Drugs for Heart Failure

HF is due to an impaired ability of the heart to adequately fill with and/or eject blood to meet the needs of the body. It is often accompanied by abnormal increases in blood volume and interstitial fluid. Underlying causes of HF include, but are not limited to, atherosclerotic heart disease, hypertensive heart disease, valvular heart disease, and congenital heart disease.

Role of physiologic compensatory mechanisms in the progression of HF

Chronic activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS) is associated with remodelling of cardiac tissue, loss of myocytes, hypertrophy, and fibrosis. So, if HF has been left untreated, it may lead to death.

Goals of pharmacologic intervention in HF

The main goals of HF treatment are to alleviate symptoms, slow disease progression, and improve survival.

There are many classes of drugs have been shown to be effective in treating HF like ACE inhibitors, ARBs, aldosterone antagonists, β-blockers and diuretics …etc

Depending on the severity of HF and individual patient factors, one or more drugs are administered.

Pharmacologic intervention provides the following benefits in HF: reduced myocardial work load, decreased extracellular fluid volume, improved cardiac contractility, and a reduced rate of cardiac remodelling.

Knowledge of the physiology of cardiac muscle contraction is essential for understanding the compensatory responses evoked by the failing heart, as well as the actions of drugs used to treat HF.

Cardiac contraction

The force of contraction of the cardiac muscle is directly related to the concentration of free (unbound) cytosolic calcium. Therefore, agents that increase intracellular calcium levels (or that increase the sensitivity of the contractile machinery to calcium) increase the force of contraction (inotropic effect).

Compensatory physiological responses in HF

The failing heart evokes four major compensatory mechanisms to enhance CO (CO). These mechanisms are:

1- Increasing sympathetic activity

Baroreceptors sense a decrease in blood pressure and activate the sympathetic nervous system. In an attempt to sustain tissue perfusion, this stimulation of β-adrenergic receptors results in an increased heart rate and a greater force of contraction of the heart muscle. In addition, vasoconstriction enhances venous return and increases cardiac preload. An increase in preload (stretch on the heart)

increases stroke volume, which, in turn, increases CO. These compensatory responses increase the workload of the heart, which, in the long term, contributes to further decline in cardiac function.

2- Activation of the renin–angiotensin–aldosterone system (RAAS)

A fall in CO decreases blood flow to the kidney, prompting the release of renin. Renin release is also stimulated by increased sympathetic activity resulting in increased formation of angiotensin II and release of aldosterone. This results in increased peripheral resistance (afterload) and retention of sodium and water. Blood volume increases, and more blood is returned to the heart. If the heart is unable to pump this extra volume, venous pressure increases, and peripheral and pulmonary oedema occur. In addition, high levels of angiotensin II and aldosterone have direct detrimental effects on cardiac muscle, favouring remodelling, fibrosis, and inflammatory changes. *Again, these compensatory responses increase the workload of the heart, contributing to further decline in cardiac function.*

3- Activation of natriuretic peptides

An increase in preload also increases the release of natriuretic peptides. Natriuretic peptides, which include atrial, B-type, and C-type, have differing roles in HF; atrial and B-type natriuretic peptides are the most important. Activation of the natriuretic peptides ultimately results in vasodilation, natriuresis, inhibition of renin and aldosterone release, and a reduction in myocardial fibrosis. This beneficial response may improve cardiac function and HF symptoms.

4- Myocardial hypertrophy

Initially, stretching of the heart muscle leads to a stronger contraction of the heart. However, excessive elongation of the fibres results in weaker contractions and a diminished ability to eject blood. This type of failure is termed “systolic failure” or HF with reduced ejection fraction (HFrEF) and is the result of the ventricle being unable to pump effectively.

Patients with HF may have “diastolic dysfunction,” a term applied when the ability of the ventricles to relax and accept blood is impaired by structural changes such as hypertrophy. The thickening of the ventricular wall and subsequent decrease in ventricular volume decrease the ability of heart muscle to relax. In this case, the ventricle does not fill adequately, and the inadequacy of CO is termed “diastolic HF” .

Acute (decompensated) HF

If the compensatory mechanisms adequately restore CO, HF is said to be compensated. If the compensatory mechanisms fail to maintain CO, HF is decompensated, and the patient develops worsening HF signs and symptoms. Typical HF signs and symptoms include dyspnoea on exertion, orthopnoea, paroxysmal nocturnal dyspnoea, fatigue, and peripheral oedema.

Therapeutic strategies in HF

Chronic HF is typically managed by

1- Fluid limitations (less than 1.5 to 2 L daily). 2-Low dietary intake of sodium (less than 2000 mg/d). 3- Treatment of comorbid conditions. 4-And judicious use of diuretics.

- Specifically for HFrEF, inhibitors of the RAAS, inhibitors of the SNS, and drugs that enhance activity of natriuretic peptides have been shown to improve survival and reduce symptoms.
- Inotropic agents are reserved for acute signs and symptoms of HF and are used mostly in the inpatient setting.
- Drugs that may precipitate or exacerbate HF, such as nonsteroidal anti-inflammatory drugs (NSAIDs), alcohol, nondihydropyridine calcium channel blockers, and some antiarrhythmic drugs, should be avoided if possible.

1- Inhibitors of the Renin–Angiotensin–Aldosterone System

As the compensatory activation of the RAAS in HF can deteriorate the HF problem, inhibition of the RAAS is an important pharmacological target in the management of HF.

a- ACE inhibitors: ACE inhibitors are a part of standard pharmacotherapy in HFrEF. These drugs block the enzyme that cleaves angiotensin I to form the potent vasoconstrictor angiotensin II. They also diminish the inactivation of bradykinin. So, ACE inhibitors decrease vascular resistance (afterload) and venous tone (preload), resulting in increased CO. ACE inhibitors improve clinical signs and symptoms of HF and have been shown to significantly improve patient survival in HF.

Therapeutic use

- ACE inhibitors may be considered for patients with asymptomatic and symptomatic HFrEF. So, <u>ACE inhibitors are indicated for patients with all stages of left ventricular failure.</u>
- ACE inhibitors are also used in the treatment of hypertension. Patients who have had a recent myocardial infarction or are at high risk for a cardiovascular event also benefit from long-term ACE inhibitor therapy.

4. Adverse effects

- These include postural hypotension, renal insufficiency, hyperkalemia, a persistent dry cough, and angioedema (rare).
- Because of the risk of hyperkalemia, K^+ levels must be monitored, particularly with concurrent use of K^+ supplements, K^+-sparing diuretics, or aldosterone antagonists. Serum creatinine levels should also be monitored, particularly in patients with underlying renal disease.
- The potential for symptomatic hypotension with ACE inhibitors is much more common if used concomitantly with a diuretic.
- ACE inhibitors are teratogenic and should not be used in pregnant women.

b- Angiotensin receptor blockers

Angiotensin receptor blockers (ARBs) are orally active compounds that are competitive antagonists of the angiotensin II type 1 receptor. Because ACE inhibitors inhibit only one enzyme responsible for the production of angiotensin II, ARBs have the advantage of more complete blockade of the actions of angiotensin II. However, ARBs do not affect bradykinin levels. Although ARBs have actions similar to those of ACE inhibitors, they are not therapeutically identical. Even so, ARBs are a substitute for patients who cannot tolerate ACE inhibitors.

Actions and pharmacokinetics

Although ARBs have a different mechanism of action than ACE inhibitors, their actions on preload and afterload are similar. Their use in HF is mainly as a substitute in patients who cannot tolerate ACE inhibitors due to cough or angioedema, which are thought to be mediated by elevated bradykinin levels. ARBs are orally active and are dosed once daily, with the exception of valsartan, which is dosed twice daily.

Adverse effects

ARBs have an adverse effect and drug interaction profile similar to that of ACE inhibitors. However, the ARBs have a lower incidence of cough and angioedema. ARBs are contraindicated in pregnancy.

c- Aldosterone receptor antagonists

Patients with HF have elevated levels of aldosterone due to angiotensin II stimulation and reduced hepatic clearance of the hormone. Spironolactone is antagonist of aldosterone at the mineralocorticoid receptor, thereby preventing salt retention, myocardial hypertrophy, and hypokalemia. Spironolactone also has affinity for androgen and progesterone receptors and is associated with endocrine-related adverse effects such as gynecomastia and dysmenorrhea. Aldosterone antagonists are indicated in patients with symptomatic HFrEF or HFrEF and recent myocardial infarction.

2- β-Blockers

Although it may seem counterintuitive to administer drugs with negative inotropic activity in HF, evidence clearly demonstrates improved systolic function and reverse cardiac remodelling in patients receiving β-blockers. These benefits arise in spite of an occasional, initial exacerbation of symptoms.

The benefit of β-blockers is attributed, in part, to their ability to prevent the changes that occur because of chronic activation of the SNS. These agents decrease heart rate and inhibit release of renin in the kidneys. In addition, β-blockers prevent the deleterious effects of norepinephrine on the cardiac muscle fibres, decreasing remodelling, hypertrophy, and cell death.

Three β-blockers have shown benefit in HFrEF: bisoprolol, carvedilol and long-acting metoprolol succinate. Carvedilol is a nonselective β-adrenoreceptor antagonist that also blocks α adrenoreceptors, whereas bisoprolol and metoprolol succinate are β1-selective antagonists. β-Blockade is recommended for all patients with chronic,

stable HFrEF. Bisoprolol, carvedilol, and metoprolol succinate reduce morbidity and mortality associated with HFrEF.

Treatment should be started at low doses and gradually titrated to target doses based on patient tolerance and vital signs. β-Blockers should also be used with caution with other drugs that slow AV conduction, such as amiodarone, verapamil, and diltiazem.

3- Diuretics

Diuretics reduce signs and symptoms of volume overload, such as dyspnoea on exertion, orthopnoea, and peripheral oedema. Diuretics decrease plasma volume and, subsequently, decrease venous return to the heart (preload). This decreases cardiac workload and oxygen demand. Diuretics may also decrease afterload by reducing plasma volume, thereby decreasing blood pressure. Loop diuretics are the most commonly used diuretics in HF. These agents are used for patients who require extensive diuresis and those with renal insufficiency. Since diuretics have not been shown to improve survival in HF, they should only be used to treat signs and symptoms of volume excess.

4- Angiotensin Receptor–Neprilysin Inhibitor (ARNI)

Neprilysin is the enzyme responsible for breaking down vasoactive peptides, such as angiotensin I and II, bradykinin, and natriuretic peptides. Inhibition of neprilysin augments the activity of the vasoactive peptides. To maximise the effect of natriuretic peptides, stimulation of the RAAS must be offset without further increase in bradykinin. Therefore, an ARB, instead of an ACE inhibitor, is combined with a neprilysin inhibitor to reduce the incidence of angioedema. Take for example, the Sacubitril /valsartan is the 1st available ARNI. This combination can lead to natriuresis, diuresis, vasodilation, and inhibition of fibrosis. So, this will decrease the afterload, preload, and myocardial fibrosis. An ARNI should replace an ACE inhibitor or ARB in patients with HFrEF who remain symptomatic on optimal doses of a β-blocker and an ACE inhibitor or ARB.

Adverse effects

The adverse effect profile is similar to that of an ACE inhibitor or ARB. Because of the added reduction of afterload, hypotension is more common with an ARNI. Due to inhibition of neprilysin with sacubitril, bradykinin levels may increase and angioedema may occur. Therefore, the combination is contraindicated in patients with a history of hereditary angioedema or angioedema associated with an ACE inhibitor or ARB. To minimize risk of angioedema, an ACE inhibitor must be stopped at least 36 hours prior to starting sacubitril/valsartan.

5- Inotropic Drugs

+VE inotropic agents enhance cardiac contractility and, thus, increase CO. Although these drugs act by different mechanisms, the inotropic action is the result of an increased cytoplasmic calcium concentration that enhances the contractility of

cardiac muscle. All +VE inotropes in HFrEF that increase intracellular calcium concentration have been associated with reduced survival, especially in patients with HFrEF. For this reason, these agents, with the exception of digoxin, are only used for a short period mainly in the inpatient setting.

A. Digitalis glycosides (DGs)

The cardiac glycosides are often called digitalis or digitalis glycosides. They are a group of compounds that can increase the contractility of the heart muscle and, therefore, are used in treating HF. The DGs have a low therapeutic index, with only a small difference between a therapeutic dose and doses that are toxic or even fatal. The only available agent is digoxin.

Mechanism of action

a- Regulation of cytosolic calcium concentration

By inhibiting the Na+/K+-adenosine triphosphatase (ATPase) enzyme, digoxin reduces the ability of the myocyte to actively pump Na+ from the cell. This ultimately results in a small but physiologically important increase in free Ca2+, thereby leading to increased cardiac contractility.

b- Increased contractility of the cardiac muscle

Digoxin increases the force of cardiac contraction, causing CO to more closely resemble that of the normal heart. Vagal tone is also enhanced, so both heart rate and myocardial oxygen demand decrease. Digoxin slows conduction velocity through the AV node, making it useful for atrial fibrillation.

Therapeutic use and Adverse effects

Digoxin therapy is indicated in patients with HFrEF who are symptomatic on optimal HF pharmacotherapy. A low serum drug concentration of digoxin (0.5 to 0.8 ng/mL) is beneficial in HFrEF.

At low serum drug concentrations, digoxin is well tolerated. However, it has a very narrow therapeutic index. Anorexia, nausea, vomiting, blurred vision, or yellowish vision may be initial indicators of toxicity.

Decreased levels of serum potassium (hypokalemia) predispose a patient to digoxin toxicity, because digoxin normally competes with potassium for the same binding site on the Na+/K+-ATPase pump. With the use of a lower serum drug concentration in HFrEF, toxic levels are infrequent. Digoxin is a substrate of P-gp (p-glycoprotien), and inhibitors of P-gp, such as clarithromycin, verapamil, and amiodarone, can significantly increase digoxin levels, necessitating a reduced dose of digoxin. Digoxin should also be used with caution with other drugs that slow AV conduction, such as β-blockers, verapamil, and diltiazem.

B. β-Adrenergic agonists

β-Adrenergic agonists, such as dobutamine and dopamine (given by IV infusion), improve cardiac performance by causing positive inotropic effects and vasodilation. β-Adrenergic agonists ultimately lead to increased entry of calcium ions into myocardial cells and enhanced contraction.

References:

1- Katzung, B.G., 2018. Basic and clinical pharmacology. Mc Graw Hill.
2- Whalen, K., 2019. Lippincott illustrated reviews: pharmacology. Lippincott Williams & Wilkins.