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Pharmacotherapy of Chronic Heart Failure with Reduced Ejection Fraction (HFrEF)

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ABSTRACT

Heart failure (HF) is a common clinical syndrome and a global health priority. It is a multifactorial, progressive and debilitating condition and requiring lifelong management. Despite the advances in drug therapy and management strategies, which is usually presents as a disease syndrome, has been a challenge to healthcare providers. This is demonstrated by high rates of hospital readmissions along with increased mortality and morbidity associated with heart failure. In this review article, we focused on pharmacotherapy of heart failure and we determined management guidelines and recent advances in the management of chronic heart failure with reduced ejection fraction (HFrEF). The standard therapy along with lifestyle modifications plays an important role in determining the prognosis of the disease. Recent advances in drug therapies and consequent use of established medication have substantially minimizes the readmissions and improves quality of life in heart failure patients with reduced ejection fraction. We consider that this article provide an extensive overview of heart failure in terms of stages, disease pathophysiology, pharmacotherapy and recent advances in the management of chronic heart failure with reduced ejection fraction.

Key words: Heart failure, ejection fraction, pharmacotherapy, management guidelines and recent advances.

1. INTRODCTION

Chronic heart failure (CHF) has become a global pandemic which is on rise in both developed and developing counties. It is a multifactorial, progressive and debilitating condition, requiring lifelong management. Globally, it affects about 1-2% of adults and 10% of geriatric population (≥70 years).[1,2] The incidence rate will further elevate as the risk factors for CHF such as hypertension and ischemic heart disease are becoming more prevalent. It is reported to have consequential effect on mortality and morbidity, comparable to that of many forms of cancers. With the progression of the disease, quality of life decreases.[3] Furthermore, its management is economically burdensome: in United Kingdom (UK) about 2% of NHS (National Health Services) budget is allocated for HF.[4] The higher prevalence, greater management cost and poor clinical outcomes, highlights CHF to be a major public health concern.

Recent advances in drug therapies and consequent use of established medication have substantially reduces the mortality and frequency of re-hospitalization in heart failure patients with reduced ejection fraction (EF) [5]. Therapeutic approaches of heart failure differ based on its presentation. Therefore, the main objective of the study is to identify the recent advances, newer drug targets and latest guidelines in the management of chronic heart failure with reduced ejection fraction.

2. DEFINITION:

The European Society of Cardiology (ESC) defined heart failure as a complex clinical syndrome that results due to the underlying structural or functional cardiac

alterations which leads to a decreased cardiac output and/ or a higher intracardiac pressure. It is characterized by typical symptoms such as shortness of breath, ankle swelling and fatigue, which usually occurs along with the other signs like elevated jugular venous pressure, pulmonary crackles and peripheral edema.[6]

3. EPIDEMIOLOGY:

HF is attributed as one of the most common reasons for the hospitalization in higher income nations. The data on HF is limited from the developing or lower income countries, hence it largely represents the patients from the developed countries.[7] Globally, HF prevalence rate is about 37.7 million. The figure is expected to increase by 25% by 2030.[8] It has been reported that, the risk for HF increases as the age progresses.[9] In elderly people (>55 years), the risk of HF is higher is men (33%) than women (28.5%).[10] The mortality rate has been reported to elevate at ~50% after 5 years of initial diagnosis.[6] Unfortunately, ~2-17% of patients hospitalized for HF dies while still in hospital. In India the prevalence of HF is about 1.3-23 million.[6]

The data on HFrEF is scarce, however, during the period of 1997 to 2010 population-based studies were done, it has concluded that the prevalence for HFrEF is about 2.4-4.8%. Males were reported to have increased rate of 3.3-7.2%, whereas females had 1.5-4.1%.[11]

4. TYPES OF HEART FAILURE:

Based on the time course of onset of signs and symptoms of HF, it is divided as acute and chronic (table 1). Heart failure encompasses a wider range of patient population, from those with normal left ventricular ejection fraction (LVEF ≥50%), mid-range EF (40-49%) to reduced EF (<40%) and as called as HF with preserved EF (HFpEF), HF with mid-range EF (HFmrEF) and HF with reduced EF (HFrEF) respectively. Categorizing the patient based on LVEF is pivotal because different etiology, demographic and co morbidities contributes for the progression of the disease. Additionally, depending upon the EF patient's response for the therapy varies.[6]

5. STAGES/CLASSIFICATION OF HEART FAILURE:

Different classifications have been used to determine the severity of the HFrEF. However, ACC/AHA and NYHA classification remains to be the most widely accepted and commonly used ones. ACC/AHA system utilizes the disease progression for classification whereas NYHA is based upon the functionality of heart. ACC/AHA classification categorizes the patients into different stages (A,B,C,D) based upon the severity of the disease the stages (table 2).[12] This also helps in identifying and providing better therapeutic care to the patients that are more prone to develop end stage HF. On the other hand, NYHA method divides the patients based on symptom development (table 3).[13]

6. AETIOLOGY:

Multiple etiological factors have been attributed in heart failure such as various cardiac diseases, hereditary defects and other systemic disorders. A person can develop heart failure due to the presence of one or more than one etiological factor. It varies for the people in developed and developing countries.[14] Globally, ischemic heart disease (IHD), chronic obstructive pulmonary disease (COPD), hypertensive heart disease and rheumatic heart disease are reported to be the primary disease conditions leading to HF in about two third of patients.[15] Among HF cases in developing nations, hypertensive heart disease, rheumatic heart disease, cardiomyopathy and myocarditis are the most common causes, whereas in developed nations, IHD and COPD are more common diseases.[16]

Table 1. Types of heart failure based on different criteria:

Basis of Classification	Criteria	Types of HF
LV Ejection fraction	40%	HFpEF
	40-49%	HFrEF
	≥50%	HFmrEF
Time course	Present for ≥3 months	Chronic HF
	Sudden onset/worsening of HF signs and symptoms	Acute HF

Table 2. ACC/AHA Classification of Heart Failure:

Class	Description	Example
A	Patients are at higher risk of developing HF due to the presence of diseases that are associated with the development of HF. There isn't any structural abnormality or signs and symptoms of HF	Systemic Hypertension Coronary heart disease Diabetes mellitus Familial history of rheumatic fever or cardiomayopathy
B	Patients with structural heart disease but has never shown any signs or symptoms of HF	LV hypertrophy or fibrosis or hypocontractility Valvular heart disease History of myocardial infarction
C	Patients who currently experiencing or has history of developing signs or symptoms of HF along with the presence of structural heart disease.	Dyspnoea or fatigue because of ventricular dysfunction Receiving treatment for HF on account of previously developing symptoms of HF.
D	Patients with deteriorating structural heart disease, experiencing symptoms of HF at rest even after receiving maximum pharmacotherapy	Hospitalized HF patients Patients requiring heart transplant

7. PATHOPHYSIOLOGY:

Heart failure is a life threatening condition where the heart is unable to pump out enough blood to meet the metabolic needs of the body. This results in the activation of a cascade of compensatory mechanisms which over the time have disastrous effects on heart, further exacerbating the symptoms and if left untreated can lead to death.

In heart failure patients, the stroke volume decreases as the cardiac functionality decreases. The key elements that influence the cardiac performance are: elevated preload, decline in contractility and higher afterload. Preload refers to the extent to which the ventricular myocardial muscles distend before it contracts. As it is related to the quantity of ventricular filling prior to systole, any changes in the volume will affect both preload and stroke volume. According to Frank-Starling mechanism, the force of contraction of myocardium is directly proportional to the extent to which the cells are stretched i.e., greater the degree of distension, greater will be the force of contraction.[17,18] Afterload is the force with which the ventricles pump out the blood against the vascular resistance. As the peripheral vascular resistance increases, the stroke volume also increases. [19]

In HFrEF, activation of Renin Angiotensin Aldosterone System (RAAS) and Sympathetic Nervous System (SNS) plays a pivotal role in ventricular remodeling and neurohumoral changes that hinders the intrinsic ability of the heart muscles to contract.[20]

7.1 Activation of RAAS:

As the renal perfusion decreases, kidneys are stimulated to release renin. The release of renin leads to the activation of angiotensinogen in liver is activated to Angiotensin I. Renin then converts Angiotensin I to Angiotensin II which in turn stimulates the release of aldosterone. Angiotensin II, a vasoconstrictor increases the blood pressure as it causes peripheral vasoconstriction. A consistently increased BP has negative effects on the heart performance.[17] Aldosterone causes sodium and water retention leading to an elevation in blood volume. A persistently higher vasoconstriction and blood volume eventually leads to increase in preload, which overtime has damaging effects on structure of ventricular myocardial cells causing its remodeling and ultimately resulting in ventricular hypertrophy.[18]

7.2 Activation of Sympathetic Nervous System:

The sympathetic nervous system gets activated when the BP and cardiac

output is low. Its activation leads to the secretion of catecholamines such as noradrenaline and norepinephrine. These catecholamines interact with the beta receptors leading to increase in the heart rate and force of contraction in order to maintain the cardiac output. Initially, this may help to compensate for decreased cardiac function but chronically it has disastrous effects. In the long run, it has been reported to be linked with decreased ability to exercise, hemodynamic abnormalities and higher rate of mortality. Prolonged activation of the SNS leads to the stimulation of RAAS.[21]

7.3. Left Ventricular Remodeling:

Ventricular remodeling refers to alterations in the size, shape and function of the ventricles, which is determined by various factors such as genetics, RAAS and neurohumoral system. Thus, any derangement in any of these factors will lead to the ventricular remodeling. In a failing heart, it is often an adaptive process. However, this could be pathological due to certain cardiac diseases such as myocardial infarction, ventricular hypertrophy, cardiomyopathy and hypertension.[22] After an ischemia or infarction, inflammation sets in in order to heal the damaged tissues. If there is prolonged inflammation, LV hypertrophy and dilation occurs because there is loss of functional myocardial cells.[23]

Injured myocardial cells stimulate the release of reactive oxygen species (ROS) which causes inflammation and cell necrosis. As a result, pro inflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis α (TNF-α). They attract the white blood cells and sets off an inflammatory response, destroying the endothelial cells. Significant destruction of endothelial cells results in decrease in the production of nitric oxide, a vasodilator. Hence, vasoconstriction sets in which activates the neurohumoral pathway and inflammation, further damaging the myocardial tissue. Eventually, LV remodeling continuously worsens causing LV dilation and reduced ejection fraction.[24,25]

Table 3. NYHA classification of Heart Failure:

Class	Description
I	No limitation. Ordinary physical activity doesn't cause typical symptoms.
II	Slight limitation. No symptoms shows up at rest. However, ordinary physical activity will cause the typical symptoms.
III	Marked limitation of physical activity. Asymptomatic at rest but any physical efforts will cause symptoms.
IV	Inability to perform any physical task without symptoms. Symptoms occur even at rest.

8. PHARMACOTHERAPY OF CHRONIC HEART FAILURE:

Goals of the treatment:

- To improve clinical status and functional capacity
- To improve quality of life
- Relieve or reduce symptoms
- Minimize hospitalization
- Slow disease progression and prolong survival

Pharmacotherapy plays a major role in obtaining these goals. Apart from these, recognition of risk factors for heart failure development and identification of its progressive nature have led to increased prominence on preventing the progression of this disorder.[26]

Although it is recognized that minimizing HF hospitalization and improving functional capacity are significant benefits to be considered if a mortality excess is ruled out.[6] In patients with reduced ejection fraction, neurohormonal activation plays key role in the development of heart failure. Alteration of this mechanism is essential not only in relieving symptoms but also in improving long-term prognosis of disease.[27] Figure 1 shows a treatment strategy for the use of drugs in patients with HFrEF. The recommendations for each treatment are summarized below. Previous studies demonstrated that the mortality benefits of neuro hormonal antagonists[6] such as angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), betablockers and the

recently approved angiotensin receptor neprilysin inhibitors (ARNIs), hyper-polarization channel blocker ivabradine and digoxin have been added to the treatment strategies in patients with HFrEF.[28] Recent trails suggested that ACE inhibitors improve survival and relieve symptoms in all stages of heart failure. It is well described that ACE inhibitors have beneficial effects in both the treatment and the prevention of heart failure by inhibition of neuro hormonal activation mechanisms.[29] Ivabradine lowers heart rate by selectively inhibiting the If channels (funny channels) on the cardiac pace maker (sinoatrial node). The SHIFT study described that addition of Ivabradine to maximum tolerated doses of beta blockers as well as ACEi/ARB and MRAs shows benefit on the combined outcomes of cardiovascular death and reducing HF hospitalisation.[30]

8.1 PHARMACOLOGICAL TREATMENT:

According to European Society of cardiology (ESC) guidelines, Neuro-hormonal antagonists have been shown to improve survival in heart patients with reduced ejection fraction (HFrEF) and are recommended for the treatment of every patient with HFrEF, unless contraindicated or not tolerated.[6] The basic mechanism involved in the treatment of heart failure is the suppression of harmful effects of the neuroendocrine compensatory mechanisms such as RAAS, sympathetic nervous system and vasopressin release.[29] Following are the most widely used treatments in patients with reduced ejection fraction as shown in figure1.

8.1.1 ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACEI):

ACE inhibitors block the cleavage of angiotensin I to angiotensin II and there by inhibit the bradykinin degradation.[29] ACE inhibitors involved in Activation of the sympathetic nervous system, promotes excretion of sodium and water by blocking the effects of angiotensin II in the kidney.[5] Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial demonstrated that the ACE inhibitors (Enalapril) have been shown to be beneficial in improving survival of patients with severe congestive heart failure when compared with placebo.[28] The SOLVD trial established further evidence of reduced incidence and hospitalization for HF with enalapril in patients with left ventricular dysfunction (≤ 35%) and mild to moderate congestive heart failure when compared to placebo.[31]

8.1.2 ANGIOTENSIN RECEPTOR BLOCKERS (ARBS):

ARBs are recommended only as an alternative in patients who are allergic or hypersensitive of an ACE inhibitor.[27] ARBs have been shown to mediate the desirable hemodynamic, neuro hormonal, and clinical effects as substantiated in different clinical trials.[32] Candesartan has been shown to reduce mortality in patients with cardio vascular diseases. Previous studies described that valsartan minimizes hospitalization for heart failure in patients with reduced ejection fraction receiving background ACEIs.[6] The ELITE study suggested that losartan shows lower incidence of side effects and drug withdrawal than captopril and a significant reduction in mortality, mainly due to a reduction in the incidence of sudden death.[29,33] The ValHeFT study provided further evidence of improved symptoms and mortality with valsartan in comparison to placebo in NYHA II patients and no benefit was shown when added to ACE inhibitors.[31] Consolidated evidence from two condesartan trails such as CHARM (Candesartan in Heart Failure Assessment of Mortality and Morbidity) trials and (CHARM-Alternative to an ACEI and CHARM-Added to an ACEI) showed reduction of cardiovascular death and heart failure hospitalization.[28]

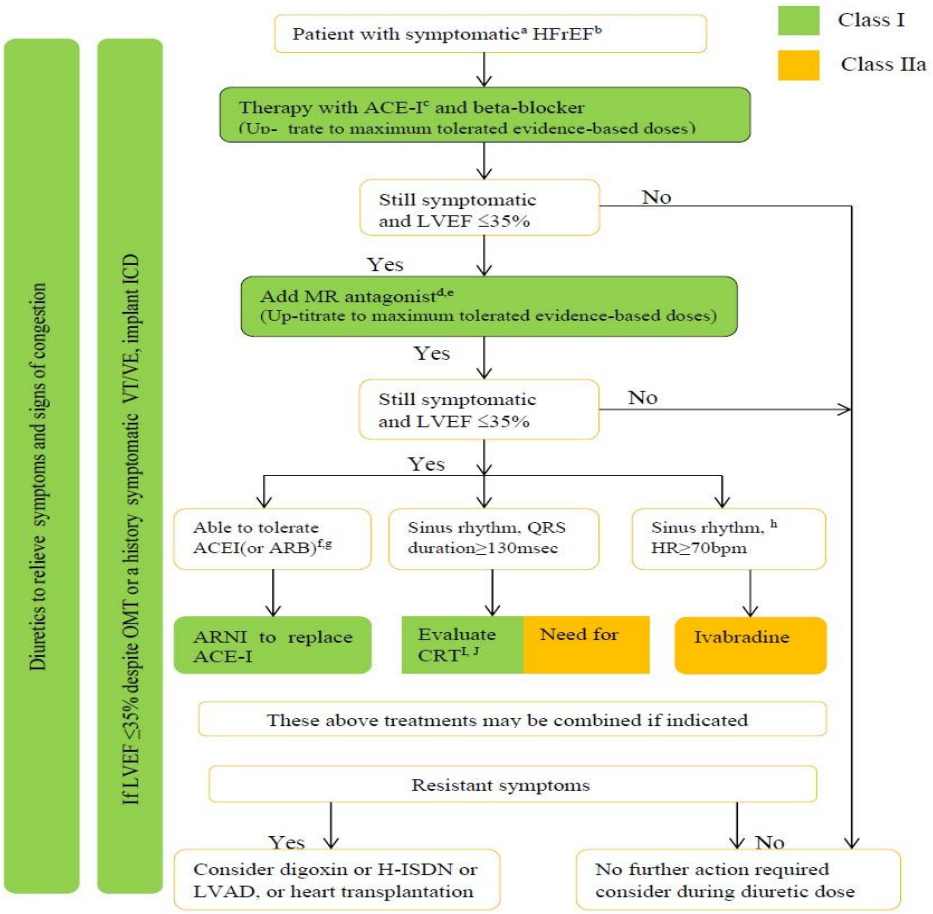

Figure 1. Therapeutic algorithm for a patient with symptomatic heart failure with reduced ejection fraction

Green indicates a class I recommendation; yellow indicates a class IIa recommendation. ACEI = angiotensin-converting enzyme inhibitor; ARB= angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; BNP = B-type natriuretic peptide; CRT = cardiac resynchronization therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; H-ISDN = hydralazine and isosorbide dinitrate; HR = heart rate; ICD= implantable cardioverter defibrillator; LBBB = left bundle branch block; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; MR = mineralocorticoid receptor; NT-proBNP = N-terminal pro-B type natriuretic peptide; NYHA = New York Heart Association; OMT = optimal medical therapy; VF = ventricular fibrillation; VT = ventricular tachycardia. [a]Symptomatic = NYHA Class II-IV. [b]HFrEF = LVEF <40%. [c]If ACE inhibitor not tolerated/contra-indicated, use ARB. [d]If MR antagonist not tolerated/contra-indicated, use ARB. [e]With a hospital admission for HF within the last 6 months or with elevated natriuretic peptides (BNP >250 pg/ml or NTproBNP >500 pg/ml in men and 750 pg/ml in women). [f]With an elevated plasma natriuretic peptide level (BNP ≥ 150 pg/mL or plasma NT-proBNP ≥ 600 pg/mL, or if HF hospitalization within recent 12 months plasma BNP ≥ 100 pg/mL or plasma NT-proBNP ≥ 400 pg/mL). [g]In doses equivalent to enalapril 10 mg b.i.d. [h]With a hospital admission for HF within the previous year. [i]CRT is recommended if QRS ≥ 130 msec and LBBB (in sinus rhythm). [j]CRT should/may be considered if QRS ≥ 130 msec with non-LBBB (in a sinus rhythm) or for patients in AF provided a strategy to ensure bi-ventricular capture in place (individualized decision).

8.1.3 ANGIOTENSIN RECEPTOR – NEPRILYSIN INHIBITORS (ARNI):

Angiotensin receptor-neprilysin inhibitors (ARNI) are the new therapeutic agents that act by the inhibition of both renin angiotensin aldosterone system (RAAS) and the neutral endo peptidase system.[6] The first agent in this class is "LCZ696," which is a molecule that consist of valsartan (ARBs) and sacubitril a neutral endopeptidase (NEP, neprilysin) inhibitor. Neprilysin plays a key role in the degeneration of natriuretic peptides.[5] The Prospective Comparison of ARNI with ACEI to determine impact on global mortality and morbidity in Heart Failure (PARADIGM-HF) trial described that sacubitril/valsartan was superior to enalapril (ACEI) in patients with reduced ejection (HFrEF).[32] The risk angioedema was addressed in PARADIGM-HF study. To reduce the risk of angioedema caused by overlapping ACE and neprilysin inhibition, the ACEI should be withheld for at least 36 h before initiating sacubitril/valsartan.[27] For patients on ARNI, NT-proBNP should be used as essential biomarker to monitor treatment and assessing the heart failure severity.[32]

8.1.4 BETA-BLOCKERS:

Previous studies demonstrated that beta-blockers can reduce morbidity and mortality like ACE inhibitors in symptomatic patients as well as improve clinical status and minimize HF hospitalization.[29] Combination therapy of beta-blockers to standard treatment in patients with HF has described significant reduction of 30-40% in cardiovascular death, sudden death, hospitalization for worsening HF.[32] Based on these evidences, beta blockers are accepted as a standard pharmacological treatment in addition to the ACEI in the management of chronic heart failure. In patients with a history of myocardial infarction and asymptomatic LV systolic dysfunction, Beta-blockers are recommended as a standard pharmacological treatment to reduce the risk of death.[6] Carvedilol, metoprolol succinate, and bisoprolol are the most widely recommended beta-adrenergic receptor blockers and have been shown to improve survival in HFrEF patients. CIBIS-II study of double-blinded multi-center clinical trial demonstrated that All-cause mortality hospitalizations and sudden cardiac death were reduced by 50% with bisoprolol in comparision to the placebo was observed in patients with heart failure.[31] Similar studies such as US Carvedilol Heart Failure Study and the Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS) evaluated outcomes of Carvedilol in patients with symptomatic heart failure.[28] Various studies including Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF), and the study of the effects of Nebivolol Intervention on outcomes and rehospitalisation in seniors with Heart Failure (SENIORS) have been shown the beneficial effects of a therapy with beta-blockers in HFrEF.[5]

8.1.5 MINERALOCORTICOID RECEPTOR ANTAGONISTS (MRAs):

Two Mineralocorticoid receptor antagonists (spironolactone and eplerenone) are recommended and have been shown to improve survival in HFrEF.[27] Elevated levels of Aldosterone commonly reported in patients with ACE inhibitor and may leads to the worsening of heart failure. Spironolactone is a competitive antagonist of aldosterone and has been shown to have additional beneficial effects in subjects already treated with an ACE inhibitor.[29] MRAs are well established in all symptomatic patients with HFrEF and LVEF ≤35%, to reduce mortality and HF hospitalization despite treatment with an ACEI and a beta-blocker.[6] RALES study compared the effects of spironolactone and placebo in 1663 patients with chronic heart failure and demonstrated 35% reduction in hospitalization and 30% reduction in mortality and symptoms.[31] Renal function and potassium levels should be monitored in

patients with spironolactone and caution should be exercised when MRAs are used in patients with impaired renal function and in those with serum potassium levels >5.0 mmol/L.[6] Additive RAS blockade in patients with severe heart failure who were on standard therapy with ARB's, an ACE inhibitors with or without beta-blocker to spironolactone. Spironolactone reduced cardiovascular mortality by 20-25%.[32] In 2011, the double blind placebo controlled EMPHASIS-HF study demonstrated reduced mortality by 7% with eplerenone in patients with chronic heart failure (NYHA II and EF < 35%).[31]

8.1.6 DIURETICS:

Diuretics are well established in patients with HFrEF to reduce the signs and symptoms of congestion but their effects on mortality and morbidity have not been described in randomized controlled trails.[6] Sodium and water retention is the important characteristic feature of chronic heart failure and diuretics are recommended treatment for patients with pulmonary or peripheral oedema.[29] Loop diuretics has a synergistic effect with the thiazide diuretic but the loop diuretics produce a more intense and shorter diuresis than thiazides and the combination may be used to treat resistant oedema.[6] Thiazides are weaker diuretics when used alone, even though they have greater effect on the blood pressure secondary to direct vasodilating effects except for metolazone, thiazide-like diuretics are less effective when creati- nine clearance (CrCl) is <30 ml/min.[33] Once the fluid retention has resolved, diuretic treatment should be maintained to prevent recurrent oedema and that may require frequent adjustments to the given dose.[29]

8.1.7 If CHANNEL INHIBITORS:

Ivabradine is an If channel (funny channel) inhibitor that slower the heart rate by selective inhibition of If channels on the cardiac pace maker.[30] It is well established in patients with sinus rhythm, who have a heart rate >70 beats per minute despite being treated with a maximum tolerated dose of a beta-blockers.[27] Previous studies have demonstrated the benefits of ivabradine in reducing the outcomes cardiovascular death or HF hospitalization in patients with HFrEF.[32] SHIFT trail was randomized controlled trial reported the significant reduction in hospitalization for worsening heart failure in patients with LVEF 35% or lower with heart rate >70 in sinus rhythm.[28,31] The administration of ivabradine in combination with beta blocker for chronic heart failure demonstrated a significant decrease in HF hospitalizations, cardiovascular mortality and there by improves quality of life in heart failure patients.[5]

8.1.8 DIGOXIN:

Digoxin is cardiac glycoside that increases vagal tone and suppresses renin secretion from the kidneys and it also works as positive inotrope.[29] Digoxin is recommended in symptomatic patients with sinus rhythm to decrease the risk of hospitalization.[6] Pooled data from Digitalis Investigation Group (DIG) trial, the post hoc subgroup analysis showed increased mortality in women with an adjusted HR and serum concentrations of > 1.2 are associated with this increased mortality.[28] Digoxin benefits were observed only at lower serum concentrations, because of this, low maintenance doses (i.e. 125 mcg per day or every other day) are typically used.[33] Cardiac glycosides should be used with caution due to its narrow therapeutic effect especially in older patients, women and patients with impaired renal function.[5]

8.1.9 HYDRALAZINE AND ISOSORBIDE DI NITRATE:

Combination of hydralazine and isosorbide dinitrate is recommended in symptomatic patients who are allergic or hypersensitive to an ACE inhibitor/ARB/ARNI.[27] A subsequent randomized control trail was conducted in self-identified black patients demonstrated reduced mortality and HF hospitalizations in patients with HFrEF and NYHA Classes

III–IV in addition of the combination of hydralazine and isosorbide dinitrate to standard therapy.[6] African-American Heart Failure Trial (A-HEFT) suggested that the combination of hydralazine and isosorbide dinitrate improved survival, quality of life, and reduced hospitalization when added to the standard therapy (ACEI or ARB and beta blockers) in African American women with moderate-severe heart failure.[28]

9. MANAGEMENT GUIDELINES FOR HEART FAILURE:

The goals of HFrEF therapy are to reduce morbidity (i.e, reduce symptoms, improve health related quality of life and functional status, and decrease the rate of hospitalization), and to reduce mortality

Management of Heart failure includes

1. Early diagnosis and prevention of heart failure
2. Management of the causes of heart failure and associated co-morbidities
3. Pharmacological Management
4. Non pharmacological management
5. Devices, surgery and percutaneous procedures
6. Vaccination
7. Drugs that should be avoided or used with caution
8. Multidisciplinary care management

1. Early diagnosis and prevention of heart failure:

Assess symptoms and signs of heart failure and that are important in monitoring a patient's response to treatment and stability over time.[6] A 12- lead electrocardiogram (ECG) is recommended to assess the cardiac rhythm, QRS duration and the presence of underlying conditions such as myocardial ischaemia or LV hypertrophy in patients with either a suspected diagnosis or new diagnosis of HF.[34] Plasma B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT proBNP) levels are used to establish the presence and severity of HF.[35] Echocardiography is recommended to identify the type of heart failure and other structural or functional abnormalities, such as valvular heart disease.[36] Other investigations such as chest x-ray, invasive coronary angiography, either computed tomography (CT) coronary angiography or cardiac magnetic resonance imaging (CMR) are used to detect signs of pulmonary congestion and to identify alternative cardiac or non-cardiac causes for the patient's symptoms.[34] Treatment of hypertension and other risk factors of heart failure should be considered to in order to prevent or delay the onset of HF.[6]

2. Management of causes of heart failure and associated co-morbidities:

Investigation and management of precipitating factors is recommended in all patients presented with heart failure.[34] Common causes involved in the development of heart failure are ischaemic heart disease, hypertension, valvular disease, and idiopathic dilated cardiomyopathy.[37] Hypertension and lipid disorders should be controlled to lower the risk of heart failure other conditions that may lead to heart failure, such as obesity, diabetes mellitus, tobacco use, and known cardiotoxic agents, should be controlled. Diuretic-based antihypertensive therapy has repeatedly been shown to prevent Heart failure in a wide range of patients.[35] Initiation of an ACEI, a beta-blocker and an MRA immediately after a myocardial infarction, reduces the rate of hospitalization for HF and mortality especially when it is associated with LV systolic dysfunction.[6] Sodium-glucose co-transporter 2 (SGLT-2) inhibitors reduces cardiovascular mortality and HF hospitalization in DM patients at a high cardiovascular risk. They are the only oral antihyperglycemic medications that have shown benefit in terms of cardiovascular event reduction.[27] Diuretics are recommended to improve symptoms and enhance survival in HF patients with rheumatic heart disease (RHD).[32] Psychosocial intervention and pharmacological treatment are beneficial, as well as exercise training, in patients with

HFrEF and depression.[6] Among various predisposing factors, coronary artery disease exhibits the strongest association for increase in the risk of developing HF. Beta-blockers and ivabradine has been shown to be beneficial in HFrEF patients with angina.[27] Treatment with Intravenous ferric carboxymaltose (FCM) in severe anaemic patients may improve functional capacity, quality of life and also associated with a significant reduction in hospitalizations for worsening HF.[6]

3. Pharmacological Management:

The primary treatment approach for heart failure patients with reduced ejection fraction (HFrEF) is neurohormonal inhibition by means of angiotensin converting enzyme (ACE) inhibitors (ACEIs), mineralocorticoid receptor antagonists (MRAs), and beta-blockers. The main goals of treatment in patients with HF are to improve short- and long-term outcomes, prevent rehospitalisation and reduce mortality.

4. Non pharmacological management:

- Salt restriction or limit salt intake especially in patients with advanced HF. Guidance on the use of salt substitutes with caution as they may contain potassium If the salt substitutes are used in large quantities with RAAS blockers, it may lead to hyperkalemia.[27]
- According to American Heart Association and the United States Department of Agriculture (USDA) sodium intake should be 2.3 gm (equivalent to 5.7 gm of common salt) per day for the general population, and 1.5 gm for those with hypertension, middle-aged and older people.[32]
- Smoking cessation is recommended to decrease the risk of cardiovascular events and decrease the risk of developing heart failure.[31]
- Avoiding excess alcohol is recommended, to decrease the risk of developing heart failure.[34]
- Regular exercise and yoga may improve patient daily functioning.
- Weight reduction is recommended in patients who are overweight or obese, to decrease the risk of developing heart failure.
- Educating patients and their carers about the self-management of heart failure is recommended in patients with heart failure to decrease hospitalization and mortality.[36]

5. Devices, surgery and percutaneous procedures:

An implantable cardioverter defibrillator (ICD) should be considered as a secondary prevention indication in patients following resuscitated cardiac arrest, sustained ventricular tachycardia in the presence of haemodynamic comprise and ventricular tachycardia associated with syncope and an LVEF <40% to reduce mortality.[6] An ICD should be considered as a primary prevention indication in patients at least 1 month following myocardial infarction associated with an LVEF of ≤30% to reduce mortality.[34] Cardiac resynchronisation therapy (CRT) should be considered for patients who have LVEF of <35% in sinus rhythm, a non-LBBB pattern with a QRS duration of 150 ms or greater, NYHA class II symptoms on GDMT and echocardiographic evidence of dyssynchrony.[32] Coronary artery bypass graft surgery (CABG) can be considered in patients with HFrEF associated with ischaemic heart disease and an LVEF of ≤35% if they have surgically correctable coronary artery disease to improve symptoms and decrease morbidity and mortality.[34]

6. Vaccination:

The vaccination plays key role in prevention and management of heart failure.[38] Previous studies described that there is significant association between heart failure and respiratory diseases and it is elicited that 50% of HF exacerbations being triggered by respiratory infections.[39] Improved vaccination rates may decrease

the incidence of respiratory infections, modify the natural history of chronic heart failure and there by prevent heart failure exacerbations, hospitalization, excess cost and associated morbidity/mortality.[38]

The most widely available respiratory vaccinations in the management of Heart failure are[27]:

Pneumococcal vaccination: First dose after confirmation of HF diagnosis and a second dose after 5 years.

Influenza vaccination: To be given every year before the onset of winter (September/October).

7. Drugs that should be avoided or used with caution:

There are some drugs which increase sympathetic tone and they may have a negative safety profile in patients with HFrEF.[6] The following drug classes increases the risk of heart failure hence, should be avoided or used in caution in patients with heart failure.[27]

Thiazolidinediones (glitazones)

Non-steroidal anti-inflammatory drugs (NSAIDs) or COX-2 inhibitors

Diltiazem/verapamil (dihydropyridine calcium channel block- ers such as amlodipine and felodipine should be used only if there is a compelling indication—management of coexistent hypertension)

8. Multidisciplinary care management[6]:

To improve heart failure outcomes through structured follow-up with patient education, optimization of medical treatment, psychosocial support and improved access to care

Provide sufficient information regarding heart failure prognosis to make decisions on lifestyle adjustment and self-care. Ideally for those patients admitted to the hospital, lifestyle advice should begin prior to discharge.

Frequent contact with providers, either by phone or in clinic.

Telemedicine in HF, which is also termed remote patient management, has variable clinical trial results. These trials include Tele-HF, TIM-HF, INH, WISH

Discharge and early post-discharge support if hospitalized

Multidisciplinary care including Cardiologists, physicians, nurses, care coordinators, social workers, pharmacists, physical therapists, nutritionists, and/or others as needed

10. RECENT ADVANCES IN TREATENT:

Due to a continuous increase in the cases and economic burden of heart failure worldwide, there is an urgent demand for newer therapeutic agents to resolve the issue in a more efficient manner. Although numerous drugs have shown promising effects in the pre-clinical studies, but most of them have failed in later stages of clinical trials. In 2015 a breakthrough was achieved when US FDA approved 2 novel drugs for heart failure: ivabradine and sacubitril/valsartan. Apart from the two approved drugs, there are some other agents that have not been approved yet but shows significant potential. Some of these other drugs are: patiromer, zirconium cyclosilicate, and urodilatin.

A. Angiotensin receptor- neprilysin inhibitors (ARNI):

One of the main strategies of managing the HF patients, is to downgrade the activated RAAS. The newer drug agent previously known as LCZ696, contains two components of compounds namely: valsartan (angiotensin receptor blocker) and sacubitril (a prodrug, neprilysin inhibitor NEPI).[40] Sacubitril gets converted into an enzyme that blocks the NEP and degrades atrial natriuretic peptide, BNP and C type natriuretic peptide.[41] In clinical trials, since sacubitril/valsartan is a complex drug, it has shown significantly effective in management. FDA approved the drug in July 2015, for chronic HF patients (EF <40%) with signs and symptoms but it is recommended to be used along with other

therapeutic agents in an attempt to decrease the mortality.

B. Ivabridine:

Elevated heart rate has been associated with increased mortality as it may be caused due to activation of the sympathetic system. Though beta blockers are administered to improve the HR in HF patients.[42] FDA approved ivabradine in 2015, for the heart failure patients with EF <35%, who despite receiving the maximum dose for beta blockers, have a HR of >70 bpm at rest. Ivabridine inhibits the *If* current channels in sinoatrial (SA) node, a pacemaker in heart. Thus, reducing the heart rate without affecting the heart contractility.[43]

10. FUTURE DIRECTIONS:

Though RAAS and MRAs are potent drugs for stabilizing the HFrEF patients, the problem arises while up titration of the dose, as they are known to cause hyperkalemia especially in patients with renal dysfunction.[44,45] There is a need for effective agents to control the potassium levels in the body when the patients are on the RAAS or MRAs therapy. Two such potential agents are patiromer and zirconium cyclosilicate, which are potassium absorbents. These are still under testing phase and till date they have not been approved by FDA.

Table 4 summarises the studies and their results related to the novel drugs.

- **Patiromer**: It s a non-absorbable polymer that entraps the potassium in gastrointestinal tract. When administrated orally it increases the excretion of potassium, thereby lowers the potassium concentrations in blood.[46]
- **Zirconium cyclosilicate**: It is an inorganic compound, that binds with the potassium in the intestines in exchange for sodium and hydrogen.[47] It also increases the excretion of potassium but in a dose dependent manner.[48]
- **Urodilatin**: Natriuretic peptides are of interest as the potential targets to manage the HF patients, as they cause vasodilation and natriuresis.[49] Synthetic NPs include: carperitide and nesiritide which are recombinant forms of ANP and BNP respectively. Ularitide is synthetic form of urodilatin, which is produced by kidneys. It is effective as it causes natriuresis, diuresis, dilation of blood vessels and blockade of RAAS. These drugs are still under clinical trials awaiting to receive approval for marketing.[50]

Table 4. Clinical studies of the drugs and their reults:

S. No.	Drug Name	Study	Results
1	Sacubitril/valsartan	PARADIGM-HF (Prospective Comparison of ARNi with ACE Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) Trial[40]	It has shown to be effective in reducing the all cause mortality, deaths due to cardiovascular causes and rate of hospitalizations. Additionally, it lowers the biomarkers in blood (NT-proBNP and troponin)
2	Ivabridine	The SHIFT (Systolic HF Treatment with I *f* Inhibitor Ivabradine) trial[51]	The results has reported that, it decreases the cardiovascular mortality, hospitalizations and mortality due to HF. It lowers the HR and improves the quality of life.
3	Eplerenone	The EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure)[52]	It significantly reduced the risk for mortality due to cardiovascular causes as well as the first incident of hospitalization.
4.	Urodilatin	SIRIUS II (The Prospective Double-blind Study in Patients with Symptomatic, Decompensated Chronic Heart Failure)[53]	In this study, the drug was shown to decrease the peripheral vascular resistance and elevate cardiac index

CONCLUSION

Heart failure is known to be a public health burden in terms of both prevalence and cost of management worldwide. One of the most cardinal strategy to prevent the progression of the disease is to identify and categorize the patients in order to provide better care from initial stages. Awareness should be spread regarding the screening tests and follow ups at regular intervals for

the patients that shows the presence of risk factors, to ensure early detection of HF. The standard therapy along with lifestyle modifications plays an important role in determining the prognosis of the disease. However, among patients with severe disease or with the presence of other co morbidities, there is an increased chance of developing adverse drug reaction which will limit the use of the drugs. This demands the need for the development of novel therapies for better disease management. Though several drugs were found to be successful in the pre-clinical studies, only limited numbers of drugs have shown to be effective in later stages of clinical trials.

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