiovascular diseases Jeffrey S. Borer : *European Heart Journal Supplements* (2007)9 (Supplement E), E2-E9
10. Cohn JN, Tognoni G. Effect of the angiotensin receptor blocker valsartan on morbidity and mortality in heart failure: The Valsartan Heart Failure Trial (Val-HeFT). Presented at the American Heart Association Scientific Sessions, 2000.
11. Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med*. 2003;349:1893-1906.t
12. Ontarget Investigators: Telmisartan, Ramipril, or Both in Patients at High Risk for vascular events: *N Engl J Med* 2008;358:1547-59.
13. CIBIS II Investigators. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;353:9e13.
14. Packer M, FowlerMB, RoeckerEB, CoatsAJ, KatusHA, KrumH, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. *Circulation* 2002;106:2194e9.
15. MERIT-HF Investigators. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;353:2001e7.
16. Flather MD, Shibata MC, Coats AJ, van Veldhuisen DJ, Parkhomenko A, Borbola J, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J* 2005;26:215e25.
17. Metra M, Torp-Pedersen C, Cleland JG, Di LA, Komajda M, Remme WJ, et al. Should beta-blocker therapy be reduced or withdrawn after an episode of decompensated heart failure? Results from COMET. *Eur J Heart Fail* 2007;9:901e9.
18. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiadu M, Greenberg BH, et al. Influence of beta-blocker continuation or withdrawal on outcomes in patients hospitalized with heart failure: findings from the OPTIMIZE-HF program. *J Am Coll Cardiol* 2008;52:190e9.
19. Jondeau G, Neuder Y, Eicher JC, Jourdain P, Fauveau E, Galinier M, et al. B-CONVINCED: Beta-blocker Continuation Vs. Interruption in patients with Congestive heart failure hospitalized for a decompensation episode. *Eur Heart J* 2009;30:2186e92.)
20. Pitt B, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. 1999;341(10):709-717.
21. Pitt B, Bakris G, Ruilope LM, DiCarlo L, Mukherjee R. Serum potassium and clinical outcomes in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS). *Circulation* 2008;118:1643e50.
22. Eschalier R, McMurray JJ, Swedberg K, et al. Safety and efficacy of eplerenone in patients at high risk for hyperkalemia and/or worsening renal function: analyses of the EMPHASIS-HF study subgroups (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) *J Am Coll Cardiol*. 2013;62:1585-1593
23. Krum H, McMurray JJ, Abraham WT, et al. The Aliskiren Trial to Minimize OutcomeS in Patients with HEart failure trial (ATMOSPHERE) : revised statistical analysis plan and baseline characteristics. *Eur J Heart Fail* 2015;17:1075-83
24. Swedberg K, Komajda M, Böhm M, et al; SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet*. 2010;376:875-885.
25. The BEAUTIFUL Study : Randomized Trial of Ivabradine in Patients with Stable Coronary Artery Disease and Left Ventricular Systolic Dysfunction Baseline Characteristics of the Study Population. *Cardiology* 2008;110:271-282.
26. McMurray JJ, Packer M, Desai AS, et al. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF) *Eur J Heart Fail*. 2013;15:1062-1073.
27. Digitalis Investigation Group The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med*. 1997;336:525-533.
28. Jankowska EA, Tkaczyszyn M, Suchocki T, et al. Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: a meta-analysis of randomized controlled trials. *Eur J Heart Fail*. 2016;18:786-795.
29. Mattia Arrigo, John T. Parissis, Eiichi Akiyama, Alexandre Mebazaa, Understanding acute heart failure: pathophysiology and diagnosis, *European Heart Journal Supplements*, Volume 18, Issue suppl_G, 28 December 2016, Pages G11-G18,
30. Nohria ATsang SWFang JCLewis EFJarcho JAMudge GHStevenson LW. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. *J Am Coll Cardiol* 2003;41:1797-1804.