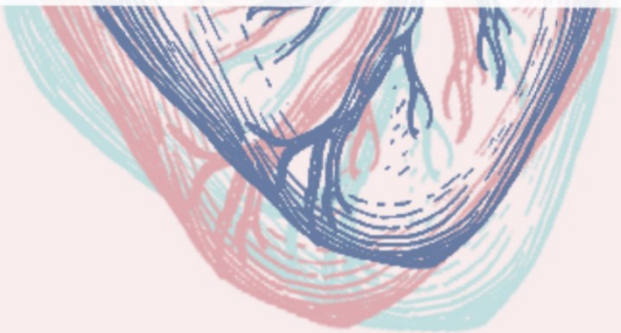
Cardio-Vascular System

7

Pharmacology



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Let's continue talking about drugs used in heart failures

Beta blockers

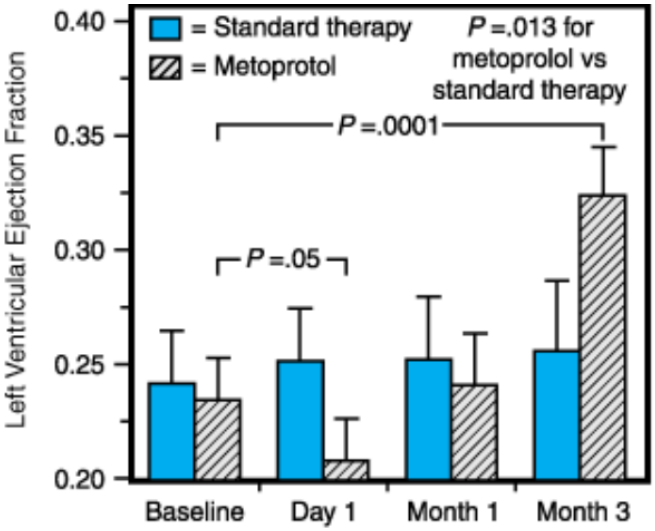
Traditionally, we know that beta 1 receptors' activation via the sympathetic nervous system stimulates the heart function with both chronotropic and inotropic effects, by that sense beta blockers should have negative inotropic effects. The patient has heart failure so do we further depress his heart????

- Nowadays there is overwhelming evidence to support the use of β-blockers in CHF.
- Not useful in refractory or severe HF. So, we limit their use for early stages of HF.
- Mechanism involved remains unclear.
- Part of their beneficial effects may derive from slowing of heart rate, decreased cardiac work and consequently decreased myocardial O2 consumption (a major factor) which leads to enhanced efficiency. This would lessen the frequency of ischemic events and arrhythmias that can complicate HF.
- Suggested mechanisms also include reduced remodeling of the heart muscle.
- β-Blockers may be beneficial through re-sensitization of the down-regulated beta receptors, thus improving myocardial contractility, this might be the most important effect.
- Should be started with low doses and gradually increased. To cope with the already down-regulated receptors.
- Recent studies with metoprolol, carvedilol, bucindolol, and bisoprolol showed a reduction in mortality in patients treated with these drugs.
- This does not mean that other older beta blockers (for example propranolol) are not effective.
- Contraindicated in severe, refractory, unstable cases.

The figure to the right shows the effect of using beta blockers in HF.

The blue columns refer to standard therapy without the use of beta blockers, while cross-hatched bars refer to the treatment using metoprolol which is a beta 1 selective blocker.

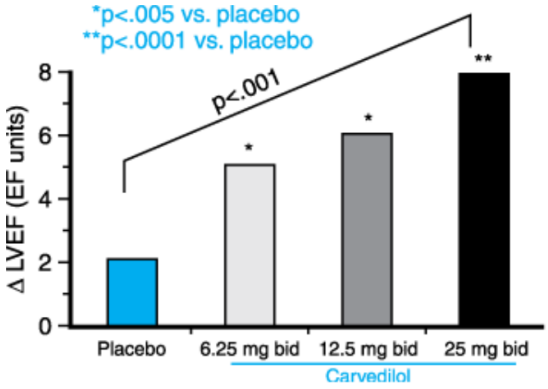
In the beginning, we started with patients having heart failure, with a low left ventricular ejection fraction (the y-axis). After one day, we notice the patients on metoprolol have even



more depressed heart, but after one month, the standard therapy improved the heart just a little bit, while the metoprolol patients have significant improvement, after 3 months, the beneficial effect of metoprolol has exceeded the effect of standard therapy.

Bottom line is that on the long run beta blockers are more effective.

This figure shows treatment with increasing doses of carvedilol

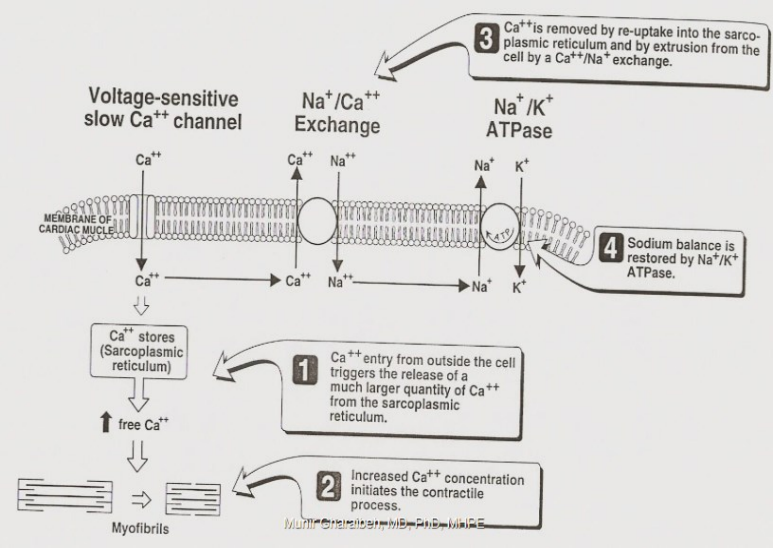


Positive Inotropic Agents

- Logically they will improve cardiac function.
- These drugs increase force of contraction by increasing intracellular cardiac Ca^{++} concentration. We have two types:

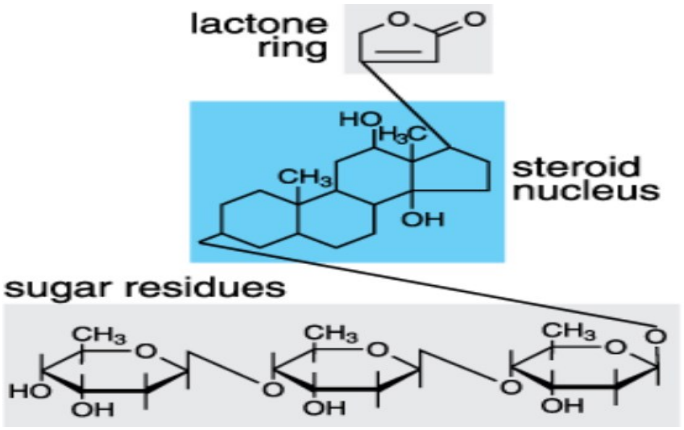
1. Cyclic AMP Independent Agents, such as:
   - ✓ Digitalis: inhibits Na/K ATPase.
   - ✓ Pimobendan: sensitizes myocytes to Ca^{++}, it also inhibits Phosphodiesterase (PDE), So it can also be included as a cAMP dependent agent.
2. Cyclic AMP Dependent Agents, such as beta-adrenergic Agonists, Phosphodiesterase Inhibitors

We are familiar with this figure, the doctor didn't add anything extra.



Digitalis Glycosides

- Digitalis was a widely used drug in the treatment of HF.
- A History lesson:
  - ✓ Egyptians got it from a plant called Squill (العنصل)
  - ✓ Chinese got it from Toad skin
  - ✓ In 1785, William Withering discovered a plant called Foxglove. And from this plant we extracted the active ingredient which we use nowadays.
- We have different species of foxglove: *Digitalis purpura*, *Digitalis lanata*, *Strophanthus*
- Doesn't work on the kidney tubules thus it doesn't have a real diuretic activity, but by enhancing the heart function, it leads to loss of fluids and relief of edema.
- The active ingredient is a glycoside, meaning it's a group of sugar residues connected to a steroid nucleus that is connected to a lactone ring.



Actions:

- Positive Inotropic Effect
- Vascular Muscle Contraction
- Vagal Stimulation, activating the PSNS which mainly affects the heart rate
- Effects on Electrical Properties of Cardiac Tissues (predominately affects the atria).

The main action is, increasing the heart contractility (this occurs in all patients). But the effect of this drug differs according to the state of patients. In HF patients it causes an increase in CO and a decrease in PVR which is good. However, in normal healthy people it was found to cause the opposite, decreasing CO and increasing PVR.

This is because, patients with HF have increased SNS activity which increases PVR to the maximum, where no further increase is possible. Giving digitalis would increase the contractility and somehow disrupt the overactive SNS activity. Now, the inhibition of SNS will cause vasodilation. The blood vessels are dilated and ready to be filled with blood (PVR is reduced) therefore the CO (the flow) will be increased.

The effects of digitalis on electrical properties of cardiac tissue:

- It has direct and indirect effects, the indirect are mainly due to stimulation of the Vagus nerve which supplies the atria and SA node only
- Increased PR is diagnostic of digitalis therapy
- The direct effects occur at high toxic doses

The table below shows the exact effect on cardiac tissues. Please read it.

TABLE 13-2 Effects of digoxin on electrical properties of cardiac tissues.

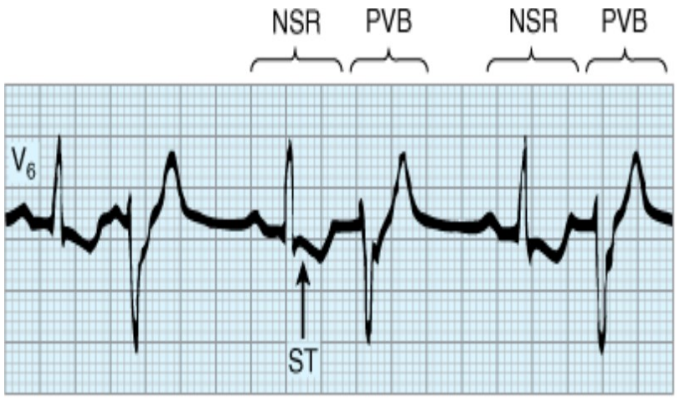
Tissue or Variable	Effects at Therapeutic Dosage	Effects at Toxic Dosage
Sinus node	↓ Rate	↓ Rate
Atrial muscle	↓ Refractory period	↓ Refractory period, arrhythmias
Atrioventricular node	↓ Conduction velocity, ↑ refractory period	↓ Refractory period, arrhythmias
Purkinje system, ventricular muscle	Slight ↓ refractory period	Extrasystoles, tachycardia, fibrillation
Electrocardiogram	↑ PR interval, ↓ QT interval	Tachycardia, fibrillation, arrest at extremely high dosage

Ventricular

Digitalis Toxicity:

- The most important are the cardiac toxicities. But it can also cause other less serious ones.
- GIT: Anorexia, nausea, intestinal cramping, diarrhea.
- Visual effects: Xanthopsia, abnormalities in color vision.
  Xanthopsia على قولة الدكتور نجوم الظهر, scientifically it is a color vision deficiency in which there is a predominance of yellow in vision due to a yellowing of the optical media of the eye.
- Neurologic: Malaise, confusion, depression, vertigo
- Cardiac: severe bradycardia, palpitations, syncope, arrhythmias, AV node block, ventricular tachycardia which might lead to ventricular fibrillation and could be lethal.
- Interactions with many drugs.
- Pharmacological and toxic effects are greater in hypokalemic patients.
- K+-depleting diuretics are a major contributing factor to digoxin toxicity. So, they should be avoided.

This is an ECG of a patient on digitalis, notice the increase in PR interval, ST depression and extrasystoles.



Treatment of Toxicity:

- Reduce the dose or stop the drug if possible.
- Cardiac pacemaker for severe heart block.
- Digitalis antibodies (Digoxin Immune Fab). This is used as an antidote for people who are trying to commit suicide by taking digoxin.
  Your mental health is more important than anything in the whole world, stay safe!!
- Arrhythmias may be converted to normal sinus rhythm by K+, so we give K+ when the plasma K+ concentration is low or within the normal range.
- If arrythmias develop when the plasma K+ concentration is high, antiarrhythmic drugs, such as lidocaine, phenytoin (strongly indicated in digitalis toxicity), procainamide, or propranolol, can be used.

Therapeutic Benefits:

- Was widely used in the treatment of heart failure.
- Nowadays, its use is restricted only to chronic congestive heart failure CCHF with supraventricular arrhythmia.
- Might decrease morbidity and improve quality of life.
- Withdrawal might be hazardous.
- Does NOT improve mortality.

Basic Data of Three Cardiac Glycosides

	Digitoxin	Digoxin	Ouabain
GI absorption	100%	70 –85%	0
Polarity	Least	Somewhat	Highest
Protein binding	97%	< 30%	5 – 10%
Half-life	4 – 7 days	1.5-1.6 days	21 hr
Excretion route	Stool and kidneys; as hepatic metabolites*	Kidneys; largely unchanged	Kidneys; largely unchanged
Enterohepatic recycling	27%	6.8%	Unknown
Optimum serum levels	20-35 ng/ml	0.5-2.5 ng/ml	Unknown
V_d	0.6 L/kg	5-10 L/kg	Unknown

* About 8% of digitoxin is metabolized and excreted as digoxin in the urine. Digitoxin seems to be largely recycled to complete its metabolic degradation.

Different cardiac glycosides:

- Nowadays only digoxin is available.
- Different oral absorption, ouabain has to be given I.V.
- Different protein binding ability, for example digitoxin has 97%, this enhances the chance of drug-drug interactions with drugs which can displace digitoxin leading to higher unbound free molecules which can be toxic.

- Different half-life, different excretion route, digitoxin is eliminated through the intestines while digoxin is through the kidneys, so in cases of renal failure we can use digitoxin.
- These drugs have to be monitored regularly.

This table isn't for memorization, just know the details mentioned above and that digoxin is somewhat in the middle between these two, and its excreted from the kidneys.

Cyclic AMP Dependent Agents

Beta-adrenergic Agonists:

- They all increase myocardial oxygen consumption, so they are not helpful for chronic use, because they might affect the efficiency of the heart.
- They may be used (IV) for short term or in acute heart failure.

- Norepinephrine (NE): Was used in cardiogenic shock (severe drop in blood pressure post-MI) and in emergencies but it caused severe vasospasm and gangrene, which could lead to amputation. So, it's no longer used.

- Epinephrine: Still used in cardiac arrest, as a final resort in CPR, by intracardiac injection. Works better in young people with better functioning hearts

Dopamine:

- Widely used in cardiogenic shock.
- It has three distinct effects depending on the given dose:
  - ✓ Low doses: stimulate DA1 receptors leading to renal vasodilation and improved renal function, used in renal failure.
  - ✓ Intermediate doses: work on β1 receptors leading to positive inotropic actions on the heart. Also used in renal failure.
  - ✓ High doses: stimulate α receptors leading to vasoconstriction and elevation of blood pressure. Can cause arrhythmias and ischemic changes, because of the increase in myocardial oxygen consumption.

Dobutamine:

- Selective β1 agonist, used intermittently (IV) in CCHF.
- Produces mild vasodilation.
- Has more inotropic than chronotropic actions.

Phosphodiesterase Inhibitors:

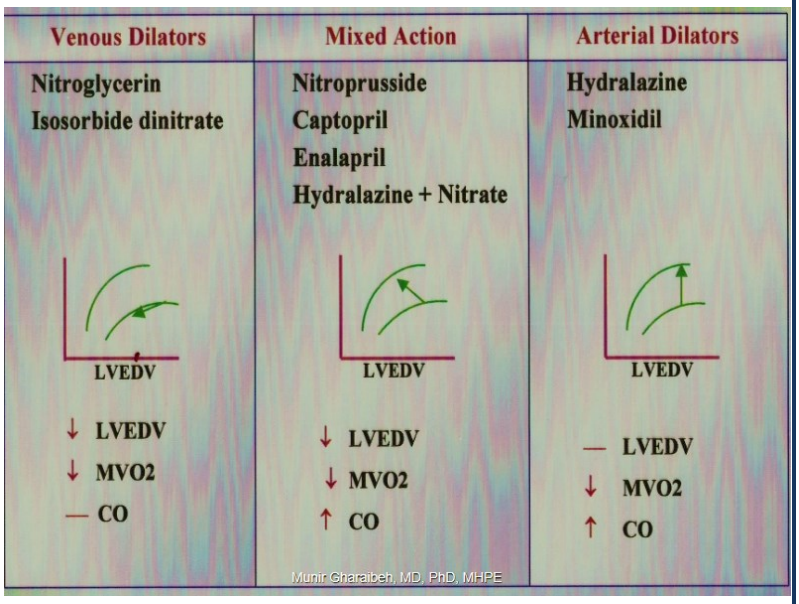
- PDE inhibition leads to accumulation of cAMP and cGMP leading to positive inotropic activity and peripheral vasodilation respectively.
- Toxic side effects: arrhythmias, and thrombocytopenia.
- Short acting, so they are reserved for parenteral therapy of acute heart failure.
- There are 5 Phosphodiesterase isozymes, inhibiting each one has a distinct effect Examples include: Inamrinone (PDE-3), Milrinone (PDE-3), Vesanirone (PDE-3), Sildenafil (Viagra, inhibits PDE-5, causes vasodilation of penile veins which treats erectile dysfunction)

Vasodilators

These are vasodilators that work directly on blood vessels.

- They affect preload and/or afterload without directly affecting contractility.
- Consequently, they can decrease myocardial ischemia, and enhance coronary blood flow and decrease myocardial oxygen consumption (MVO2).
- Can be used in acute heart failure and for short periods in CCHF, they are not good for chronic use.
- We have 3 types, atrial, venous and mixed dilators.
- Hydralazine (an arterial dilator)-Isosorbide dinitrate (a venous dilator) combination was documented to decrease mortality, maybe by reducing remodeling of the heart.
- Can be combined with ACEI, diuretics and digitalis.

About the figure, The upper curves are healthy people, the lower curves are HF patients, and the arrow indicates the shift that occurs after taking the corresponding drug.

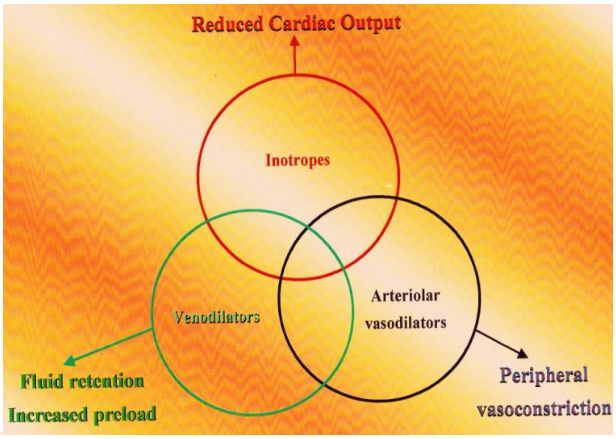


Venous dilators will cause pooling of blood in veins which will reduce the burden on the right heart. Causing decrease in left ventricular end diastolic volume LVEDV and decrease in MVO2 but no effect on cardiac output. Unlike in healthy people, decreasing the venous return in HF patients will not affect the CO, because it decreases the congestive symptoms of heart failure (There is already an increased volume of blood [congestion])

Arterial dilators, these don't affect the LVEDV, but they will reduce PVR and thus increasing the cardiac output CO, reducing the stress on the left heart and improving organs' blood perfusion.

Mixed action drugs, will produce the two effects together reducing LVEDV, MVO2 and increasing CO.

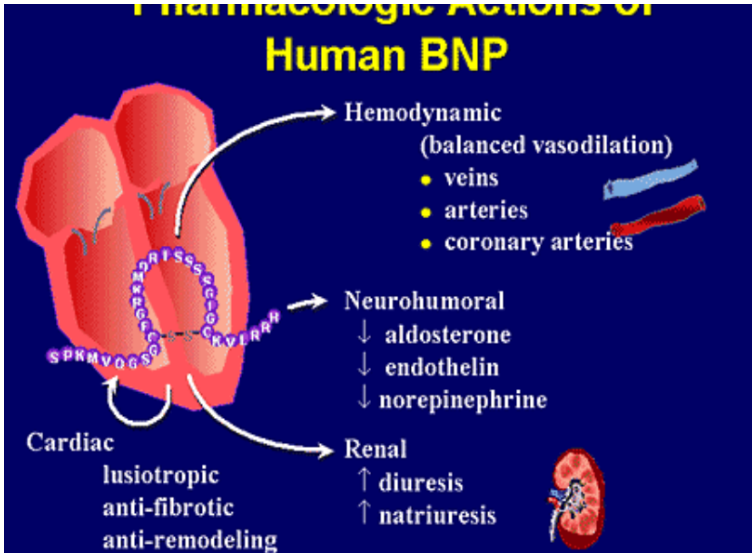
DRUG CLASS	EXAMPLES	MECHANISM OF VASODILATING ACTION	PRELOAD REDUCTION	AFTERLOAD REDUCTION
Organic nitrates	Nitroglycerin, isosorbide dinitrate	NO-mediated vasodilation	+++	+
Nitric oxide donors	Nitroprusside	NO-mediated vasodilation	+++	+++
Angiotensin-converting enzyme inhibitors	Captopril, enalapril, lisinopril	Inhibition of Ang II generation, decreased bradykinin degradation	++	++
Angiotensin receptor blockers	Losartan, candesartan	Blockade of AT_1 receptors	++	++
Phosphodiesterase inhibitors	Milrinone, inamrinone	Inhibition of cyclic AMP degradation	++	++
Direct-acting K^+-channel agonist	Hydralazine	Unknown	+	+++
	Minoxidil	Hyperpolarization of vascular smooth muscle cells	+	+++
$_1$ Adrenergic antagonists	Doxazosin, prazosin	Selective $_1$ adrenergic receptor blockade	+++	++
Nonselective $^{\alpha}$ adren ergic antagonists	Phentolamine	Nonselective adrenergic receptor blockade	+++	+++
Vasodilating $^{\beta}$ $_1$ adrenergic antagonists	Carvedilol, labetalol	Selective $_1$ adrenergic receptor blockade	++	++
Ca^{2+} channel blockers	Amlodipine, nifedipine, felodipine	Inhibition of L-type Ca^{2+} channels	+	+++
adrenergic	Isoproterenol	Stimulation of vascular	+	++



Depending on the specific case of the patient we choose the appropriate drug. For example, if the patient has increased preload & reduced CO we give drugs that treat both. Look at the Venn diagram.

BNP - Niseritide

- Brain natriuretic peptide (BNP) is secreted constitutively by ventricular myocytes in response to stretch.
- BNP increases levels of cGMP.
- BNP is released under atrial and ventricular stress leading to vasodilation, natriuresis and diuresis.
- BNP is cleaved by Neprilysin.
- Niseritide is a recombinant human BNP approved for treatment of acute decompensated CHF.



The actions of BNP:

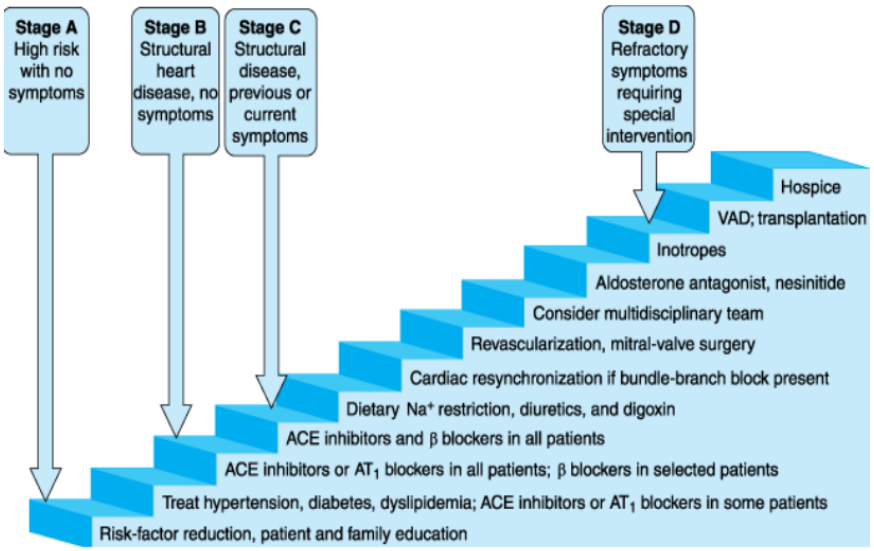
- Reduces systemic and pulmonary vascular resistances, causing an indirect increase in cardiac output and diuresis.

- Effective in HF and pulmonary hypertension because of reduction in preload and afterload.
- Hypotension is the main side effect

Sacubitril:

- Is a Neprilysin inhibitor used in combination with valsartan (an ARB) to reduce the risk of cardiovascular events in patients with chronic heart failure.
- Neprilysin also breaks down angiotensin I and II, endothelin-1 and peptide amyloid beta-protein.
- Inhibition of Neprilysin therefore leads to reduced breakdown of endogenous natriuretic peptides in addition to increased levels of vasoconstricting hormones such as angiotensin II.

Management of HF starting from high risk to end stages of the disease:



Errors in Management of HF:

- Missed diagnosis.
- Improper dosage of diuretics.
- Failure to assess quality of life.
- Failure to consider long term therapeutic goals.
- Under-prescribing of ACEI.
- Use of potentially harmful drugs.
- Failure to use hydralazine-isosorbide combination which has proved evidence of benefit.

Good luck