Therapy of Chronic Heart Failure

Yacoub Irshaid, MD, PhD, ABCP
Department of Pharmacology, Faculty of Medicine

Chronic Heart Failure

- **Heart failure (HF) is a progressive clinical syndrome associated with impairment of the ability of the ventricle to fill with or eject blood.**
- **HF may be caused by an abnormality in systolic function, diastolic function, or both.**
- **The leading causes of HF are coronary artery disease and hypertension.**

Chronic Heart Failure

- **In heart failure with reduced ejection fraction (HFrEF) there is a decrease in cardiac output, resulting in activation of compensatory responses that attempt to maintain adequate cardiac output.**

Chronic Heart Failure

- **These responses include: activation of the sympathetic nervous system (SNS) and the renin–angiotensin–aldosterone system (RAAS), resulting in vasoconstriction, sodium and water retention, ventricular hypertrophy and remodeling.**

Chronic Heart Failure

- **Pharmacotherapy targeted at antagonizing the neurohormonal activation has slowed the progression of HFrEF and improved survival.**
- **Heart failure with preserved ejection fraction (HFpEF) is primarily due to diastolic dysfunction of the heart (or disturbances in relaxation).**
- **It may be treated differently from HFrEF.**

Causes of Heart failure

Causes of systolic dysfunction (decreased contractility):

1) **Reduction in muscle mass (myocardial infarction).**
2) **Dilated cardiomyopathies.**
3) **Ventricular hypertrophy.**
4) **Pressure overload (systemic or pulmonary hypertension, aortic or pulmonary valve stenosis).**
5) **Volume overload (valvular regurgitation, shunts, high-output states).**

Causes of Heart failure

Causes of diastolic dysfunction (restriction in ventricular filling):

1) **Increased ventricular stiffness.**
2) **Ventricular hypertrophy (hypertrophic cardiomyopathy, others).**
3) **Infiltrative myocardial diseases (amyloidosis, sarcoidosis, endomyocardial fibrosis).**
4) **Myocardial ischemia and infarction.**
5) **Mitral or tricuspid valve stenosis.**
6) **Pericardial disease (pericarditis, pericardial tamponade).**

Factors Precipitating/Exacerbating Heart Failure

A. **Cardiac events:** myocardial ischemia and infarction, atrial fibrillation, uncontrolled HTN.
B. **Noncardiac events:** pulmonary infections, pulmonary embolus, diabetes, worsening renal function, **hypothyroidism, and hyperthyroidism**.
C. **Nonadherence** with prescribed HF medications or with dietary recommendations, such as sodium intake and fluid restriction.

Factors Precipitating/Exacerbating Heart Failure

D. **Drugs can precipitate or exacerbate HF by one or more of the following mechanisms:**

1) **Negative inotropic effects.**
2) **Direct cardiotoxicity.**
3) **Increased sodium and/or water retention.**

Factors Precipitating/Exacerbating Heart Failure

Negative Inotropic Effect:

- **Antiarrhythmics (disopyramide, flecainide, propafenone).**
- **Beta-blockers (propranolol, metoprolol, carvedilol).**
- **Calcium channel blockers (verapamil, diltiazem).**

Cardiotoxicity:

Doxorubicin, epirubicin, daunomycin, ethanol, cyclophosphamide, trastuzumab, bevacizumab, ifosfamide, lapatinib, sunitinib, imatinib, amphetamines, cocaine.

Factors Precipitating/Exacerbating Heart Failure

Sodium and Water Retention:

NSAIDs, COX_2-inhibitors, rosiglitazone and pioglitazone, glucocorticoids, androgens and estrogens, high dose salicylates, high sodium-containing drugs (ticarcillin disodium)

Factors Precipitating/Exacerbating Heart Failure

- **Many of these precipitating factors are preventable.**
- **Medication history and discontinuation of medications known to exacerbate HF are part of therapy.**

Ventricular Hypertrophy and Remodeling

- **Left ventricular hypertrophy and remodeling are key elements in the pathogenesis of progressive myocardial failure.**
- **Ventricular remodeling is a broad term describing changes in both myocardial cells and extracellular matrix that result in changes in the size, shape, structure, and function of the heart.**

Ventricular Hypertrophy and Remodeling

- These progressive changes result in a change in shape of the left ventricle from an ellipse to a sphere.
- The change in ventricular size and shape further depresses the mechanical performance of the heart, increases regurgitant flow through the mitral valve, and thus, sustains progression of remodeling.

Ventricular Hypertrophy and Remodeling

- **Ventricular hypertrophy and remodeling can follow any condition that causes myocardial injury.**
- **The onset of the remodeling process precedes the development of HF symptoms.**

Ventricular Hypertrophy and Remodeling

- **The progression of the remodeling process leads to reductions in myocardial systolic and/or diastolic function, which results in further myocardial injury, perpetuating the remodeling process and the decline in left ventricular performance.**

Ventricular Hypertrophy and Remodeling

- **Angiotensin II, NE, endothelin, aldosterone, vasopressin, and numerous inflammatory cytokines, play an important role in initiating the signal transduction cascade responsible for ventricular remodeling.**
- **These mediators are also toxic to other organs and provide evidence that HF is a systemic as well as a cardiac disorder.**

Therapy of Chronic Heart Failure

Desired Outcomes:

- **The goals of therapy in management of chronic HF are to:**

1) **Improve the patient's quality of life**
2) **Relieve or reduce symptoms**
3) **Prevent or minimize hospitalizations**
4) **Slow progression of the disease**
5) **Prolong survival.**

Therapy of Chronic Heart Failure

- **The general principles used to guide the treatment of HFrEF are based on numerous large, randomized, double-blind, multicenter clinical trials.**
- **Until recently, NO such randomized trials had been performed in patients with HFpEF.**
- **The guidelines for the management of HFpEF are based primarily on studies in relatively small groups of patients and on clinical experience.**

Therapy of Chronic Heart Failure

General Measures:

- **The complexity of the HF syndrome necessitates a comprehensive approach to management.**
- **This approach includes:**

a) **Accurate diagnosis.**

b) **Identification and treatment of risk factors.**

c) **Elimination or minimization of precipitating factors.**

d) **Appropriate pharmacologic and nonpharmacologic therapy.**

e) **Close monitoring and follow up.**

Therapy of Chronic Heart Failure

- **The first step in management of chronic HF is to determine the etiology and/or precipitating factors.**
- **Appropriate treatment of underlying disorders (hyperthyroidism, valvular heart disease, ..etc) may avoid the need for specific HF treatment.**
- **Revascularization or anti-ischemic therapy in patients with CHD may reduce HF symptoms.**
- **Drugs that aggravate HF should be discontinued if possible.**

Therapy of Chronic Heart Failure

- **Restriction of physical activity reduces cardiac workload and is recommended for all patients with acute congestive symptoms, until patient's symptoms have stabilized and excess fluid is removed.**
- **Exercise training may improve functional status & quality of life, and may reduce hospitalizations and death from cardiovascular causes.**

Therapy of Chronic Heart Failure

- **Restriction of dietary sodium and fluid intake is an important life-style intervention for both HFrEF and HFpEF, to allow use of lower and safer diuretic doses.**
- **In patients with hyponatremia (Na <130 mEq/L) or those with persistent volume retention despite high diuretic doses and sodium restriction, daily fluid intake should be limited to 2 L/day from all sources.**

Therapy of Chronic Heart Failure

- **You should be careful with sodium and fluid restriction in patients with HFpEF, because excessive restriction can lead to hypotension, low-output state, and/or renal insufficiency.**

Therapy of Chronic Heart Failure

General Approach to Treatment:

- **The ACC/AHA treatment guidelines are organized around the four identified stages of HF.**

New York Heart Association Functional Classification

Functional classes:

A. **Patients with cardiac disease but without limitations of physical activity. Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation.**

B. **Patients with cardiac disease that results in slight limitations of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina.**

C. **Patients with cardiac disease that results in marked limitation of physical activity. Although patients are comfortable at rest, less than ordinary activity will lead to symptoms.**

D. **Patients with cardiac disease that results in an inability to carry on physical activity without discomfort. Symptoms of congestive heart failure are present even at rest. With any physical activity, increased discomfort is experienced.**

Therapy of Chronic Heart Failure

Heart Failure with Preserved Ejection Fraction:

- **Less information on the treatment of HFpEF is available.**
- **Guidelines recommend treating co-morbid conditions by controlling HR and BP, alleviating causes of myocardial ischemia, reducing volume, and restoring and maintaining sinus rhythm in patients with atrial fibrillation.**

Treatment Approach of HFpEF

Symptom-targeted treatment	Rationale	Agent
Decrease pulmonary venous pressure	Reduce left ventricular volume	Diuretics, nitrates, salt restriction
Reduce myocardial oxygen demand	Reduce heart rate, control blood pressure	B-blockers, (verapamil, diltiazem), (ACEIs, ARB), other calcium channel blockers
Maintain atrial contraction	Restore sinus rhythm	Cardioversion of atrial fibrillation
Improve exercise tolerance		Use positive inotropic agents with caution

Disease-targeted treatment		
Prevent or treat myocardial ischemia		B-blockers, nitrates, (verapamil, diltiazem)
Prevent or regress ventricular hupertrophy		Antihypertensive therapy
Mechanism-targeted treatment		
Modify myocardial and extramyocardial mechanisms		Possibly (ACEIs, ARB), diuretics, spironolactone
Modify intracellular and extracellular mechanisms		Possibly (ACEIs, ARB), diuretics

Therapy of Chronic Heart Failure

Diuretics:

- **A loop or a thiazide diuretic should be considered for patients with volume overload.**
- **Caution is warranted NOT to lower preload excessively, which may reduce stroke volume and cardiac output.**
- **Aldosterone antagonists can be considered to reduce the risk of hospitalization in patients that do NOT have contraindications or who are NOT at risk of hyperkalemia development.**

Therapy of Chronic Heart Failure

ACE inhibitors:

- **ACE inhibitors should be considered in all patients who have symptomatic atherosclerotic cardiovascular disease or diabetes and one additional risk factor.**
- **Angiotensin receptor blockers are alternatives in patients who are intolerant of ACE inhibitors.**

Therapy of Chronic Heart Failure

β-Blockers:

- **They should be considered in patients with one or more of the following conditions:**

a) **Myocardial infarction.**

b) **Hypertension.**

c) **Atrial fibrillation requiring ventricular rate control.**

Therapy of Chronic Heart Failure

Calcium channel blockers:

- **In patients with atrial fibrillation who are intolerant to or have NOT responded to a β-blocker; diltiazem or verapamil may be considered.**
- **A nondihydropyridine or dihydropyridine calcium channel blocker can be considered for angina and hypertension.**

Therapy of Chronic Heart Failure

Treatment of Stage A Heart Failure:

- **Risk factors (HTN, dyslipidemia, diabetes, obesity, metabolic syndrome, smoking, and coronary artery disease) identification and treatment to prevent the development of structural heart disease and subsequent HF is important.**
- **Risk factors act synergistically to develop both HFrEF and HFpEF.**
- **ACE inhibitors (or ARBs) and statins are recommended for HF prevention in patients with multiple cardiovascular risk factors.**

Therapy of Chronic Heart Failure

Treatment of Stage B Heart Failure:

- **Patients in Stage B have structural heart disease (left ventricular hypertrophy, recent or old MI, valvular heart disease, or LVEF < 0.4), but do NOT have HF symptoms.**
- **Treatment aims at minimizing additional injury and preventing or slowing the remodeling process.**
- **In addition to management of risk factors, ACEIs (or ARBs) and β-blockers are important components of therapy, to prevent development of HF, whether or NOT they have had an MI.**
- **Patients with a previous MI and reduced LVEF should also receive an ACEI (or ARB), evidence-based β-blocker, and a statin.**

Therapy of Chronic Heart Failure

Treatment of Stage C HF:

- **Patients with structural heart disease and previous or current symptoms are classified as Stage C and can have HFrEF or HFpEF.**
- **In addition to management of risk factors, patients with HFrEF in Stage C should be treated with an ACEI (or ARB) and an evidence-based β-blocker.**
- **These drugs slow HF progression, reduce morbidity and mortality, and improve symptoms.**
- **Loop diuretics, aldosterone antagonists, and hydralazine–isosorbide dinitrate may be used in these patients.**

Therapy of Chronic Heart Failure

- Digoxin can be considered in selected patients, as can two newly approved medications, ivabradine and sacubitril/valsartan.
- **Nonpharmacologic therapy with devices such as an implantable cardiovertor-defibrillator (ICD) or cardiac resynchronization therapy (CRT) with a biventricular pacemaker is also indicated in certain patients with HFrEF in Stage C.**

Therapy of Chronic Heart Failure

Treatment of Stage D HFrEF:

- **Stage D HF is advanced, refractory, or end-stage HF.**
- **Patients should be referred to HF management programs to receive specialized therapies: mechanical circulatory support, continuous IV positive inotropic therapy, and cardiac transplantation in addition to standard treatments outlined in stages A-C.**
- **Restriction of sodium and fluid intake, high doses of diuretics, combination therapy with a loop and thiazide diuretic, or ultrafiltration to remove excess fluid may be required.**

Therapy of Chronic Heart Failure

- **Patients in Stage D may be less tolerant to ACE inhibitors (hypotension, worsening renal insufficiency) and β-blockers (worsening HF).**
- **Initiation of therapy with low doses, slow upward dose titration, and close monitoring for signs and symptoms of intolerance are essential.**

Therapy of Chronic Heart Failure

- **With a few exceptions, many of the drugs used to treat HFrEF are the same as those for treatment of HFpEF.**
- **The rationale for their use, and the dosing regimen may be different.**
- **β-blockers are recommended for the treatment of both HFrEF and HFpEF.**

a) **In HFpEF, β-blockers are used to decrease HR, prolong diastole, and modify hemodynamic response to exercise.**

b) **In HFrEF, β-blockers are used in the long term to improve the inotropic state and modify LV remodeling.**

Therapy of Chronic Heart Failure

- Diuretics also are used in the treatment of both HFrEF and HFpEF.
- The doses of diuretics used to treat HFpEF are much smaller than those used to treat HFrEF.
- Antagonists of the RAAS are useful in lowering BP and reducing LVH.
- Some drugs, are used to treat either HFrEF or HFpEF:
- Calcium channel blockers (diltiazem, amlodipine, and verapamil) may be useful in the treatment of HFpEF.
- They have little utility in the treatment of HFrEF.

Diuretics

- **Diuretic therapy and sodium restriction, are recommended in all patients with fluid retention.**
- **Once fluid overload has been resolved, many patients require chronic diuretic therapy to maintain euvolemia.**

Benefits:

1. **Reduction of symptoms associated with fluid retention**
2. **Improvement of exercise tolerance and quality of life**
3. **Reduction of hospitalizations from HF.**
4. **Reduction of pulmonary and peripheral edema through reduction of preload.**

Diuretics

- **Diuretics do NOT prolong survival or alter disease progression.**
- **Over-diuresis leads to reduction in cardiac output, and renal hypoperfusion.**
- **Hypotension or worsening renal function (increased creatinine) may be indicative of volume depletion and necessitate a reduction in the diuretic dose.**
- **Diuretic therapy is usually initiated at low doses in the outpatient setting, with dosage adjustments based on symptom assessment and daily body weight.**

Diuretics

- **Over-diuresis may produce hypotension with ACE inhibitor or β-blocker therapy.**
- **In patients with HFpEF, diuretic treatment should be initiated at low doses in order to avoid hypotension and fatigue.**
- **Hypotension can be a significant problem in the treatment of HFpEF because a small change in volume causes a large change in filling pressure and cardiac output.**

Diuretics

- **After the acute treatment of HFpEF has been completed, long-term treatment should include small - moderate oral doses of diuretics (furosemide 20-40 mg/day, chlorthalidone 25-100 mg, or hydrochlorothiazide 12.5-25 mg/day).**

Thiazide diuretics:

- **Thiazide or the thiazide-like diuretics (metolazone, indapamide) can be used in combination with loop diuretics to promote a very effective diuresis.**

Diuretics

- **Thiazide diuretics may be preferred in patients with mild fluid retention and elevated BP because of their more persistent antihypertensive effects compared with loop diuretics.**

Loop Diuretics:

- **Loop diuretics are usually necessary to restore and maintain euvolemia in HF.**
- **Probenecid or organic by-products of uremia can inhibit delivery of loop diuretics to their site of action and decrease effectiveness.**

Diuretics

- **Loop diuretics induce a prostaglandin-mediated increase in renal blood flow, which contributes to their natriuretic effect.**
- **Coadministration of NSAIDs, including COX-2 inhibitors, blocks the prostaglandin-mediated effect and can diminish diuretic efficacy.**
- **Unlike thiazides, loop diuretics maintain their effectiveness in the presence of impaired renal function, although higher doses are necessary to obtain adequate delivery of the drug to the site of action.**

ACE Inhibitors

- **ACE inhibitors are key component of therapy of patients with HFrEF.**
- **They decrease the production of angiotensin II and aldosterone.**
- **This decrease in angiotensin II and aldosterone attenuates ventricular remodeling, myocardial fibrosis, myocyte apoptosis, cardiac hypertrophy, norepinephrine release, vasoconstriction, and sodium and water retention.**
- **Bradykinin is increased by ACE inhibitors along with the release of vasodilatory prostaglandins and histamine.**

ACE Inhibitors

- **The most common cause of HFrEF is ischemic heart disease, which 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

- **ACE inhibitors may have favorable effects on concomitant disorders (HTN, previous MI).**
- **ACE inhibitors lower glomerular capillary pressure, decrease proteinuria, and may halt progressive glomerular injury and loss of renal function in experimental chronic renal failure (CRF).**

ACE Inhibitors

- **However, these patients should be monitored carefully for the development of worsening renal function and/or hyperkalemia.**
- **ACE inhibitors improve survival by 20 - 30% compared with placebo.**

Angiotensin II Receptor Blockers

- **Angiotensin II can be formed in a number of tissues, including the heart, through non-ACE-dependent pathways (chymase, cathepsin, and kallikrein).**
- **By blocking the angiotensin II receptor subtype, AT1, ARBs attenuate the effects of angiotensin II on ventricular remodeling, regardless of the site of origin of the hormone.**
- **These agents do NOT affect bradykinin, which is linked to ACEIs-induced cough and angioedema.**

Angiotensin II Receptor Blockers

- **ARBs include candesartan, losartan, or valsartan which can reduce mortality and hospitalizations and improve symptoms.**
- **ARBs are indicated in patients who are unable to tolerate cough produced by ACE inhibitors.**
- **The role of ARBs in the treatment of HFpEF is less clear.**

β-Blockers

- β-blockers reduce morbidity and mortality in patients with HFrEF.
- They should be used in all stable patients with HF and a reduced left ventricular EF in the absence of contraindications or a clear history of β-blocker intolerance.
- Patients should receive a β-blocker when their symptoms are mild or well-controlled with diuretic and ACE inhibitor therapy.
- They are also recommended for asymptomatic patients with a reduced left ventricular EF to decrease the risk of progression to HF.

β-Blockers

- **Three β-blockers have been shown to significantly reduce mortality compared with placebo: carvedilol, metoprolol succinate (CR/XL), and bisoprolol.**
- **They have been shown to decrease ventricular mass, improve the sphericity of the ventricle, and reduce systolic and diastolic volumes.**
- **These effects are collectively called reverse remodeling, which means return of the heart toward more normal size, shape, and function.**

β-Blockers

- **Initiating a β-blocker first may be of benefit for patients with evidence of excessive SNS activity (tachycardia), and for patients whose renal function or potassium concentrations preclude starting an ACE inhibitor (or ARB) at that time.**
- **However, the risk for decompensation during β-blocker initiation may be greater in the absence of preexisting ACE inhibitor therapy, and careful monitoring is essential.**

β-Blockers

- **β-Blockers favorable effects include: antiarrhythmic effects, attenuating or reversing ventricular remodeling, decreasing myocyte death from catecholamine-induced necrosis or apoptosis, preventing fetal gene expression, improving left ventricular systolic function, decreasing HR and ventricular wall stress thereby reducing myocardial oxygen demand, and inhibiting plasma renin release.**
- **β-blockers should NOT be started in patients on IV inotropic support.**

β-Blockers

- **They should be started in very low doses with slow upward dose titration (not < 2 weeks), and close monitoring to minimize acute decompensation.**
- **Dose up-titration is a long and gradual process.**
- **Response to therapy may be delayed and HF symptoms may actually worsen during the initiation period.**
- **β-blockers are recommended as standard therapy for all patients with HFrEF, regardless of the severity of their symptoms.**

β-Blockers

- In patients with HFpEF, β-blockers may help to lower and maintain low pulmonary venous pressure by decreasing HR and increasing the duration of diastole.
- Tachycardia is poorly tolerated in patients with HFpEF because rapid HRs cause an increase in myocardial oxygen demand and a decrease in coronary perfusion time, which can promote ischemia even in the absence of epicardial CAD.

β-Blockers

- **A rapid rate reduces diastolic filling time.**
- **However, excessive bradycardia can result in a fall of cardiac output despite an increase in LV filling.**

Aldosterone Antagonists

- **Spironolactone and eplerenone inhibit sodium reabsorption and potassium excretion, thus, they have potassium-sparing effects (and protons).**
- **Aldosterone antagonists inhibit cardiac extracellular matrix and collagen deposition, thereby attenuating cardiac fibrosis and ventricular remodeling.**
- **They attenuate the systemic pro-inflammatory state, atherogenesis, and oxidative stress caused by aldosterone.**

Aldosterone Antagonists

- **Spironolactone reduces mortality by 30% and eplerenone by 15% in HFrEF.**
- **The most common adverse effects of spironolactone are gynecomastia and hyperkalemia, while that of eplerenone is hyperkalemia.**
- **There are NO clear guidelines on aldosterone antagonist use for patients with HFpEF.**

Aldosterone Antagonists

Factors contributing to the high incidence of Hyperkalemia with aldosterone antagonists:

1) **The initiation of aldosterone antagonists in patients with impaired renal function or high serum K^+.**
2) **The failure to decrease or stop potassium supplements when starting aldosterone antagonists.**
3) **Diabetes mellitus.**
4) **High potassium intake with food.**
5) **Concomitant use of ACE inhibitors /ARBs and NSAIDs.**

Aldosterone Antagonists

Strategies for reducing the risk for hyperkalemia with aldosterone antagonists:

1. **Avoid starting aldosterone antagonists in patients with any of the following:**

a) **Serum creatinine concentration >2.0 mg/dL in women or >2.5 mg/dL in men or a CrCL <30 mL/min.**

b) **Recent worsening of renal function.**

c) **Serum K^+ >5 mEq/L.**

d) **History of severe hyperkalemia.**

Aldosterone Antagonists

2. **Start with low doses (12.5 mg/day for spironolactone and 25 mg/day for eplerenone) especially in the elderly, patients with diabetes, or a CrCL <50 mL/min.**
3. **Decrease or discontinue potassium supplements when starting an aldosterone antagonist.**
4. **Avoid concomitant use of NSAIDs (COX-1 or COX-2 inhibitors.**
5. **Avoid concomitant use of high-dose ACE inhibitors or ARBs.**

Aldosterone Antagonists

6. Monitor serum K^+ and renal function within 3 days and 1 week after the initiation or dose titration of an aldosterone antagonist or any other medication that could affect potassium.
7. Thereafter, K^+ and renal function should be monitored monthly for the first 3 months, and then every 3 months.
8. If K^+ exceeds 5.5 mg/dL at any point during therapy, discontinue any potassium supplementation or, in the absence of potassium supplements, reduce or stop aldosterone antagonist therapy.

Aldosterone Antagonists

9. **Counsel patients to:**

a) **Limit intake of high potassium-containing foods and salt substitutes.**

b) **Avoid the use of over-the-counter NSAIDs.**

c) **Temporarily discontinue aldosterone antagonist therapy if diuretic therapy is interrupted.**

Drug Therapies for Selected Patients with HFrEF

Nitrates and Hydralazine:

- **Nitrates and hydralazine are combined in the treatment of HFrEF because of their complementary hemodynamic actions.**
- **Nitrates cause venodilation and decrease preload.**
- **Hydralazine is a direct-acting arterial vasodilator causing a decrease in afterload.**

Drug Therapies for Selected Patients with HFrEF

- **Hydralazine and ISDN reduce all-cause mortality.**
- **By serving as a nitric oxide donor, nitrates increase nitric oxide bioavailability.**
- **Nitric oxide attenuates myocardial remodeling by reducing cardiac myocyte hypertrophy, cardiac dilation and mortality.**
- **Thus it may play a protective role in HF.**

Drug Therapies for Selected Patients with HFrEF

- **Hydralazine reduces oxidative stress.**
- **The combination requires frequent dosing three times daily.**
- **In the absence of another indication for nitrate therapy (angina), nitrates provide limited benefits to patients with HFpEF.**

Drug Therapies for Selected Patients with HFrEF

ARB/Neprilysin Inhibitor (fixed dose combination):

- **The natriuretic peptides ANP and BNP cause vasodilation, natriuresis, and diuresis.**
- **They inhibit renin secretion, aldosterone production and attenuate ventricular hypertrophy and fibrosis.**
- **Neprilysin is a zinc-dependent metalloprotease that breaks down the natriuretic peptides ANP & BNP bradykinin and other peptides.**
- **Neprilysin is also involved in the clearance of amyloid-β from the brain and CSF.**

Drug Therapies for Selected Patients with HFrEF

- **Valsartan/Sacubitril can be used for the treatment of patients with HFrEF.**
- **Sacubitril is prodrug, which inhibits the action of neprilysin.**
- **Natriuretic pepetides are beneficial because they cause vasodilation, increased glomerular filtration, natriuresis, and diuresis.**
- **The combination reduces mortality and hospitalizations in patients with HFrEF.**

Drug Therapies for Selected Patients with HFrEF

Adverse Effects:

- **Hypotension, dizziness, hyperkalemia, worsening renal function, and cough – most common.**
- **Angioedema.**

Drug interactions:

1. **Should NOT be used concurrently with ACE inhibitors or ARBs. ACEIs should be discontinued 36 hours prior to initiating sacubitril/valsartan.**
2. **Should be avoided with aliskiren (direct renin inhibitor).**

Drug Therapies for Selected Patients with HFrEF

Sacubitril/valsartan contraindications:

1. **Patients with history of angioedema**
2. **Pregnancy**
3. **Hyperkalemia**
4. **Renal artery stenosis**
5. **Severe hepatic impairment**
6. **Renal dysfuntion**
7. **Diabetic patients taking aliskiren due to an increased risk of hypotension, hyperkalemia, and renal impairment.**

Drug Therapies for Selected Patients with HFrEF

Ivabradine:

- Ivabradine blocks the I_f current in the SA 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 it does not affect myocardial contractility, or AV conduction.

Drug Therapies for Selected Patients with HFrEF

- **Used for patients with HFrEF in sinus rhythm with a heart rate ≥ 70 beats/min that are receiving maximally tolerated treatment with β-blockers or have contraindications to β-blockers.**
- **Ivabradine is extensively metabolized by intestinal and hepatic CYP3A4.**
- **Co-administration with CYP3A4 inhibitors (itraconazole, macrolide antibiotics, HIV protease inhibitors, verapamil, diltiazem, grapefruit juice) is contraindicated because of the large increase in exposure and potential for bradycardia.**

Drug Therapies for Selected Patients with HFrEF

- **Use with CYP3A inducers (St. John's wort, rifampin, phenytoin) should be avoided.**
- **Because QT interval prolongation can be increased by slower heart rates, ivabradine should be used cautiously, if at all, with other agents known to prolong the QT interval.**

Adverse Effects:

1. **Bradycardia in ~ 10% of patients.**
2. **Effects on vision primarily manifesting as phosphenes (transient brightness in portions of the visual field).**
3. **Atrial fibrillation.**

Drug Therapies for Selected Patients with HFrEF

Digoxin:

- **It has a positive inotropic effect on the heart.**
- **It improves cardiac function, quality of life, exercise tolerance, and HF symptoms in patients with HFrEF (decreases morbidity)**
- **No apparent benefit of digoxin on hospitalizations or mortality.**
- **It is not a first line agent in HF.**
- **It helps control of ventricular response in patients with HFrEF and supraventricular arrhythmias, although β-blockers are generally more effective, especially during exercise.**
- **There is NO established role for digoxin in HFpEF when patients are in normal sinus rhythm, but may be of benefit in patients with concomitant HFpEF and atrial fibrillation.**

Drug Therapies for Selected Patients with HFrEF

Calcium Channel Blockers:

- They can provide symptom-targeted treatment in patients with HFpEF by decreasing HR.
- They may be used to treat concomitant HTN and CAD.
- They provide both short- and long-term improvement in exercise capacity in patients with HFpEF.
- Verapamil and diltiazem are the most effective because they lower heart rate in addition to lowering BP.
- They should be avoided in patients with HFrEF.

Drug Monitoring

ACE inhibitors:

Adverse Effect:

- **Angioedema, cough, hyperkalemia, hypotension, renal dysfunction**

Monitoring Parameters:

- **BP, electrolytes, BUN, and creatinine at baseline and 1-2 weeks after initiation or increase in dose.**

Comments:

- **Contraindicated in patients with bilateral renal artery stenosis, history of angioedema, or pregnancy.**

Drug Monitoring

ARBs:

Adverse Effect:

- **Hyperkalemia, hypotension, renal dysfunction**

Monitoring Parameters:

- **BP, electrolytes, BUN, and creatinine at baseline and 1-2 weeks after initiation or increase in dose.**

Comments:

- **Contraindicated in patients with bilateral renal artery stenosis or pregnancy.**
- **Use with caution in patients with a history of ACE inhibitor-associated angioedema.**

Drug Monitoring

Sacubitril/valsartan:

Adverse Effect:

- **Angioedema, hyperkalemia, hypotension, dizziness, renal dysfunction.**

Monitoring Parameters:

- **BP, electrolytes, BUN, and creatinine at baseline and 1-2 weeks after initiation or dose increase.**

Comments:

- **Contraindicated in patients with a history of angioedema associated with ACE inhibitor or ARB therapy or in pregnancy.**
- **Start with a low dose and double the dose every 2-4 weeks as tolerated based on BP, serum potassium, and renal function.**

Drug Monitoring

Aldosterone antagonists:

Adverse Effect:

- **Gynecomastia, breast tenderness, menstrual irregularities (spironolactone), hyperkalemia, worsening renal function**

Monitoring Parameters:

- **BP, electrolytes, BUN, and creatinine at baseline.**
- **Check potassium 3 days and 1 week after initiation and then monthly for the first 3 months.**

Comments:

- **Change to eplerenone if gynecomastia develops with spironolactone.**

Drug Monitoring

β-blockers:

Adverse Effect:

- **Bradycardia, heart block, bronchospasm, hypotension, worsening HF.**

Monitoring Parameters:

- **BP, HR, ECG, signs and symptoms of worsening HF, blood glucose**

Comments:

- **Start with low dose and titrate upward no more often than every 2 weeks as tolerated based on BP, HR, and symptoms.**
- **Patients may feel worse before they improve.**

Drug Monitoring

Digoxin:

Adverse Effect:

- **GI and CNS adverse effects, brady- and tachyarrhythmias**

Monitoring Parameters:

- **electrolytes, BUN, creatinine, ECG, serum digoxin concentration.**

Comments:

- **Target serum digoxin concentration 0.5-0.9 ng/mL.**

Drug Monitoring

Ivabradine:

Adverse Effect:

- **Bradycardia, hypotension, atrial fibrillation, luminous phenomena (phosphenes, transiently enhanced brightness in a portion of the visual field).**

Monitoring Parameters:

- **BP, HR, ECG.**

Comments:

- **Start with 5 mg twice daily and after 2 weeks adjust dose to achieve a resting HR 50-60 b/m.**
- **Only use for patients in sinus rhythm.**

Drug Monitoring

Diuretics (thiazide and loop diuretics):

Adverse Effect:

- **Hypovolemia, hypotension, hyponatremia, hypokalemia, hypomagnesemia, hyperuricemia, hyperglycemia, renal dysfunction, thirst.**

Monitoring Parameters:

- **BP, electrolytes, BUN, creatinine, glucose, uric acid, changes in weight, jugular venous distension.**

Comments:

- **Dose should be adjusted based on volume status, renal function, electrolytes, and BP.**
- **Reassess these parameters 1-2 weeks after dose changes.**

Drug Monitoring

Hydralazine:

Adverse Effect:

- **Hypotension, headache, rash, arthralgia, lupus, tachycardia.**

Monitoring Parameters:

- **BP, HR.**

Nitrates:

Adverse Effect:

- **Hypotension, headache, lightheadedness.**

Monitoring Parameters:

- **BP, HR.**