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Review Article

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A REVIEW OF CURRENT DRUG THERAPY IN CHRONIC HEART FAILURE

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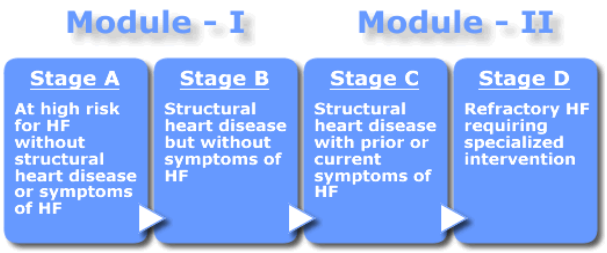
ABSTRACT

Heart Failure (HF) is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. This is further subdivided into HF with reduced left ventricular ejection fraction (HFrEF) and HF with preserved left ventricular ejection fraction (HFpEF) previously known as diastolic HF. HF may be caused by disease of the myocardium, pericardium, endocardium, heart valves, vessels, or by metabolic disorders. Most patients with HFrEF should be routinely treated with guideline directed medical therapy (GDMT) that includes an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and a *β*-blocker. Selected patients should also receive loop diuretics, hydralazine/nitrates, or aldosterone antagonists. The benefits of these medications on slowing HF progression, reducing morbidity and mortality, and/or improving symptoms are clearly established, Digoxin is potentially beneficial in symptomatic patients with HFrEF already receiving optimal medical therapy to decrease HF hospitalizations. There is little clinical trial evidence to guide which treatment are optimal to use in HFrEF.

KEYWORDS: Heart failure, Pharmacotherapy. Diuretics, ACEI &ARBs, Beta blocker, Role of pharmacist.

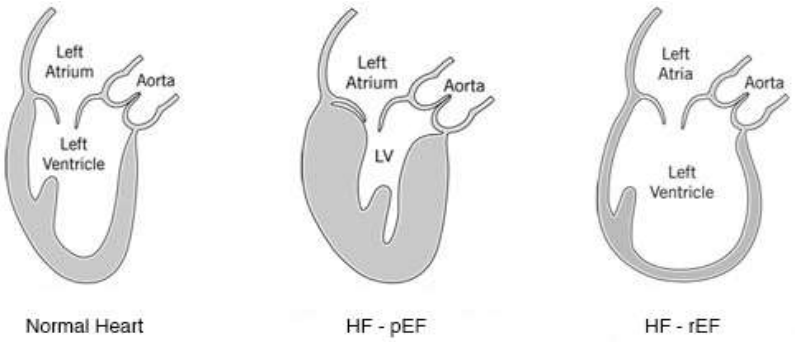
INTRODUCTION

Over the years, several different paradigms have guided our understanding of the pathophysiology and treatment of HF.The descriptive terminology, diagnostic techniques, and treatment of HF have undergone significant change in the past 20 years. Since 1994, a series of consensus and evidence based practice guidelines have been published in an effort to standardize HF management. Guidelines from European society of cardiology, American college of cardiology, Heart failure society of America, have been revised and updated to reflect ongoing changes in the management of HF. These guidelines use the four disease stages of HF first signed by ACC/AHA 2001 guidelines**.**



A recent study showing that use of guideline directed medical therapy (GDMT) improves mortality in patients with HFrEF reinforces the importance for clinicians to be familiar with these recommendations.—However, clinicians should also remember that these are only *guidelines* and that evaluation and treatment should be individualized for each patient.

Pathophysiology



In health, cardiac output at rest is approximately 5L /min with a mean heart rate of 70 beats per minute and stroke volume of 70ml, in heart failure the Ejection Fraction is reduced to below 45%, and when EF fall below 10%, patient have the added risk of thrombus formation with in the left ventricle and in most cases anticoagulation with warfarin is indicated.

In response to a decrease in cardiac output, a number of compensatory responses are activated in an attempt to maintain adequate cardiac output, including activation of the sympathetic nervous system (SNS) and the renin–angiotensin–aldosterone system (RAAS),Vasopressin, and numerous pro inflammatory cytokines, which may leads to vasoconstriction, sodium and water retention as well as ventricular hypertrophy/remodeling. These compensatory mechanisms are responsible for the symptoms of HF and contribute to disease progression.

HF patients are now broadly categorized into HF with a reduced EF (HFrEF; formerly *systolic failure*) or HF with a preserved EF (HFpEF; formerly *diastolic failure*). HF with a preserved ejection fraction can be defined as a condition in which myocardial relaxation and filling are impaired and incomplete. The ventricle is unable to accept an adequate volume of blood from the venous system. And in HfrEF (Systolic dysfunction) impaired contractility, and is reflected in a low EF and cardiac dilation.

The management of HFpEF differs from the management of HF with reduced EF (HFrEF) given differences in the evidence base for therapy. The results of clinical trials have demonstrated that while neuro humoral antagonists such as beta blockers, angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) as well as cardiac resynchronization are effective in HFrEF, these therapies do not decrease morbidity and mortality in HFpEF. These data suggest that there are fundamental differences in the pathophysiology underlying HFrEF versus HfpEF.

Overview of Treatment Principles

Improvement in symptoms and Prolongation of patient survival has been documented with a combination of ACEI or an ARBs, and a beta blocker, Diuretics are recommended for patients with sign of congestion, digoxin can be added any time to reduce symptoms and prevent hospitalization, and aldosterone antagonist is a fifth class of drug recommended for patients with advanced HF or after MI in the presence of symptoms or diabetes and a low EF. When ACE inhibitors are contraindicated or not tolerated, an ARB or the combination of hydralazine and Isosorbide dinitrate is a reasonable alternative.

Approach to Pharmacotherapy: (Practice points.)

The goals of therapy for the management of HF is to improve the patient's quality of life, relieve or reduce symptoms, prevent or minimize hospitalizations, slow progression of the disease, and prolong survival. Pharmacotherapy plays a key role in achieving these goals.

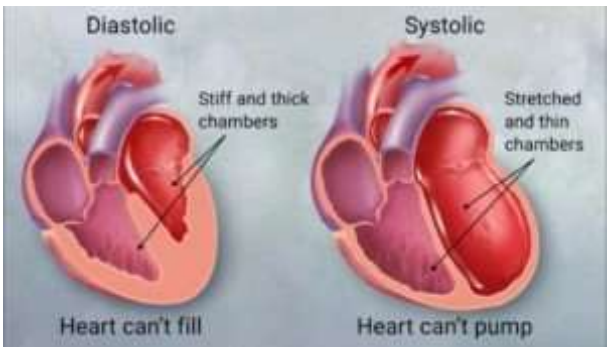
Diuretics

Excessive volume increases the work load of a compromised heart, and diuretic are an integral part of the therapy. They relieve pulmonary and peripheral edema within hour. However diuretic should not be used alone, they are ineffective in maintaining clinical stability for long periods without the addition of other drugs.

Once fluid overload has been resolved, many patients require chronic diuretic therapy to maintain euvolemic. Among the drugs used to manage HF, diuretics are the most rapid in producing symptomatic benefits. Diuretic therapy is usually initiated in low doses in the outpatient setting, with dosage adjustments based on symptom assessment and daily body weight. Change in body weight is a sensitive marker of fluid retention or loss, and it is recommended that patients monitor their status by taking daily morning body weights. In the acute situation doses of loop diuretics are titrated to produce a weight loss of 0.5–1 kg per day. Thiazides or the thiazide-like diuretic metolazone can be used in combination with loop diuretics to promote a very effective diuresis.

Furosemide is a commonly used loop diuretic because of clinical experience and low cost. Bumetanide and Torsemide are preferred in some settings because of more predictable absorption, ethacrynic acid does not contain a sulfonamide moiety, and it mainly reserved for patient with severe sulfonamide allergies to other loop diuretics.

Some patients respond promptly and vigorously to small oral doses of furosemide, whereas others require large IV doses to achieve only minimal diuresis. Part of these differences can be explained by the drugs pharmacokinetics



Mineralocorticoid (Spironolactone & eplerenone)

Aldosterone-mediated sodium retention and its key role in volume overload and edema have long been recognized as important components of the HF syndrome. Circulating aldosterone is increased in HF due to stimulation of its synthesis and release from the

adrenal cortex by angiotensin II and due to decreased hepatic clearance from reduced hepatic perfusion. Recent studies demonstrate direct effects of aldosterone on the heart that may be even more important than sodium retention in HF pathophysiology.

Current research shows that extra-adrenal production of aldosterone in the heart, kidneys, and vascular smooth muscle also contributes to the progressive nature of HF through target organ fibrosis and vascular remodeling. Aldosterone also may increase the risk of ventricular arrhythmias through a number of mechanisms, including creation of reentrant circuits as a result of fibrosis, inhibition of cardiac NE reuptake, depletion of intracellular potassium and magnesium, and impairment of parasympathetic traffic.

Clinical trials with the aldosterone antagonist's spironolactone and eplerenon showing significant reductions in morbidity and mortality in patients with HFrEF provide compelling evidence of the important role of aldosterone in the initiation and progression of this syndrome.

ACE inhibitors

Hypertension is the primary indication for all of the ACEIs, Not all ACEIs have an indication for Heart failure. The following ACEIs are considered first-line option to treat HF based on clinical trials: Captopril, Enalapril, Ramipril, Fosinopril, Lisinopril, Perindopril, Quinapril, and Trandolapril.

Balanced (arterial and venous) vasodilation with ACE inhibitors was the basis for initial clinical trials with these agents. Subsequent discovery that ACE inhibitors provided benefits beyond their vasodilating effects, followed by the positive results with β-adrenergic receptor blockers and aldosterone antagonists, by blocking the conversion of angiotensin I to angiotensin II by ACE, the production of angiotensin II and, in turn, aldosterone is decreased, but not completely eliminated, This decrease in angiotensin II and aldosterone attenuates many of the deleterious effects of these neurohormones that drive HF progression including ventricular remodeling, myocardial fibrosis, myocyte apoptosis, cardiac hypertrophy, NE release, vasoconstriction, and sodium and water retention.
The persistence of clinical benefits with ACE inhibitors despite the fact that angiotensin II and aldosterone levels return to pretreatment levels in some patients suggests these are potentially important effects.

The most common cause of HFrEF is ischemic heart disease, where MI results in loss of myocytes, followed by ventricular dilation and remodeling. Captopril, Ramipril, and trandolapril all benefit post-MI patients whether therapy is initiated early or late after the infarct.

ACE inhibitors administered after MI improve overall survival, decrease development of severe HF, and reduce reinfarction and HF hospitalization rates. Post-MI patients without HF symptoms or reduced LVEF (Stage B) should also receive ACE inhibitors to prevent the development of HF and to reduce mortality.

Chronic kidney disease should not be an absolute contraindication to ACE inhibitor use in patients with reduced LVEF. However, these patients should be monitored carefully for the development of worsening renal function and/or hyperkalemia with special attention to risk factors associated with this complication of ACE inhibitor therapy.

Current Guidelines recommend that all patients with HFrEF, regardless of whether or not symptoms are present, should receive ACE inhibitors, unless there are contraindications.

Angiotensin II Receptor Blocker (ARBs)

ACE inhibitors decrease angiotensin II production in the short term, but these agents do not completely suppress generation of this hormone and angiotensin II can be formed in a number of tissues, including the heart, through non-ACE-dependent pathways (eg, chemise, cathepsin, and kallikrein). By blocking the angiotensin II receptor subtype, AT1, ARBs attenuate the deleterious effects of angiotensin II on ventricular remodeling, regardless of the site of origin of the hormone. Since ARBs do not inhibit the ACE enzyme, these agents do not affect bradykinin, which is linked to ACE inhibitor cough and angioedema. Although a number of ARBs are currently available, candesartan, losartan, or valsartan are recommended by the guidelines as the efficacy of these agents has been demonstrated in clinical trials. In these studies, ARBs reduced mortality and hospitalizations and improved symptoms.

ARBs are not an alternative in patients with hypotension, hyperkalemia, or renal insufficiency secondary to ACE inhibitors because they are as likely to cause these adverse effects. Also, the combined use of ACE inhibitors, ARBs, and aldosterone antagonists is not recommended because of the increased risk of renal dysfunction and hyperkalemia.

Importance of Beta blocker in HF

The use of three beta blockers (Bisoprolol, Metoprolol succinate, or Carvedilol) is associated with a consistent 30% reduction in mortality and a 40% reduction in hospitalizations in patient with HF.

The ACC/AHA guidelines recommend Bisoprolol, Metoprolol succinate, or Carvedilol for all patient with HFrEF unless there is a contraindication to their use. Patient should receive beta blocker to slow the rate of disease progression and reduce the risk of sudden death. If patient taking low dose of an ACEI, the addition of beta blocker produce a greater reduction in symptoms and in the risk of death than an increase in the dose of an ACEI.

Treatment with beta blocker should be initiated at low doses, followed by gradual increments in dose every 2 weeks as tolerated by the patient. Patient should be monitored daily for changes in vital signs, (Pulse and BP), bradycardia, heart block and hypotension can be asymptomatic and require no intervention other than instructing the patient not to arise too quickly from a lying position to avoid postural changes. If either of these complications is accompanied by dizziness, lightheadedness, or blurred vision, it may be necessary to reduce the dose of beta blocker.

Because initiation of beta blocker therapy can also cause fluid retention, beta blockers should only be started if the patient is euvolemic.

Carvedilol is a beta blocker with some alpha blocking activity, it is also having antioxidant effects, which can protect against loss of cardiac myocytes and scavenge oxygen free radicals that are thought to potentiate myocardial necrosis. Taking Carvedilol with food slow the rate of absorption and reduces the incidence of orthostatic hypotension.

Side effect and patient tolerability are similar among beta blockers in most trial. Carvedilol cause more hypotension and dizziness than Metoprolol and Bisoprolol. Thus Metoprolol or Bisoprolol may be preferred in patient with hypotension or with complaint of dizziness, conversely, Carvedilol may be preferred in patients with inadequately controlled HTN.

Currently Nebivolol, Bisoprolol, and Carvedilol are the only licensed beta blockers for the treatment of HF in UK.

Digoxin

The primary benefits of digoxin in systolic HF was assumed to be an increase in the force of contraction of the failing heart to increase EF and CO. Monotherapy with digoxin or in combination with only diuretics is no longer recommended. Digoxin can also be considered in patients with HF who also have atrial fibrillation, although beta blocker may be more effective than dioxin in controlling the ventricular response, especially during exercise.

In patients with atrial fibrillation and a rapid ventricular response, the historic practice of increasing digoxin doses (and concentrations) until rate control is achieved is no longer recommended. Digoxin alone is often ineffective to control ventricular response in patients with atrial fibrillation and increasing the dose only increases the risk of toxicity.

Nitrates and Hydralazine

Nitrates and hydralazine were originally combined in the treatment of HFrEF because of their complementary hemodynamic actions. By serving as a nitric oxide donor, nitrates increase nitric oxide bioavailability and hydralazine reduces oxidative stress.

Combined afterload and preload reduction is clearly of benefit improving symptoms and enhancing long term survival. Nitrates alone are indicated for those patients with sign and symptoms of pulmonary and venous congestion. Use of an arterial dilator is beneficial in a patient with high SVR and low CO.

Hydralazine- Isosorbide combination provides more improvement in exercise tolerance. Generally the use of the two drugs together is not accompanied by reflex tachycardia or hypotension. Hydralazine and a nitrate might be reasonable in patients unable to tolerate either an ACE inhibitor or ARB because of renal insufficiency, hyperkalemia, or possibly hypotension.

Ivabradine: Elevated resting heart rate (greater than 70-80 BPM) is emerging as an important independent risk factor for adverse outcomes in patients with HF and is associated with increased hospital admissions, disease progression, and mortality in April 2015, FDA approved **Ivabradine** for symptomatic chronic HF with LVEF less than 35%, to reduce the risk of hospitalization for worsening HF in Adult, This agent has a unique pharmacology as it blocks the I_f current in the Sino atrial node that is responsible for controlling the heart rate.by blocking this current, ivabradine slows the spontaneous depolarization of the sinus node resulting in a dose-dependent slowing of the heart rate. Ivabradine's effects are specific to the I_f current and this agent does not affect BP, myocardial contractility, or AV conductions.

Ivabradine is a best option for s patients with chronic HFrEF (with LVEF ≤35 percent) in sinus rhythm with a resting heart rate ≥70 bpm and who are either on a maximum tolerated dose of beta blocker or have contraindication to beta blocker use.

Neprilysin Inhibitor: In heart failure, addition to RAAS, and sympathetic nervous system the natriuretic peptide (NP) system play a fundamental role among compensating mechanism. Dual inhibitor of angiotensin II receptor and neprilysin, may benefit millions of patients living with HF in the future.

Calcium Channel Blocker

Only amlodipine and felodipine have been documented to be safe in HF, but only a small subset of patients with non-ischemic dilated cardiomyopathy actually had a beneficial effect of improved survival with amlodipine. Calcium channel blocker other than amlodipine and felodipine are contraindicated in patient with systolic dysfunction. On the other hand, verapamil and Diltiazem are safe to use in HFPEF and may improve symptoms by reducing HR and allowing more time to fill the ventricle.

ROLE OF PHARMACIST

Pharmacists can play an important role in the multidisciplinary team management of HF taking on such responsibilities as medication evaluation and therapeutic recommendations, improved use of GDMT, patient education, and follow-up telephone monitoring to reduce hospitalizations for HF, evaluation of adverse drug events, and medication errors.

Educate the patient to understand the need for treatment and the benefits and risks offered by prescribed medication before concordance with a treatment plan can be reached, appropriate patient education is necessary to encourage an understanding of their condition and how prescribed drug treatment will work and affect their daily lives.

Patients should be made aware that diuretics will increase urine production, and that doses are usually timed for the morning to avoid nocturea. Counsel the patient to monitor and record their weight on daily basis, to detect fluid retention and modify Diuretic dosages. Timing of doses is also important, if a nitrate regimen is being used, then patients must be made aware that the last dose of the nitrate should be taken mid to late afternoon to ensure that a nitrate free period occur overnight, reducing the risk of nitrate tolerance. Where renal function is compromised, careful attention to dosage selection is required for drug excreted largely unchanged in the urine.

Number of issues around the safe use of medication must be considered. There is an increased risk of drug-drug and drug-disease interactions, it is important to aware of clinically important interactions and to investigate potentially problematic combinations, as well as to regularly assess the patient for any signs or symptoms of drug therapy problems, monitoring for problems such as negative inotropic effects, excessive blood pressure reduction, salt and fluid retention should be undertaken and, where appropriate laboratory measurement of serum drug concentration (Digoxin) or physiological markers (Potassium, creatinine) should be performed to confirm or exclude adverse effect.

CONCLUSION

Heart failure is one of the most common and costly diseases, and the number of HF-related deaths is increasing. Pharmacists are integral to multidisciplinary TOC teams in HF. During the transition from hospital to ambulatory home- or community-based care, pharmacy services (including medication reconciliation, identification and prevention of adverse drug events, suggestions for improving medication access, and patient education) can improve outcomes and decrease the risk for hospitalization. Cohesive multidisciplinary team approaches can improve medication adherence and provide a trusted resource for patients' questions. Novel technologies and expanded access to pharmacy services can improve current limitations of transitional care in HF and other chronic diseases.

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