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Review Article

PHARMACOTHERAPY OF HEART FAILURE

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ABSTRACT

Heart failure (HF) is one of the major problems related to heart diseases in the modern era. Multiple comorbidities such as coronary artery disease, hypertension, diabetes mellitus, and anemia have a great contribution in the development of HF. It is primarily two types systolic and diastolic HF. Insufficient or decreased pumping of the heart is systolic HF, whereas diastolic HF is because of lack of ability of the heart to relax or increased muscle inflexibility. The pathophysiology of HF is due to enhanced activity of sympathetic system, renin angiotensin system, and structural changes in the wall of ventricle. The two definite targets of medical treatment in HF are as follows: (1) Alleviation of obstructive (or) decreased output manifestations and replenishment of cardiac function. The drugs used are frusemide, thiazides, angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs), amrinone/milrinone, dopamine/dobutamine, levosimendan, digoxin, hydralazine, nitroprusside, nitrate, bisoprolol, metoprolol, nebivolol, and carvedilol. (2) Prevention of advancement of HF and extension of patient survival - drugs used are β blockers, ACE inhibitors/ARBs, spironolactone, and eplerenone.

Keywords: Digoxin diuretics Angiotensin converting enzyme inhibitors.

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INTRODUCTION

"Heart failure (HF) is a clinical syndrome that occurs in patients because of an inherited or acquired abnormality of cardiac structure and/or function, clinical symptoms (dyspnea and fatigue), and signs (edema and rales) that lead to frequent hospitalizations, a poor quality of life, and a shortened life expectancy" [1]. In systolic dysfunction (depressed ejection fraction [EF]), heart fails to pump the required amount of blood to the body and is characterized by an impaired left ventricle (LV) function or low EF, whereas diastolic dysfunction (sustained EF) is another kind of cardiac failure where the myocardium is unable to accommodate the blood due to failure of relaxation or due to muscle stiffening, but here initially the LV function is preserved [2].

PATHOPHYSIOLOGY OF HF

Increased activity of sympathetic nervous system

Baroreceptors detect a decrease in blood pressure and trigger the activation of β-1 adrenergic receptors in the cardiac tissue resulting in the rise of heart rate and cardiac contractility. α-1 adrenergic receptors-mediated vasoconstriction enhances the venous return and increases preload. The increase in heart rate, contractility, and preload initially increases the cardiac output. Vasoconstriction increases the afterload and also causes a decrease in EF. Cardiac output finally decreases which reduces renal perfusion [3]. Evidence of sympathetic activation is due to elevated levels of circulating noradrenaline which increases activity in direct sympathetic nerves and finally increases noradrenaline release from the heart and other various organs. As normal functioning of heart worsens, response to noradrenaline decreases due to reduced sensitivity of baroreceptors, down-regulation of adrenergic receptors in heart, and signal transduction. This decreased sensitivity may again trigger the sympathetic response in advanced HF patients indicated by decreased cardiac output and hypotension. The glomerular filtration rate is reduced, and the Na+ and water retention become resistant to treatment with diuretics. Increased plasma norepinephrine is related with poor prognosis. Other catecholamine role remains unclear [4].

Stimulation of renin–angiotensin aldosterone system (RAAS)

Low cardiac output decreases the blood flow to the kidneys. This results in the release of renin, activation of angiotensin II, and release of aldosterone [3]. Angiotensin II causes a rise in blood pressure by constriction of blood vessels, and it increases glomerular filtration by enhancing the renal blood pressure and maintaining the glomerular flow. Aldosterone triggers retention of sodium and it reestablishes normal cardiac output by increasing intravascular volume [4]. Thus, blood volume is increased and there is an increase in preload. Since afterload also increases with increase in peripheral vascular resistance, the heart is unable to pump the extra volume. The resulting fluid goes back to the LV and lungs, then to right ventricle, causing pulmonary edema and peripheral edema [3].

Other neurohormonal systems

Elevated circulating and tissue levels of vasodilatory prostaglandins improve glomerular hemodynamics. Endothelin, arginine, and vasopressin are elevated in many HF patients. Arginine and vasopressin induce vasoconstriction through vasopressin-1 (V-1) receptor and reduce free water clearance through vasopressin-2 (V-2) receptor. Endothelin causes prolonged vasoconstriction, reduction in glomerular filtration, and pulmonary arteriolar constriction [1].

Cytokine activation

Circulating levels of cytokines which trigger inflammation such as tumor necrosis factor-alpha, interleukin (IL)-1β, and IL-6 are increased in relatively severe cardiac failure cases and are involved in the syndrome of cardiac cachexia. These cytokines cause contractile dysfunction, myocardial fibrosis, and myocyte necrosis and mediate some of the bad responses to catecholamines and angiotensin II [4].

Left ventricular remodeling and progression of HF

The most important intrinsic compensatory mechanism is ventricular hypertrophy. The LV progressively dilates and changes from the normal ellipsoid shape to a more spherical geometry. This cardiac remodeling is accompanied by changes in the cardiac interstitium that leads to altered orientation of the myofibrils and progressive

fibrosis [4]. Cardiac remodeling happens under the influence of angiotensin II. Initially, the increase in muscle mass helps to maintain the cardiac performance. After the initial beneficial effects of hypertrophy, it leads to ischemic changes and alterations in ventricular geometry. The ventricular wall tension rises, mechanical performance decreases, and blood in both the ventricles is retained leading to worsening of cardiac remodeling. Finally, myocytes in the failing heart die through apoptosis leaving the remaining myocytes with increased workload [4].

The two definite targets of medical treatment in HF are as follows:

A. Alleviation of obstructive (or) decreased output manifestations and replenishment of cardiac function. The drugs used are as follows:
    1. Inotropic agents: Digoxin, dobutamine, dopamine, amrinone, milrinone, and levosimendan.
    2. Diuretics: Frusemide and thiazides.
    3. RAAS inhibiting drugs: Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs).
    4. Vasodilators: Hydralazine, nitrate, and sodium nitroprusside.
    5. Beta blockers: Metoprolol, nebivolol, carvedilol, and bisoprolol.
B. Prevention of advancement of HF and extension of patient survival. Drugs used are as follows:
    1. ACE inhibitors, ARBs, and beta-blockers.
    2. Antagonists of aldosterone are spironolactone and eplerenone.

DIGOXIN

Mechanism of action

With each cardiac myocyte depolarization, sodium and calcium ions shift into the intracellular space. Calcium enters the cell through the L-type Ca2+ channel during depolarization triggers the release of stored intracellular Ca2+ from the sarcoplasmic reticulum (SR) through the ryanodine receptor. This increases the level of cytosolic Ca2+ available for interaction with myocyte contractile proteins and increases myocardial contraction force. During myocyte repolarization and relaxation, Ca2+ present in the cell is resequestered by the sarcoplasmic reticular Ca2+-ATPase (SERCA2) and is eliminated by the Na+-Ca2+ exchanger and to a lesser extent, by the sarcolemmal Ca2+-ATPase. Digoxin binds and inhibits the phosphorylated subunit of the sarcolemmal Na+K+-ATPase, thereby decreasing Na+ extrusion and increasing cytosolic Na+. This decreases the transmembrane Na+ gradient that drives Na+–Ca2+ exchange during myocyte repolarization. As a result, less Ca2+ is removed from the cell and more Ca2+ is accumulated in the SR by SERCA2. This increase in releasable Ca2+ (from the SR) is the primary mechanism by which digoxin enhances myocardial contractility [5].

Other effects of digoxin [6]

1. Digitalis increases peripheral resistance in normal individuals due to vasoconstriction. However, in HF patients, reflex sympathetic overactivity is withdrawn, and hence, peripheral resistance decreases.
2. Diuresis occurs in HF patients due to improvement in circulation and renal perfusion.
3. In higher doses digoxin causes nausea, vomiting, and central sympathetic stimulation.

Pharmacokinetics of digoxin [6]

1. Oral absorption: 60–80%.
2. Binding to the proteins within plasma: 25%.
3. Time track of drug action:
    - Onset of action: 15–30 min.
    - Optimum levels attained in 2–5 h.
    - Period of action: 2–6 days.
4. Plasma half-life: 40 h.
5. Therapeutic action: 0.5–1.4 ng/mL.
6. Toxic concentration: >2 ng/mL.
7. Daily maintenance dose: 0.125–0.5 mg.
8. Daily elimination: 35%.
9. Route of elimination: Renal.
10 Route of administration: Oral, intravenous.

Adverse effects of digoxin [6]

Extracardiac: Anorexia, nausea, vomiting and abdominal pain, fatigue, feeling of uneasiness, hyperpnoea, severe mental disorders, and vision problems.

Cardiac: Pulsus bigeminus, ventricular extrasystoles, ventricular tachycardia, atrioventricular block, and bradycardia.

Contraindications of digoxin [6]

1. Hypokalemia: Enhances digitalis toxicity.
2. Aged people, patients with kidney or liver ailments: More susceptible to digoxin toxicity.
3. Myocardial ischemia: Severe arrhythmias.
4. High risk of digitalis arrhythmias in thyrotoxicosis patients.
5. Patients with myxedema excrete digoxin slowly.
6. Digitalis is contraindicated in ventricular tachycardia because it may provoke ventricular fibrillation.
7. Partial atrioventricular block may be converted to complete atrioventricular block by digoxin.
8. Acute myocarditis: Inotropic response to digitalis is less and also there is risk of arrhythmias.
9. Wolff–Parkinson–White syndrome: Digitalis is not given.

Interactions of digoxin [6]

1. Diuretics: Cause hypokalemia which increases the risk of digitalis arrhythmias.
2. Calcium and digitalis combination has synergistic effect which is dangerous.
3. Quinidine minimizes coupling of digoxin with tissue proteins and also decreases biliary and renal elimination by suppressing efflux transporter P-glycoprotein causing doubling of plasma levels of digoxin resulting in toxicity.
4. Adrenergic drugs: Can provoke arrhythmias in digitalis taking individuals.
5. Absorption of digoxin may be diminished by sucralfate, antacids, neomycin and sulfasalazine, and metoclopramide.
6. Tricyclic antidepressants enhance the absorption of digoxin.
7. Succinylcholine: Can induce arrhythmias in digitalized patients.

Dosage of Digoxin

In mild–to-moderate HF, digoxin therapy is initiated with the estimated maintenance doses (0.125–0.25 mg/day) without any loading dose. Full response takes 5–7 days. In case of inadequate response, the dose is increased to 0.375 and 0.5 mg/day at weekly intervals. Diminution in heart rate and relief of HF symptoms are the best guide for dosing. Current data suggest that using of submaximal inotropic doses (causing steady-stage digoxin concentrations <1 ng/mL) in maintenance therapy may have the advantage by opposing neurohormonal triggering of congestive HF (CHF) with no toxicity [6].

Key evidence in trials

1. In the digitalis investigation group study, patients having EF ≤45% and in the New York Heart Association (NYHA) functional Class II–IV were randomly allocated to placebo or digoxin (dose 0.25 mg OD [once daily]) given along with an ACE inhibiting drug and a diuretic. 28% decrease in cardiovascular death was observed within 3 years of starting the drug [7].
2. Two large studies - "randomized assessment of digoxin on inhibition of ACE" and - "prospective randomized study of ventricular failure and efficacy of digoxin" on CHF patients in sinus rhythm revealed that stopping of digitalis showed decreased capacity of exercise and hemodynamic worsening in a considerable subset of patients even after the use of diuretic without discontinuation and with or without ACE inhibitor [6].

DOPAMINE

Dopamine is an endogenous catecholamine with only limited use in the therapy of most cases with cardiogenic circulatory failure. The pharmacologic and hemodynamic effects of dopamine are concentration dependent. Low doses (2 mcg/kg lean body mass/min) induce vascular smooth muscle vasodilation (predominantly renal) and cause activation of D2 receptors on sympathetic nerves in the peripheral circulation. It also inhibits norepinephrine release and reduces adrenergic stimulation of vascular smooth muscle particularly in splanchnic and renal arterial beds. Therefore, low-dose dopamine infusion is often used to increase renal blood flow and thereby maintains an adequate glomerular filtration rate in hospitalized CHF patients with impaired renal function refractory to diuretics. Dopamine also exhibits a pro-diuretic effect directly on renal tubular epithelial cells that contribute to volume reduction. At intermediate infusion rates (2–5 mcg/kg/min), dopamine directly stimulates cardiac receptors (β1) and vascular sympathetic neurons that enhance myocardial contractility and neural NE (norepinephrine) release. At higher infusion rates (5–15 mcg/kg/min), adrenergic receptor stimulation (α1) mediated peripheral arterial and venous constriction occurs. However, high-dose dopamine infusion has little role in the treatment of patients with primary cardiac contractile dysfunction. Increased vasoconstriction will lead to increased afterload and worsening of LV performance [5].

DOBUTAMINE

In the treatment of CHF patients with systolic function impairment, dobutamine is the β-agonist of choice. It results in a positive inotropic effect in humans by stimulating the β1 adrenergic receptor in the myocardium. Thus, the principal hemodynamic effect of dobutamine is an increase in stroke volume due to positive ionotropy. Continuous dobutamine infusions are typically initiated at 2–3 g/kg/min without a loading dose and uptitrated until the desired hemodynamic response is achieved. Pharmacologic tolerance may limit infusion efficacy beyond 4 days and addition or substitution with a Class III phosphodiesterase (PDE) inhibitor may be necessary to maintain adequate circulatory support. The major side effects of dobutamine are tachycardia, supraventricular, or ventricular arrhythmias which may require a reduction in dosage [5].

PDE INHIBITORS

Inamrinone and milrinone

The cyclic adenosine monophosphate phosphate (cAMP) - PDE inhibitors decrease cellular cAMP degradation resulting in increased concentrations of cAMP in cardiac and smooth muscle myocyte. The physiologic effects of this are positive myocardial inotropism and dilation of resistance and capacitance vessels. PDE inhibition improves cardiac output through inotropy and by decreasing preload and afterload. Parenteral formulations of inamrinone and milrinone are approved for short-term circulation support in advanced CHF. As a result of its effect on LV contractility, the increase in cardiac output due to milrinone is superior to nitroprusside despite a comparable decrease in systemic vascular resistance. The arterial and venodilatory effects of milrinone are prominent than those of dobutamine at concentrations that cause almost identical increases in cardiac output. For inamrinone, a 0.75-mg/kg bolus injection given over 2–3 min is typically followed by a 2–20 mcg/kg/min infusion [5].

Sildenafil

In contrast to inamrinone and milrinone, sildenafil inhibits PDE5 which is the most common PDE isoform in lung tissue. The primary clinical application of sildenafil in CHF has mainly been limited to those with isolated right ventricular systolic failure from pulmonary artery hypertension [5]. However, recently published reports suggest that sildenafil favorably influences capacity of exercise and right-heart hemodynamics in pulmonary hypertensive patients from LV systolic dysfunction as well [8].

LEVOSIMENDAN

Levosimendan exerts vasodilatory properties through activation of K+-ATP (ATP-dependent potassium channels) in smooth muscles of pulmonary, coronary, and peripheral vessels with a unique mechanism of action. It enhances myofilament responsiveness to calcium by binding to cardiac troponin C. This stabilizes the tropomyosin molecule and prolongs the period of actin-myosin sliding with no effect on intracellular calcium levels and with no increasing myocardial oxygen consumption [9]. It also activates K+-ATP channels which are important mediators of ischemia and reperfusion injury, results in coronary vasodilatation to improve heart oxygenation, and shows protective effects on the myocardium [10]. Thus, they decrease both preload and afterload, increase coronary circulation, and result in anti-ischemic effect. It is classified as an inotropic agent with anti-ischemic property [11].

DIURETICS

Loop diuretics (high ceiling diuretics)

Loop diuretics inhibit Na+-K+-2Cl– symporter on the apical membrane of renal epithelial cells in the ascending limb of the Henle's loop and increase sodium, fluid delivery to distal nephron segments. These drugs also augment K+ secretion, particularly in the presence of increased aldosterone concentrations. High ceiling diuretics such as frusemide, bumetanide, and also torsemide are commonly utilized in CHF management. The bioavailability of orally administered furosemide ranges from 40% to 70% [5].

Thiazides

Monotherapy with thiazide diuretics has a limited role in CHF. However, combination therapy with loop diuretics is often effective in those refractory to loop diuretics alone. Thiazide diuretics act on the Na+Cl– cotransporter in the distal convoluted tubule and are associated with a greater degree of K+ wasting per fluid volume reduction when compared to high ceiling diuretics [5].

Potassium sparing diuretics

These drugs inhibit apical membrane Na+-conductance channels in renal epithelial cells or act as mineralocorticoid (e.g., aldosterone) and receptor antagonists (e.g., canrenone, spironolactone, and eplerenone). These agents are weak diuretics but have historically been used to achieve volume reduction with limited K+ and Mg2+ wasting [5]. Refer to Table 1 for dosage of various diuretics.

Key features of diuretic usage in clinical practice

1. Two major roles of diuretic: (a) Reduce preload and enhance ventricular working ability by decreasing the circulatory volume and (b) reduce peripheral accumulation of fluid and also pulmonary congestion [6].
2. In cases having obvious fluid accumulation, frusemide is given at a dose of 40 mg or BD (twice daily), and then, dose is raised until requisite diuresis is attained. Serum electrolytes and renal function are often monitored in these cases or in those for whom a rapid diuresis is necessary[5].
3. In patients with decompensated CHF warranting hospital admission, repetitive intravenously administered boluses or a constant infusion titrated to achieve a desired response may be needed to provide expeditious diuresis [12].
4. Studies have demonstrated that the diuretics can enhance excretion of Na+ in urine and minimize physical manifestations of fluid accumulation in cases of HF [13].
5. Several studies have shown diuretics to relieve symptoms and increase exercise capacity in HF patients [14].
6. Diuretics are given together with an ACE inhibiting drug, aldosterone antagonist, and β blocker. Without the use of diuretics, some HF patients not able to maintain target weight [15].
7. Diuretics are usually given along with moderate reduction in dietary sodium. If patients are taking high quantities of sodium in diet or consume medication that can reduce the action of diuretics

(e.g., NSAIDs), then they may become refractory to increased doses of diuretics [15].
8. Resistance to diuretics can be overcome by giving diuretics through intravenous route or combining drugs from different diuretic classes [15].
9. Diuretics side effects are fluid reduction, electrolyte imbalance, hypotension, hypokalemia, hypomagnesaemia, and azotemia [15].
10. A retrospective study conducted by us demonstrated that while patient admission, the extent of prescription of loop diuretics was high for left ventricular systolic dysfunction cases than preserved systolic function ones [16].

DRUGS ACTING ON RENIN–ANGIOTENSIN SYSTEM

ACE inhibitors

These drugs inhibit the conversion of non-functioning decapeptide angiotensin I to the active octapeptide angiotensin II by inhibiting the ACE. Excessive angiotensin II causes stimulation of angiotensin II type 1 receptor subtype (AT1R) resulting in vasoconstriction (increases ventricular afterload), excessive growth of myocyte, left ventricular remodeling, stimulation of the sympathetic nervous system, prothrombotic actions, arginine vasopressin (AVP) release, and retention of sodium. ACE inhibitors also decrease the breakdown of bradykinin leading to accumulation of bradykinin which is responsible for adverse drug reactions of ACE inhibitors (cough and angioedema) [17]. Refer to Table 2 for dosage of various ACE inhibitors.

Key evidence in trials

1. Two trials which are randomized controlled studies such as Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) and studies of left ventricular dysfunction (SOLVD) treatment randomly allocated HF subjects who were having mild-to-severe symptoms to placebo or enalapril. Results of these studies demonstrated that management with enalapril decreased the cardiovascular-related death in both CONSENSUS and SOLVD treatment by 27% and 16%, respectively [18,19].
2. Within 3 months duration, treatment with ACE inhibitors in small placebo-controlled RCTs demonstrated a significant decrease in cardiovascular-related death [20].
3. In the "assessment of treatment with lisinopril and survival" (ATLAS) study, 3164 HF cases having moderate-to-severe symptoms were given lisinopril in low or high dose. Lisinopril group with high dose was differentiated from low dose by 15% decrease in mortality or hospitalization due to HF [21].
4. SOLVD prevention study demonstrated 20% decrease in mortality or hospitalization due to HF [22].
5. ACE inhibiting drugs should only be given in cases having appropriate functioning of kidney (creatinine ≤ 221mmol/L or ≤2.5 mg/dL or eGFR ≥30 mL/min/1.73 m^2) and adequate serum K+ levels [23].

Indications of ACE inhibitors [17]

1. Patients having HF and a reduced EF.
2. In NYHA Class II-IV, HF patients as a first-line therapy in conjunction with β-blockers.
3. Patients having left ventricular systolic function impairment without symptoms (NYHA Class I).

ARBs

These drugs prevent the binding of angiotensin II with AT1R. ARBs are not involved in inhibition of kinase II or the degradation of bradykinin, so there is no cough and no significant angioedema compared to ACE inhibitors [17]. Refer to Table 3 for dosage of various ARBs.

Key evidence in trials

1. Two placebo-controlled RCTs, Val-HeFT - "Valsartan HF trial" and CHARM-added - "candesartan in HF assessment of reduction in mortality and morbidity-added" randomly allocated cases having mild–to-severe HF symptoms to placebo or an ARB, given along with an ACE inhibitor. These Val-HeFT and CHARM-added studies showed decreased risk of hospitalization associated with HF by 24% and 17%, respectively, but not the risk associated with rehospitilization. The same studies also demonstrated that ARBs caused improvement of symptoms and quality of life [24,25].
2. CHARM alternative study involving candesartan including 2028 cases who were having left ventricular EF (LVEF) ≤40% (do not tolerate ACE inhibiting drugs) showed 23% decrease in mortality or HF hospitalization [26]. Valsartan also has a useful effect in certain cases (patients not treated by ACE inhibiting drugs) of Val-HeFT [27].
3. One more study, "evaluation of losartan in the elderly II" was failed in demonstrating that 50 mg once in a day dose of losartan was equal efficacious as 50 mg thrice in a day dose of captopril [28]. Later, studies such as "HF Endpoint evaluation of angiotensin II antagonist losartan (HEAAL)" demonstrated that losartan 150 mg once in a day was effective than 50 mg once in a day and supported results of the ATLAS study with the lisinopril [29]. In HEAAL trial, high-dose losartan group showed 10% decrease in mortality or HF hospitalization. These ATLAS and HEAAL studies showed that better results were achieved by administering larger doses of lisinopril and losartan [28].

Prescription of ARB's was more in cases of preserved systolic function than left ventricular systolic dysfunction during patient admission as well as discharge [16].

Indications of ARBs [5]

1. All patients with HF.
2. In NYHA class II-IV HF cases who are intolerant to ACE inhibitor.
3. Second-line management following optimization of ACE inhibiting drug and β-blocker in cases of NYHA Class II–IV HF.

RENIN INHIBITORS

"Aliskiren" is the first orally administered direct inhibitor of renin to receive approval from the FDA. Pilot clinical trials in humans established that aliskiren induces a concentration-dependent decrease in plasma renin activity in Angiotensin I and Angiotensin II levels that were associated with a decrease in systemic blood pressure without significant reflex tachycardia [30]. The safety profile of aliskiren in CHF was established recently by the 'Aliskiren Observation of Heart Failure Treatment' study. Aliskiren was given at a dose 150 mg/day as adjunct treatment in the trial. Outcome from this trial also demonstrated that compared to placebo, aliskiren significantly decreased plasma N-terminal-proBNP levels, a clinically useful neurohumoral biomarker of active CHF. These findings affirm that inhibition of renin activity is an important potential target for decreasing symptoms and increasing functional capacity in CHF [31]. However, available data on aliskiren and its efficacy in management of CHF are less because well-organized RCT (Randomized controlled trials) are not yet conducted.

BETA-BLOCKERS

Research and trials in previous 30 years have confirmed the usefulness of β1-blockers (primarily bisoprolol, metoprolol, nebivolol) and carvedilol in patients of mild-to-moderate symptomatic CHF who were treated by ACE inhibiting drugs ± diuretic and digitalis. Although β-blockers instantly reduce contractility of the heart and EF, progressive improvement in these features occurs over weeks. Few months later, EF is greater than baseline and gradual incremental doses further improve cardiac function. The advantages of β blockers are said to be due to opposing effects on increasing ventricular wall stress, stimulation of apoptosis, and abnormal remodeling changes of sympathetic overactivity in CHF, in addition to minimization of the occurrence of dangerous arrhythmias. The occurrence of unexpected cardiac associated deaths as well as deterioration of CHF is reduced. Beta-blockers decrease plasma markers of stimulation of sympathetic system, renin-angiotensin systems, and also endothelin-1 [17]. Refer to Table 4 for dosage of various beta blockers.

Key evidence in trials

1. Studies such as - "cardiac insufficiency bisoprolol study II," - "carvedilol prospective randomized cumulative survival,"

and merit-HF - "metoprolol CR/XL randomized intervention trial in CHF" randomized subjects having mild-to-severe symptoms of HF to placebo or a beta receptor blocker (bisoprolol, carvedilol, or metoprolol succinate CR/XL). more than 90% of the subjects received an ACE inhibiting drug or ARB. Results of these studies demonstrated that there was 34% decrease in mortality in each trial and 28–36% decrease in HF hospitalization by treatment with β-blocker within a year of introduction of therapy [32-36].

2. One more study, "evaluation of losartan in the elderly II" failed to demonstrate that 50 mg once in a day dose of losartan was equally efficacious as 50 mg thrice in a day dose of captopril [37].
3. US carvedilol studies and meta-analysis of some minitrials involving β-blockers showed 23% decrease in mortality by using carvedilol [38].
4. A randomized control trial such as "beta-blocker evaluation of survival trial" involving bucindolol failed to show a considerable decrease in mortality [39].
5. "Carvedilol Or Metoprolol European trial" demonstrated that treatment with carvedilol has better survival rate than short-acting metoprolol tartrate [40].
6. Another study suggested that carvedilol in combination with conventional therapy has increased the patient survival rate and decreased the hospitalization rate when compared to Metoprolol [41].

Indications of beta-blockers [5]

1. Stable mild-to-moderate HF cases.
2. Stable NYHA Class II–III cardiac failure cases as a first-line treatment with ACE inhibitors.

ALDOSTERONE ANTAGONISTS

In CHF patients, there is an increase in aldosterone levels in plasma, and its' established function of sodium and water retention has a major role in disease advancement. Various factors contributing to worsening of CHF include: (a) Increase in extracellular fluid volume→raise in preload, (b) fibroblast proliferation and fibrous connective tissue deposition in myocardium→deterioration of systolic function and harmful remodeling effects, (c) decline in potassium and magnesium levels→raise in possibility of ventricular arrhythmias, unexpected cardiac associated death, and (d) augmentation of cardiotoxic and remodeling changes of excessive sympathetic stimulation. Spironolactone, it has aldosterone antagonistic and also weak diuretic action. It is useful in CHF by antagonizing the above actions of aldosterone. It may be useful in reestablishment of diuretic action to frusemide when the response of frusemide is attenuated [17]. Eplerenone in combination with conventional therapy is usually prescribed for HF as well as left ventricular dysfunctioning patients to decrease the cardiovascular mortality [42]. Refer to Table 5 for dosage of various aldosterone antagonists.

Key evidence in trials

1. The "randomized aldactone evaluation study" (RALES) was conducted by giving spironolactone to subjects having severe HF. In this study, subjects having EF ≤35% and NYHA functional class III (having been in class IV within the previous 6 months) were randomly allocated to placebo or 25–50 mg dose of spironolactone once in a day. Results showed 30% decrease in mortality and 35% decrease in HF hospitalization within 2 years of introducing therapy [43].
2. In EMPHASIS-HF study (patients aged ≥55 years with NYHA functional class II symptoms and an EF ≤30%), subjects who were administered with eplerenone of dose up to 50 mg once in a day showed 37% decrease in mortality or HF hospitalization and benefits were acquired within 21 months of introducing therapy [44].
3. One more RCT, "eplerenone post-acute myocardial infarction HF efficacy and survival study," including subjects 3–14 days after acute myocardial infarction having EF≤40% and HF or diabetes. Subjects were randomly allocated to placebo or 25–50 mg dose of eplerenone once in a day given along with conventional treatment. Results demonstrated 15% decrease in cardiovascular-related death with eplerenone [45].

Indications of aldosterone antagonists [17]

1. HF cases having symptoms (Class II-IV NYHA).
2. Second-line treatment (following ACE inhibitors and β-blockers) in patients with NYHA Class II–IV HF.

VASODILATORS

Vasodilators were first used intravenous for treating sudden cardiac failure which usually takes place in severe cases. Their use by oral route has been extended to long-term therapy of persistent CHF. Vasodilators other than ACE inhibitors/ARBs have only limited utility. Nitrates promote accumulation of blood in veins, resulting in reduce preload (reduction in ventricular end diastolic pressure and volume). Hence decrease in size and volume of ventricles, results in decrease in cardiac work (according to law of laplace, the tension upon the muscle fibers in the heart wall is the pressure within the ventricle multiplied by the ventricular radius) and better ventricular emptying during systole. Hydralazine causes dilation of resistance vessels and decreases the impedance of aorta, and hence, even weaker contraction of ventricle can eject large amount of blood and systolic wall stress is decreased. It is effective in forward failure when cardiac index (CI=min output/body surface area) is low (<2.5 L/min/m2) without a significant rise in central venous pressure [17].

Key evidence in trials

1. In "Vasodilator HF Trial-I" (V-HeFT-I), subjects were randomly allocated to placebo, prazosin, or hydralazine-isosorbide Dinitrate (H-ISDN) given along with diuretic plus digoxin. Patients were not treated with a beta-blocker or an ACE inhibitor. In H-ISDN group, 22% decrease in all-cause mortality, but there was no significant variation in mortality rates in other groups [46].
2. In the African-American Heart Failure Trial (A-HeFT), both men and women from Africa and America with NYHA class III or IV were randomly allocated to placebo or H-ISDN added to a diuretic (90%), digoxin (60%), ACE inhibitor (70%), ARB (17%), beta-blocker (74%), and spironolactone (39%). The starting dose of therapy was 20 mg ISDN/37.5 mg hydralazine 3 times in a day and increased to a target of 40 mg/75 mg 3 times in a day. Results showed 43% decrease in cardiovascular-related death and 33% decrease in the risk associated with HF hospitalization [47].
3. In V-HeFT-II, subjects were randomly allocated to enalapril or H-ISDN given along with diuretic plus digoxin. Results showed a rise in all-cause mortality throughout the follow-up period (mean 2.5 years) and H-ISDN group showed 28% relative hike in risk [48].

Nitrates, inotropic drugs, and ACE inhibitors usage were more in cases of left ventricular systolic dysfunction than preserved systolic function [16].

VASOPRESSIN ANTAGONISTS

In response to serum hypertonicity induced activation of anterior pituitary osmoreceptors and a perceived drop in blood pressure detected by baroreceptors in the carotid artery, aortic arch and left atrium, AVP ae secreted into the systemic circulation. The AVP-V2 receptor interaction on the basolateral membrane of the collecting ducts of kidney stimulates synthesis of aquaporin-2 water channels that mediate free water reabsorption, thereby impairing diuresis and correcting plasma hypertonicity. Additional cell signaling pathways important in the pathophysiology of CHF include vasoconstriction, cell hypertrophy, and increased platelet aggregation mediated by activation of V1a receptors present in smooth muscle cells of blood vessels and cardiac myocytes. In addition, angiotensin II-mediated activation of centrally located AT1 receptors is associated with increased AVP levels in CHF and may represent one mechanism by which AT1-receptor antagonists are effective in the clinical management of these patients [17]. Conivaptan has dual vasopressin receptor antagonistic

function, and it causes increase in output of urine and decreases both pulmonary capillary wedge pressure and pressure in right atrium in systolic HF patients when compared to placebo [49]. Tolvaptan, which is an antagonist of a V1a receptor, also promotes a rise in output of urine and reduce body weight without a remarkable change in kidney function [50,51]. Refer to Table 6 for dosage of various vasodilators

Key evidence in trials

1. "Efficacy of vasopressin antagonism in heart failure outcome study with tolvaptan" study, involved subjects of those who were hospitalized for deteriorating cardiac failure and reduced LV efficiency (EF<40%). Subjects were randomized to oral tolvaptan or placebo. After a median follow-up duration of 9.9 months, it was observed that no variation in the all-cause mortality and death from cardiovascular etiology or HF hospitalization. However, there were improvements in patient-assessed dyspnea, body weight, and edema. Hyponatremia patients showed a prominent rise in Na+ concentration [52,53].

IVABRADINE

Ivabradine is a novel agent which particularly decreases heart rate by altering electrical currents in the sinus node. It is an inhibitor of the I_f current [54] in the SA-node leading to a decrease in heart rate without affecting blood pressure, contractility, and other aspects of intracardiac conduction. In LV systolic dysfunction and coronary artery diseases, this drug is used [55].

Key evidence in trials

1. The "systolic HF treatment with the I_f inhibitor ivabradine trial" enrolled subjects of NYHA functional class II–IV and having sinus rhythm of rate ≥70 beats per min, EF ≤35%. Patients were randomly allocated to ivabradine (uptitrated to a maximal dosage of 7.5 mg

Table 1: Dose and duration of oral diuretics [15]

Drug	Dialy dose (initial)	Maximum total daily dose	Duration of action
High ceiling diuretics			
1. Bumetanide	0.5–1.0 mg OD or BD	10 mg	4–6 h
2. Furosemide	20–40 mg OD or BD	600 mg	6–8 h
3. Torsemide	10–20 mg OD	200 mg	12–16 h
Thiazide diuretics			
1. Chlorothiazide	250–500 mg OD or BD	1000 mg	6–12 h
2. Hydrochlorothiazide	25 mg OD or BD	200 mg	6–12 h
3. Indapamide	2.5 mg OD	5 mg	36 h
4. Metolazone	2.5 mg OD	20 mg	12–24 h
Potassium-sparing diuretics			
1. Amiloride	5 mg OD	20 mg	24 h
2. Spironolactone	12.5–25 mg OD	50 mg	1–3 h
3. Triamterene	50–75 mg BD	200 mg	7–9 h
Sequential nephron blockade			
1. Metolazone	2.5–10 mg OD+high ceiling diuretic		
2. Hydrochlorothiazide	25–100 mg OD+high ceiling diuretic		
3. Chlorothiazide (IV)	500–1000 mg OD+high ceiling diuretic		
Drug	Dialy dose (initial)	Maximum total daily dose	Duration of action
High ceiling diuretics			
1. Bumetanide	0.5–1.0 mg OD or BD	10 mg	4–6 h
2. Furosemide	20–40 mg OD or BD	600 mg	6–8
3. Torsemide	10–20 mg OD	200 mg	12–16 h
Thiazide diuretics			
1. Chlorothiazide	250–500 mg OD or BD	1000 mg	6–12 h
2. Hydrochlorothiazide	25 mg OD or BD	200 mg	6–12 h
3. Indapamide	2.5 mg OD	5 mg	36 h
4. Metolazone	2.5 mg OD	20 mg	12–24 h
Potassium-sparing diuretics			
1. Amiloride	5 mg OD	20 mg	20 mg
2. Spironolactone	12.5–25 mg OD	50 mg	1–3 h
3. Triamterene	50–75 mg BD	200 mg	7–9 h
Sequential nephron blockade			
1. Metolazone	2.5–10 mg OD+high ceiling diuretic		
2. Hydrochlorothiazide	25–100 mg OD+high ceiling diuretic		
3. Chlorothiazide (IV)	500–1000 mg OD+high ceiling diuretic		

OD: Once daily

Table 2: Dosage of ACE inhibitors [5,15]

Drug	Initial daily dose	Maximum dose	Maximum dose achieved in clinical trials
1. Captopril	6.25 mg TID (3 times in a day)	50 mg TID	122.7 mg/day
2. Enalapril	2.5 mg BD	10–20 mg BD	16.6 mg/day
3. Fosinopril	5–10 mg OD	40 mg	
4. Lisinopril	2.5–5 mg	20–40 mg	32.5–35 mg/day
5. Perindopril	2 mg OD	8–16 mg OD	
6. Quinapril	5 mg BD	20 mg BD	
7. Ramipril	1.25–2.5 mg OD	10 mg OD	
8. Trandolapril	1 mg OD	4 mg OD	

ACE: Angiotensin-converting enzyme

Table 3: Dosage of ARBs [23]

Drug	Initially daily dose	Maximum dose	Mean dose achieved in clinical trials
1. Candesartan	4–8 mg once	32 mg once	24 mg/day
2. Losartan	25–50 mg once	50–150 mg once	129 mg/day
3. Valsartan	20–40 mg twice	160 mg twice	254 mg/day

ARBs: Angiotensin receptor blockers

Table 4: Dosage of beta blockers [15]

Drug	Initial daily doses	Maximum dose
1. Bisoprolol	1.25 mg OD	10 mg OD
2. Carvedilol	3.125 mg BD	50 mg BD
3. Carvedilol CR	10 mg OD	80 mg OD
4. Metoprolol succinate extended release (metoprolol CR/XL)	12.5–25 mg OD	200 mg OD

Table 5: Dosage of aldosterone antagonists [15]

Drug	Initial daily dose	Maximum dose
1. Spironolactone	12.5–25 mg once	25 mg once or twice
2. Eplerenone	25 mg/day	50 mg once

2 times in a day) or placebo and added to a diuretic (in 84%), digoxin (22%), an ACE inhibitor (79%), an ARB (14%), a beta-blocker (90%), and a MRA (60%). Results showed 18% decrease in mortality and 26% decrease in the risk of HF hospitalization [56].

2. Evaluation of the I_f inhibitor ivabradine patients with coronary disease and left ventricular dysfunction (BEAUTIFUL) in which subjects having coronary heart disease and an EF<40% was received ivabradine 7.5 mg 2 times in a day or placebo. Ivabradine failed to decrease the myocardial infarction, cardiovascular-related death, and HF hospitalization but it was well tolerated [57].

STATINS

Statins are inhibitors of HMG-CoA reductase enzyme [58] show various beneficial cardiovascular effects in addition to LDL (low-density lipid) reduction. Statins are associated with positive LV remodeling, increased arteriolar blood flow, and decreased circulating platelet aggregation. Intermediate by-products of mevalonate metabolism are linked to impaired vascular function by increasing levels of oxidant stress and decreasing bioavailable nitric oxide levels. Statins inhibit these intermediary pathways and appear to restore endothelium-dependent and endothelium-independent vascular function [5].

Key evidence in trials

1. CORONA trial enrolled patients of age ≥60 years who were having HF symptoms (NYHA class II– IV) of ischemic etiology and EF ≤40%. Rosuvastatin failed to decrease stroke, mortality, myocardial infarction, and all-cause mortality [59].
2. In the GISSI-HF statin study, subjects who were having HF symptoms (NYHA class II–IV) of both ischemic as well as non-ischemic origin were enrolled. Patients had an EF ≤40% and were randomly allocated to placebo or rosuvastatin 10 mg once in a day. Rosuvastatin failed to decrease all-cause mortality and hospitalization [60].

OMEGA-3-FATTY ACIDS

The small treatment effect of n-3 polyunsaturated fatty acids (PUFAs) in the Gruppo Italiano per lo Studio dellaSopravvivenza nell'Infarto miocardico-HF (GISSI-HF) study demonstrated no effect on HF hospitalization [61].

ADENOSINE ANTAGONISTS

Adenosine receptors (A1) are present in the renal afferent arteriole and proximal convoluted tubule. They are involved in constriction of these arterioles and tubuloglomerular feedback [62,63]. In cardiac failure patients, increase in Na+ levels in the distal tubule stimulates a feedback mechanism to the macula densa resulting in the release of adenosine which causes augmentation in sodium reabsorption by the proximal convoluted tubule and constriction of afferent arterioles, resulting in lowering of filtering capacity of kidney [63]. Hence, these drugs significantly increase natriuresis in HF without altering renal function [64].

Key evidence in trials

1. In the pilot phase of the placebo-controlled randomized control trial of the drug rolofylline which is a antagonist of selective A1 adenosine receptor, enrolled subjects were hospitalized cases with sudden cardiac failure were randomly allocated to be given one of three doses of rolofylline or placebo. Rolofylline recipients showed a decrease in 60-day mortality and readmission for cardiovascular or renal cause and lesser increase in serum creatinine level [65,66].

ULARITIDE

Ularitide binds to natriuretic peptide receptors located on medullary collecting duct cells and vascular smooth muscle cells, which leads to increased diuresis, natriuresis, and arterial and venous vasodilation [67]. Clinically, ularitide has been shown to induce natriuresis and at the same time decrease plasma concentrations of renin, aldosterone, and angiotensin II [68,69].

Key evidence in trials

1. In the "safety and efficacy of an intravenous placebo-controlled randomized infusion of Ularitide"-II trial, 221 patients with HF were randomly given one of three doses of ularitide or placebo in addition to baseline loop and thiazide diuretics. Subjects treated with ularitide exhibited an improvement in dyspnea and hemodynamic parameters. A trend toward improved rates of 30-day mortality was noted in the ularitide recipients. The most common side effect of ularitide was hypotension which was most prominent with the highest dose. No significant worsening of renal function was noted [70].

ISTAROXIME

Istaroxime is a contractility-enhancing agent that inhibits sodium-potassium ATPase and increases the activity of SERCA. Increased SERCA activity results in accumulation of calcium within the myocyte during systole and rapid extrusion of calcium in diastole which lead to an improvement in both inotropic function [55].

Key evidence in trials

1. A phase II study of Effects of Istaroxime in subjects having deteriorating HF and decreased LV Systolic Function (HORIZON-HF) showed a significant decrease in pulmonary capillary wedge pressure in comparison to placebo. Prominent reduction in heart rate and a raise in systolic blood pressure was noted. Prominent reduction in heart rate and a raise in systolic blood pressure wee noted. Patients with the highest dose showed an increase in CI, a decrease in left ventricular end-diastolic volume, and improvement in diastolic parameters on echocardiography without a prominent change in LVEF [71].

METABOLIC MODULATORS

Perhexiline

By inhibiting carnitine palmitoyltransferase-1 enzyme, perhexiline reduces mitochondrial FFA transport that causes increased glucose metabolism [72]. A small trial of 56 subjects having chronic NYHA

Table 6: Dosage of vasodilators [15]

Drug	Initial daily dose	Maximum doses	Mean dose achieved in clinical trials
Hydralazine/isosorbide dinitrate			
1. Fixed dose combination	37.5 mg hydralazine/20 mg isosorbide dinitrate 3 times a day	75 mg hydralazine/40 mg isosorbide dinitrate 3 times a day	175 mg hydralazine/90 mg isosorbide dinitrate daily
2. Hydralazine and isosorbide dinitrate	Hydralazine: 25 to 50 mg, 3 or 4 times in a day, and isosorbide dinitrate: 20–30 mg 3 or 4 times in a day	Hydralazine: 300 mg daily in divided doses and isosorbide dinitrate: 120 mg daily in divided doses	

functional Class II or III systolic cardiac failure were randomly allocated to perhexiline or placebo administration. After 8 weeks, perhexiline-treated cases showed a remarkable improvement in left ventricular function along with increased oxygen utilization during exercise in contrast to the placebo group [73].

Trimetazidine

This drug inhibits long-chain 3-ketoacyl coenzyme A thiolase, and this enzyme has a crucial role in free fatty acid oxidation, resulting in increased utilization of myocardial glucose [74]. Fragasso *et al.* randomly allocated 55 cases with ischemic and non-ischemic cardiomyopathy (NYHA functional Classes II–IV) to trimetazidine or placebo administration besides conventional HF treatment. A mean follow-up for 13 months demonstrated that the trimetazidine recipients showed remarkable improvement in exercise capacity, and LVEF, and a decrease in end-systolic volume of LV in contrast to placebo group. Trimetazidine administered cases showed no increase in adverse events [75].

Ranolazine

Ranolazine alters the transcellular late sodium flow which results in decrease in overload of intracellular calcium [76]. It also involved in the oxidation of glucose and a decrease in FFA oxidation with a prominent decrease in ischemia as well as angina [77]. In cardiac failure cases with normal EF, changes in echocardiographic features of diastolic HF are being evaluated in a minor clinical study [78].

L-carnitine

L-carnitine is an essential cofactor in FFA metabolism. It prevents the accumulation of FFA, prevents generation of lactic acid, and also increases utilization of glucose [79]. L-carnitine deficiency is associated with cardiomyopathy [80]. In HF patients, acute administration of propionyl l-carnitine (IV bolus, 30 mg/kg body weight) showed reduction in pulmonary artery pressure and also pulmonary capillary wedge pressure. Propionyl-L-carnitine increases exercise capacity and reduces ventricular size in patients with CHF [81].

SACUBITRIL+VALSARTAN

It is a combination drug consisting of two antihypertensives (blood pressure lowering drugs) in a 1:1 mixture by molecule count. The combination is often described as a dual-acting angiotensin receptor-neprilysin inhibitor although the two effects are achieved by two different molecules [82]. It is approved as a treatment to reduce the risk for cardiovascular death and hospitalization in patients with chronic HF (NYHA Class II-IV) associated with reduced EF [83]. Valsartan is ARB and sacubitril is a prodrug that is activated to LBQ657 by de-ethylation through esterases which inhibits the enzyme neprilysin which causes degradation of atrial and brain natriuretic peptide. Thus, both the blood pressure lowering peptides work mainly by reducing blood volume. The double-blind study for this combination of two drugs is the largest ever of a HF treatment and involved 8,842 patients in 47 countries who were followed for 27 months. Results from the clinical trial showed : (a) 20% reduction in cardiovascular-associated mortality, (b) 21% decrease in risk associated with HF hospitalization, and (c) 16% decrease in all-cause mortality [84].

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