Pharmacotherapy of Heart Failure with Reduced LVEF

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ABSTRACT

Heart failure with reduced ejection fraction is a common clinical syndrome resulting from any structural or functional cardiac disorder that impairs the ability of ventricle to contract and which in turn causes inability of the heart to supply tissues with enough bloodto meet their metabolic needs. This review gives an overview and update on pharmacotherapy of heart failure with reduced ejection fraction.

Introduction :

Heart failure (HF) affects 6 to 10% of people older than 65 years. Approximately half of patients who develop HF have a normal or preserved EF (EF of 40 to 50% or higher). CAD has become an important cause in men and women, and is responsible for 60 to 75% of cases of HF. Hypertension contributes to the development of HF in 75% of patients, including most patients with CAD[1].

Although several reports have suggested that the mortality for HF patients is improving, the overall mortality rate remains higher than for many cancers, including those involving the bladder, breast, uterus and prostate.In the Framingham Study, the median survival in HF was found to be 1.7 years for men and 3.2 years for women, with only 25% of men and 38% of women surviving 5 Years[1].

Precipitating factors :

Among the most common causes of acute decompensation in a previously stable patient are dietary indiscretion and inappropriate reduction of HF therapy, either from patient self-discontinuation of medication or from physician withdrawal of effective pharmacotherapy (e.g. because of concern over azotemia). NSAIDS, including COX-2 inhibitors, are not recommended in patients with chronic HF because the risk of renal failure and fluid retention is marked.

Precipitating factors for acute decompensation in chronic heart failure patients
Dietary indiscretion
Inappropriate reduction in heart failure medications
Myocardial ischemia/infarction
Arrhythmias
Infection
Anaemia
Initiation of medications that worsen heart failure Calcium antagonists (diltiazem, verapamil) Beta-blockers NSAIDs Class I antiarrhythmics
Alcohol consumption
Pregnancy
Worsening hypertension

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MANAGEMENT :

1) MANAGEMENT OF VOLUME OVERLOAD

a) Diet : Dietary restriction of sodium (2 to 3 gm. daily) is recommended in all patients with the clinical syndrome of HF and preserved or depressed EF. Further restriction (less than 2 gm daily) may be considered in moderate to severe HF. Fluid restriction is generally unnecessary unless the patient is hyponatremic (sodium less than 130 mEq / liter) which may develop because of activation of renin-angiotensin system, excessive secretion of arginine vasopressin (AVP), or loss of salt in excess of water from prior diuretic use. Fluid restriction (less than 2 liters / day) should be considered inhyponatremic patients or for those patients whose fluid retention is difficult to control despite high doses of diuretics and sodium restriction. The use of dietary supplements (nutraceuticals) should be avoided in the management of symptomatic HF because of the lack of proven benefit and the potential for significant interactions with proven HF therapies.

b) Diuretics :

i) *Loop Diuretics :* The loop diuretics increase sodium excretion by up to 20 to 25% of the filtered load of sodium, enhance free water clearance and maintain their efficacy unless renal function is severely impaired. In contrast, the thiazide diuretics increase the fractional excretion of sodium to only 5 to 10% of the filtered load, tend to decrease free water clearance, and lose their effectiveness in patients with impaired renal function (creatinine clearance less than 40 ml / min).Consequently, the loop diuretics have emerged as the preferred diuretic agents for use in most patients with HF.

A typical starting dose of furosemide for patients with systolic HF and normal renal function is 40 mg. Although furosemide is the most commonly used loop diuretic, the oral bioavailability of furosemide is approximately 40 to 79%. Bumetanide or torsemide may be preferable because of its more than 80% oral bioavailability. With the exception for torsemide, the commonly used loop diuretics are short-acting (less than 3 hours). For this reason, loop diuretics usually need to be given at least twice daily.

ii) *Potassium Sparing Diuretics :* Triamterene and amiloride are referred to as potassium sparing diuretics. These agents share the common property of causing a mild increase in Na+ excretion, as well as having antikaluretic properties.

Side effects of Diuretics -

The major complications of diuretic use include electrolyte and metabolic disturbances, volume depletion, and worsening azotemia. The interval for reassessment should be individualized based on severity of illness and underlying renal function, use of concomitant medications such as ACEIs, angiotensin receptor blockers (ARBs), or aldosterone antagonists, past history of electrolyte imbalances, and / or need for more aggressive diuresis.

Electrolyte and Metabolic Disturbances

Diuretic use can lead to potassium depletion, which can predispose the patient to significant cardiac arrhythmias. Serum K+ level should be maintained between 4.0 and 5.0 meq / liter. The use of aldosterone receptor antagonists is often associated with the development of life-threatening hyperkalemia, particularly when they are combined with ACEIs and / or ARBs. Potassium levels and renal function should be checked within 3 days and again at 1 week after initiation of an aldosterone antagonist.

Diuretics may be associated with a number of other metabolic and electrolyte disturbances, including hypernatremia, hypomagnesaemia, metabolic alkalosis, hyperglycemia, hyperlipidemia, and hyperuricemia. Hypernatremia can usually be treated by more stringent water restriction.

Both loop and thiazide diuretics can cause hypomagnesaemia, which can aggravate muscle weakness and cardiac arrhythmias. Magnesium replacement should be administered for signs or

symptoms of hypomagnesaemia (e.g., arrhythmias, muscle cramps), and can be routinely given (with uncertain benefit) to all those receiving large doses of diuretics or requiring large amounts of K+ replacement.

Ototoxicity

Ototoxicity which is more frequent with ethacrynic acid than with the other loop diuretics, can manifest as tinnitus, hearing impairment, and deafness. Hearing impairment and deafness are usually but not invariably reversible. Ototoxicity occurs most frequently with rapid intravenous injections and least frequently with oral administration.

c) Digitalis : Role of Digitalis in management of CHF is controversial particularly in patients in sinus rhythm. The large randomized DIG trial[2] clearly showed that although digitalis administration results in symptomatic improvement, it does not prolong survival. Moreover, a narrow therapeutic window makes its use difficult and can result is Digitalis toxicity if drug levels are not monitored and hypokalemia is not prevented. Presence of S^3 gallop is a good clinical predictor of response to Digitalis in patients with sinus rhythm.

2) PREVENTING DISEASE PROGRESSION -

Drugs that interfere with the excessive activation of the rennin angiotensin-aldosterone system and the adrenergic nervous system can relieve the symptoms of HF with a depressed EF by stabilizing & reversing cardiac remodeling. In this regard ACEIs, ARBs, and beta-blockers have emerged as cornerstones of modern HF therapy for patients with a depressed EF.

Angiotensin Converting Enzyme Inhibitors (ACE-I)

There is overwhelming evidence that ACEIs should be used in symptomatic & asymptomatic patients with a reduced EF (< 40%) ***(Tables 1 & 2).*** ACEIs interfere with the RAAS by inhibiting the enzyme that is responsible for conversion of angiotensin I to angiotensin II. ACEIs prevent LV remodeling, improve symptoms, prevent hospitalization and prolong life.

ACEIs should be initiated in low doses, followed by increments in dose if lower doses have been well tolerated. Titration is generally achieved by doubling doses every 3 to 5 days. The dose of ACEI should be increased until the doses used are similar to those that have been shown to be effective in clinical trials ***(Table 3).*** Higher doses are more effective than lower doses in preventing hospitalization. For stable patients, it is acceptable to add therapy with beta-blocking agents before full target doses of ACEIs are reached.

SOLVD prevention[3] & TRACE4trials have shown that asymptomatic patients with LV dysfunction will have less development of symptomatic HF and hospitalization when treated with an ACEI. Furthermore, the absolute benefit is greatest in patients with the most severe HF. Indeed, the patients with NYHA Class IV HF in CONSESUS I trial had a much larger beneficial effect than the SOLVD trial.

Side effects of ACE-I

i) *Related to kinin potentiation :* nonproductive cough (10-15%), angioedema (1%) & rash

ii) Unrelated to kinin potentiation : hyperkalemia, renal insufficiency

In patients who cannot tolerate ACEIs because of cough or angioedema, ARBs are the next recommended line of therapy. Patients intolerant ACEIs because of hyperkalemia or renal insufficiency are likely to experience the same side effects with ARBs. The combination of hydralazine & an oral nitrate should be considered for these latter patients.

Angiotensin Receptor Blockers

ARBs are well tolerated in patients who are intolerant of ACEIs because of cough, skin rash, and angioedema and should therefore be used insymptomatic and asymptomatic patients with an EF less than 40 percent who are ACEI intolerant for reasons other than hyperkalemia or renal insufficiency.

Three of these losartan, valsartan and candesartan have been extensively evaluated in the setting of HF.

In symptomatic HF patients who are intolerant to ACEIs, the aggregate clinical data suggested that ARBs are as effective as ACEIs in reducing HF morbidity and mortality.

Side effects of ARB -

Both ACEIs and ARBs have similar effects on blood pressure, renal function, and potassium levels. Therefore, the problems of symptomatic hypotension, azotemia, and hyperkalemia will be similar for both of these agents.

In patients who are intolerant of ACEIs and ARBs, the combined use of hydralazine and isosorbidedinitrate may be considered as a therapeutic option.

Mineralocorticoid Receptor Antagonists

Recommended for patients with NYHA class III or Class IV HF who have a EF < 35% and who are receiving standard therapy, including diuretics, ACEIs and beta blockers. Spironolactone and Eplerenone are synthetic mineralocorticoid receptors that act on the distal nephron to inhibit Na+ and K+ excretion at the site of aldosterone action. Spironolactone has anti-androgenic and progesterone-like effects which may cause gynecomastia or impotence in men and menstrual irregularities in women. Eplerenone has greater selectivity for the mineralocorticoid receptor than for steroid receptors, and has fewer sex hormone side effects than spironolactone. Eplerenone is further distinguished from spironolactone by its shorter half-life.Spironolactone should be initiated at a dose of 12.5 to 25 mg daily. RALES trial[5], which evaluated spironolactone (25 mg / day initially, titrated to 50 mg / day for signs of worsening HF) versus placebo in NYHA Class III or IV HF patients with a LVEF less than 35%, who were being treated with an ACEI, a loop diuretic and, in most cases, digoxin. The primary endpoint was death from all causes. Spironolactone led to a 30% reduction in total mortality when compared with placebo (p = 0.001), which was attributed to a lower risk of death from progressive pump failure and sudden death. The frequency of hospitalization for worsening was also 35% lower in the spironolactone group than in the placebo group. In addition, patients who received spironolactone had a significant improvement in the NYHA functional class (p < 0.001). In the RALES trial, the serum potassium levels were 0.3 mEq / liter higher in the spironolactone group than in the placebo group (p = 0.001)[22], which could have played a major role in reducing sudden or even pump failure - related deaths. Although spironolactone was well tolerated in the RALES trial, gynecomastia was reported in 10% of men.

Eplerenone should be initiated at a dose of 25 mg per day, increasing to 50 mg daily. EPHESUS[6], a double-blind, placebo-controlled study that evaluated the effect of Eplerenone on morbidity and mortality in patients with acute myocardial infarction complicated by LV dysfunction and HF. Patients were randomly assigned to Eplerenone (25 mg / day initially, titrated to a maximum of 50 mg / day. There was a significant decrease in all-cause death in patients who were randomized to receive eplerenone.

Approximately 50 mg of Eplerenone is equivalent to 25 mg of spironolactone. Unlike spironolactone it is not associated with gynecomastia. Aldosterone antagonists are not recommended when serum creatinine level is higher than 2.5 mg / dl, creatinine clearance is less than 30 ml / min or the serum K level is higher than 5.5 mmol / liter.

Beta-Adrenergic Receptor Blockers

Indicated for patients with symptomatic or asymptomatic HF and a depressed EF of lower than 40 percent. There are three beta-blockers that have been shown to be effective in reducing the risk of death in patients with chronic HF - Bisoprolol and sustained-release Metoprolol succinate both competitively blocks the beta1 receptors, and Carvedilol competitively blocks the beta1-, beta2-, and alpha-adrenergic receptor.

However, unlike ACEIs, which may be up-titrated relatively rapidly, the dose titration of beta blockers should proceed no sooner than at 2-weekly intervals because the initiation and/or increased dosing of the agents may lead to worsening fluid retention caused

by abrupt withdrawal of adrenergic support to the heart and circulation. Therefore it is important to optimize the dose of diuretic before starting therapy with beta blockers. If worsening fluid retention does occur, it is likely to occur within 3 to 5 days of - initiating therapy and will manifest as an increase in body weight and/or symptoms of worsening HF. The increased fluid retention can usually be managed by increasing the dose of diuretics.

Beta blocker therapy is well tolerated by the great majority of HF patients (more than 85 percent). Nonetheless, there is a subset of patients (10 to 15 percent) who remain intolerant to beta blockers because of worsening fluid retention or symptomatic hypotension.

The first placebo-controlled multicenter trial with a beta-blocking agent was the Metoprolol in Dilated Cardiomyopathy (MDC)[7] trial, which used the shorter acting tartrate preparation at a target dose of 50mg three times a day in symptomatic HF patients with idiopathic dilated cardiomyopathy. A more efficacious formulation of Metoprolol was subsequently developed, Metoprolol (succinate) CR/XL, which has a better pharmacological profile than Metoprolol tartrate because of its controlled-release profile and longer half life. In the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF)[8], Metoprolol CR/XL, provided a significant relative risk reduction of 34 percent reduction in mortality in subjects with mild to moderate HF and moderate to severe systolic dysfunction when compared with the placebo group. Importantly Metoprolol CR/XL reduced mortality from both sudden death and progressive pump failure.

The first trial performed with Bisoprolol was the Cardiac Insufficiency Bisoprolol Study I (CIBIS-I)[9]. In CIBIS-II[10], Bisoprolol reduced all cause mortality by 32 percent (11.8 versus 17.3 percent, P = 0.002), sudden cardiac death by 45 percent (3.6 versus 6.4 percent P = 0.001), HF hospitalizations by 30 percent (11.9 percent Bisoprolol versus 17.6 percent placebo, P < 0.001), and all cause hospitalization by 15 percent (33.6 percent versus 39.6 percent, P = 0.002). The CIBIS-III trial[11] addressed the important question of whether an initial treatment strategy using the beta blocker Bisoprolol was noninferior to treatment strategy using an ACEI (Enalapril) first in patients with newly diagnosed mild to moderate HF.

Current guidelines continue to recommend starting with an ACE inhibitor, followed by the subsequent addition of a beta blocker.

Of the three beta blockers approved for the treatment of HF, Carvedilol has been studied most extensively. The phase III U.S. Trials Program, composed of four individual trials managed by a single Steering and Data and Safety Monitoring Committee, was stopped prematurely because of a highly significant (P < 0.0001) 65 percent reduction in mortality by Carvedilol that was observed across all four trials.

COPERNICUS study[12] extended these benefits to patients with more advanced HF. In COPERNICUS patients with advanced HF, symptoms had to be clinically euvolumic, with a LVEF < 25%. In COMET trial[13], Carvedilol was associated with a significant 33% reduction in all-cause mortality when compared with Metoprololtartrate (33.9 Vs 39.5%; HR, 0.83; 95% CI, 0.74 to 0.93, P= 0.0017)

Side effects

Fluid retention & aggravation of HF, development of heart block, bronchospasm

Angiotensin Receptor Naprilysin Inhibitors (ARNI)

Recently published PARADIGM trial[14] clearly showed that ARNI (LCZ696) which is a combination of Sacubitril (Naprilysin inhibitor) and Valsartan (ARB) was superior to Enalapril in reducing mortality in patients with class II, III and IV CHF. The difference was so significant that the trial was stopped prematurely. Thus the mortality benefit of ARNI is over and above that offered by RAAS blockade and beta-blockers. Naprilysin is an enzyme that degrades various natriuretic peptides that are beneficial in patients with CHF. ARNI has been approved by USFDA and has a class IIA indication in CHF according to AHA/ACC guidelines. It will be available in India for commercial use in next 3-4 months. ARNI should

never be used with an ACE-inhibitor which should be discontinued for at least a week before initiating it.

Ivabradine

Tachycardia is an important adverse prognostic marker in patients with CHF. SHIFT[15] and BEAUTIFUL[16] trials have shown that addition of Ivabradine to slow the heart rate in patients with CHF whose heart rate continues to be over 70 beats per minute despite maximally tolerated dose of beta-blockers, resulted in significant reduction in re-hospitalizations with decompensated CHF and a marked trend towards reduction in mortality.

Table 1 : **Total mortality or hospitalization for heart failure by duration of follow-up and agent for randomized trials of angiotensin converting enzyme inhibitors**

Agent	No. of trials	ACE inhibitors (no. of Events / no. randomized)	Controls (no. of Events / No. randomized	OR (95 % CI)
90 days or less of follow - up				
Captopril	4	27/292	42/288	0.60 (0.36-1.00)
Enalapril	7	157/1690	259/1691	0.52 (0.42-0.65)
Lisinopril	4	10/351	10/195	0.50 (0.19-1.27)
Quinapril	5	3/548	3/327	0.68 (0.13-3.66)
Ramipril	6	33/714	44/513	0.52 (0.32-0.83)
All other trials	4	9/215	14/164	0.51 (0.21-1.24)
Total	30	239/3810	372/3178	0.53 (0.44-0.63)
More than 90 days Of follow - up				
Captopril	3	52/214	66/206	0.68 (0.44 -1.04)
Enalapril	3	559/1282	592/1187	0.78 (0.66-0.91)
Lisinopril	0	-	-	-
Quinapril	2	2/218	2/210	0.96 (0.14-6.87)
Ramipril	2	2/120	3/83	0.58 (0.10 -3.48)
Total	10	615/1834	663/1686	0.76 (0.66-0.88)

Table 2 : **Selected clinical trials establishing the benefit of angiotensin-converting enzyme inhibitors in symptomatic and asymptomatic left ventricular systolic dysfunction**

Trial (Ref.) (no. of patients, Average follow up)	Study Population	ACE inhibitor and dose	Key results
CONSENSUS I (n = 253 ; 6 mo)	NYHA IV	Enalapril versus placebo 2.5 mg twice daily daily titrated to 20 mg twice daily	6-mo mortality decreased 40 % 1-y mortality decreased 31% Improvement in NYHA class Decrease in cardiac size

V-HeFT II (n= 804; 2.5 y)	NYHA II-IV LVEF < 45 %	Target enapril 10 mg twice daily versus hydralazine 75 mg four times daily + isosorbidedinitrate 40 mg four times daily	2- y mortality decreased 28 % No difference in HF hospiotalization Lesser improvement in exercise capacity and ventricular function With enalapril
SOLVD Treatment Trial (n=2569; 41 mo)	NYHA II-IV (90 % II-III) LVEF ,< 35 %	Enalapril versus placebo 2.5 mg twice Daily titrated to 10 mg Times daily	16% decrease in mortality 22 % decrease in progressive HF Mortality 26 % decrease in either death or HF hospitalization 8.6 mo increase in median life expectancy [77]
SOLVD Preventation Trial (n=4228;37.4 mo)	NYHA I LVEF < 35 %	Enalapril versus placebo 2.5 mg twice Daily titrated to 10 mg Times daily	20% decrease in either death or HF hospitalization 29% decrease in either death or development of HF

Table 3 : **Recommended doses of angiotensin-converting enzyme inhibitors in heart failure**

Drug	Initial dose	Target / maximum dose
Captopril	6.25 mg three times daily	50 mg three times daily
Enalapril	2.5 mg twice daily	10 to 20 mg twice daily
Fosinopril	5 to 10 mg once daily	40 mg once daily
Lisinopril	2.5 to 5.0 mg once daily	20 to 40 mg once daily
Quinapril	10 mg twice daily	40 mg twice daily
Ramipril	1.25 to 2.5 mg once daily	10 mg once daily
Perindopril	2 mg once daily	8 to 16 mg once daily
Trandolapril	1 mg once daily	4 mg once daily

Summary :

The major aims in pharmacotherapy of heart failure with low LVEF are 1. Improving symptoms by controlling volume overload and 2. Improving survival by limiting LV remodeling. Volume overload is controlled by judicious use of diuretics and dietary salt restriction. LV remodeling is prevented by RAAS inhibitors, Aldosterone antagonists and Beta-blockers. Recently ARNI combination of Sacubitril and Valsartan- has been shown to reduce mortality in PARADIGM trial and is expected to be the leading drug in the armamentarium of drugs used in treatment of CHF. Control of heart rate to less than 70 per minute achieved by beta-blockers and Ivabradine- has also been found to reduce morbidity in heart failure.

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