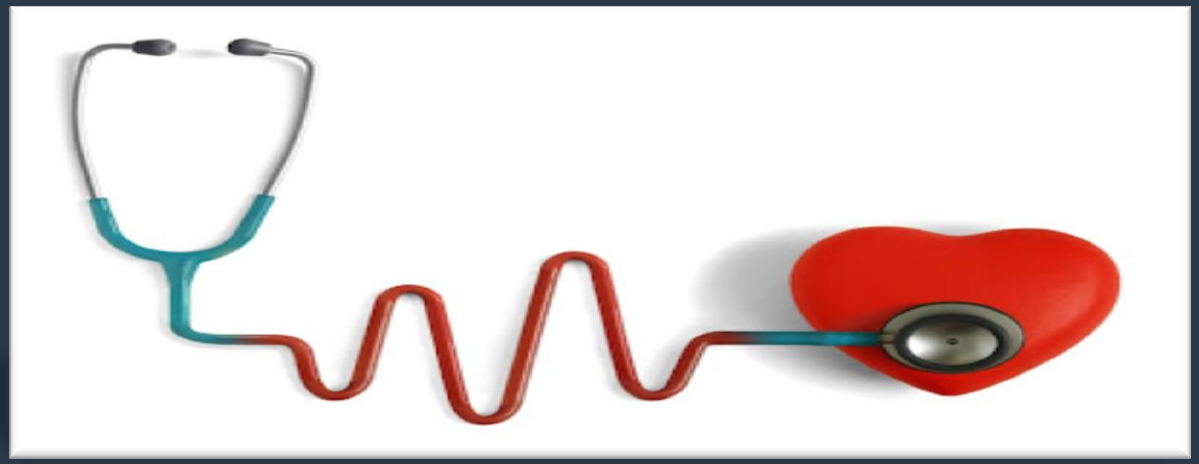
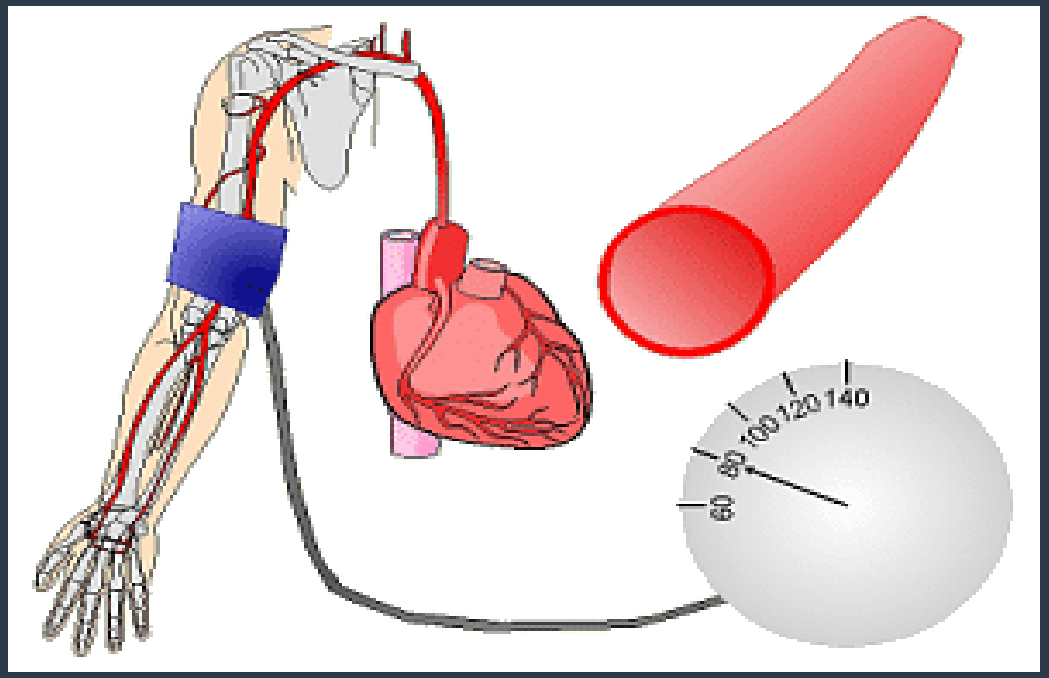
Antihypertensive Drugs



‘’hypertension also called The Silent killer’’

Sustained Elevation of blood pressure systolic and diastolic….



High blood pressure (hypertension)

sometimes called **arterial hypertension occur when** the blood pressure in the arteries is elevated.

Blood pressure involves two measurements.

The systolic pressure :

When the ventricle is contracting & pump blood into arterial circulation.

The diastolic pressure:

is the pressure recorded when the heart is filling & the value obtained reflects predominantly the total peripheral resistance (TVR) in the vascular beds.

Blood Pressure Classification

Blood Pressure Category	Systolic mm Hg (upper #)		Diastolic mm Hg (lower #)
Normal	less than **120**	and	less than **80**
Prehypertension	**120 – 139**	or	**80 – 89**
High Blood Pressure (Hypertension) **Stage 1**	**140 – 159**	or	**90 – 99**
High Blood Pressure (Hypertension) **Stage 2**	**160** or higher	or	**100** or higher
Hypertensive Crisis (Emergency care needed)	Higher than **180**	or	Higher than **110**

Essential hypertension

- ✓ In 80 % of cases the cause isn't known= **Essential (primary) Hypertension.**
- ✓ Symptomatic treatment i.e. reduce blood pressure .

Secondary hypertension

There are a specific causes of hypertension …….

At the beginning we have to treat the cause.

Causes of secondary hypertension

I. Phaeochromocytoma.

II. Chronic kidney disease.

III. Primary aldosteronism.

Target organ damage

1. (CVS) Herat :-

- Left ventricular hypertrophy.
- Coronary artery disease.
- MI.
- Herat failure.

2. (CNS)Brain :-

- Stroke or transient ischemic attacks.

3. (Renal system)Chronic kidney disease or kidney failure.

4.(Retinopathy)Retinal damage.

Management

1- Non-pharmacological Management.

2- Pharmacological Management.

Mean arterial pressure

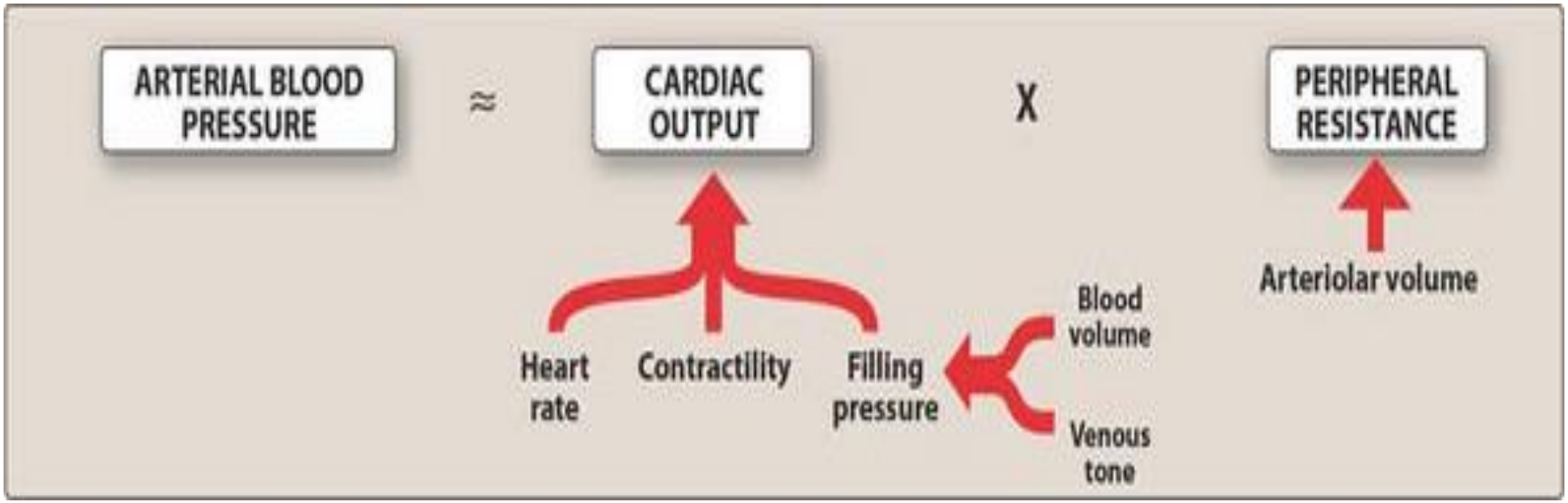
Depend on diameter. (thickness) more force to pump blood

Volume of blood pump by heart

MAP (BP) = CO X PVR

CO = HR X SV

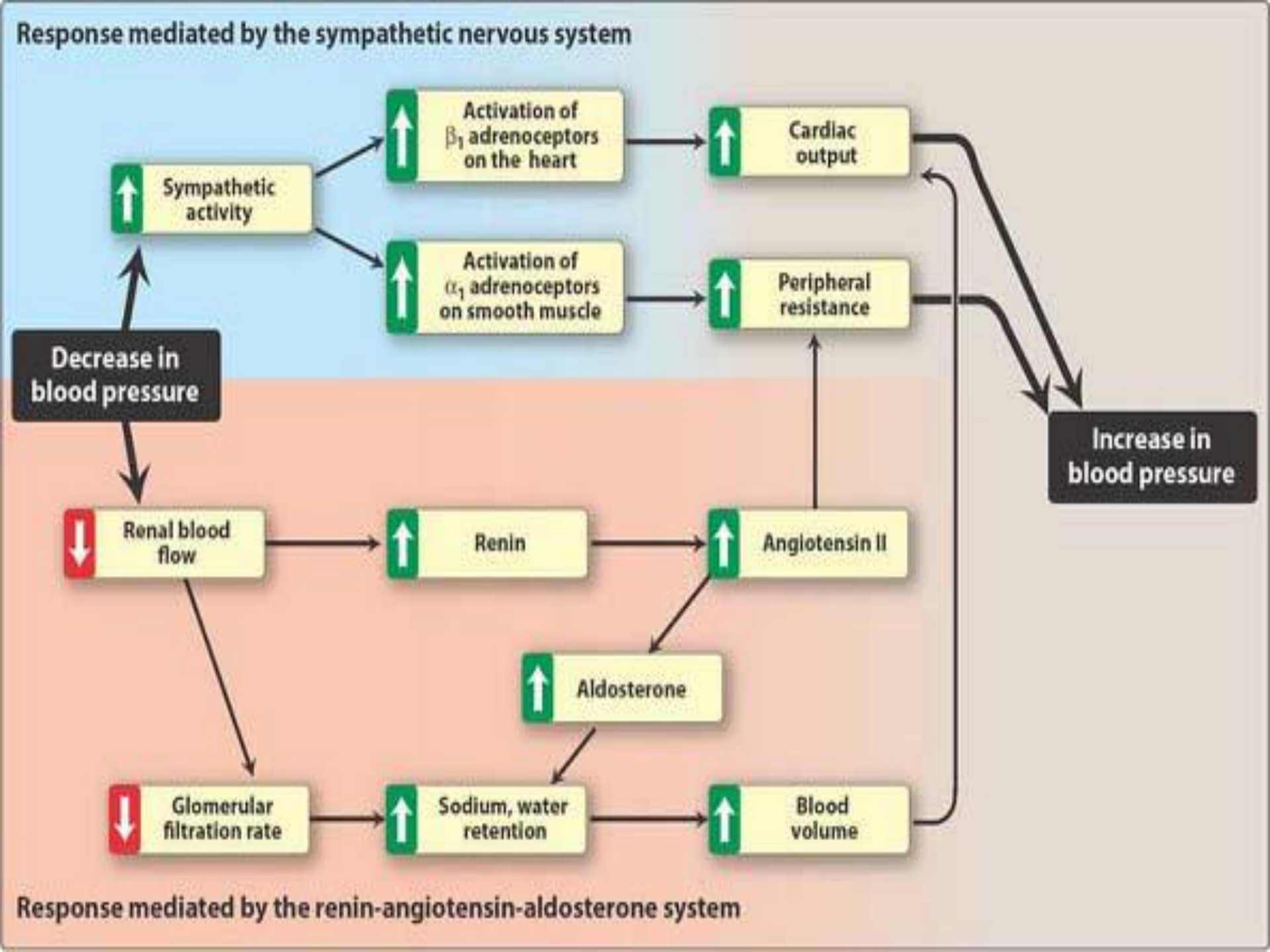
Vol of blood by 1 beat



BP is controlled by

1- Baroreceptors & the Sympathetic nervous system.

2- Renin angiotensin aldosterone system. (RAAS)


Response mediated by the sympathetic nervous system
Activation of β_1 adrenoceptors on the heart
Cardiac output
Sympathetic activity
Activation of α_1 adrenoceptors on smooth muscle
Peripheral resistance
Decrease in blood pressure
Increase in blood pressure
Renal blood flow
Renin
Angiotensin II
Aldosterone
Glomerular filtration rate
Sodium, water retention
Blood volume
Response mediated by the renin-angiotensin-aldosterone system

BP= (CO *PVR)

So, if I want to reduce the BP what the strategies to do that?

Decrease cardiac output, peripheral vascular resistance and central venous pressure WITH MORE DETAILS:

To decrease the cardiac output

1_reduce heart rate

2_reduce contractility

3_ reduce conduction velocity

All these thing can be achieved by beta blockers & calcium channel blockers

4- decrease blood volume → Diuretics

To decrease the peripheral vascular resistance

1- Use vasodilators

2-decrease vasoconstrictors

A) Calcium channel blockers

Which inhibit smooth muscle contraction in blood vessels

B) Direct vasodilators

Major controller of vasoconstriction in our body Is the RAAS system so we use RAAS INHIBITOR.

3- Alpha blocker

Reduce the sympathetic tone (It is regulated majorly by alpha 1 receptor) in our body

Antihypertensive drugs classifications

The most important before beginning of treatment make diagnosis at least three independent measurement not on single reading

&

Determine If the patient primary H.T or secondary H.T.

Actions site for drugs:

1- CNS,ANS → Decrease sympathetic tone.

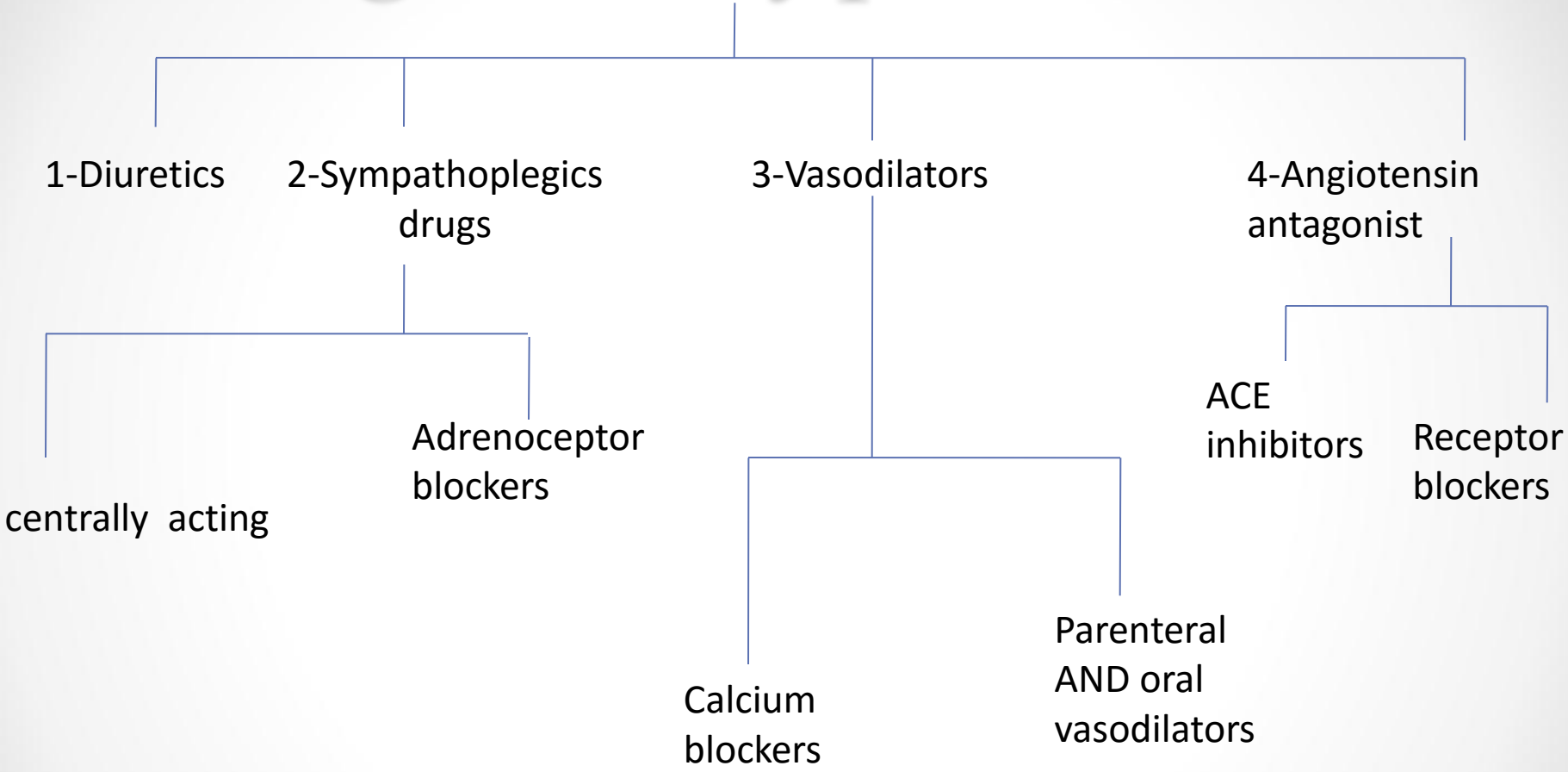
2- Heart → Decrease Cardiac output.

3- veins → dilate → decrease preload (amount of blood which comes to the heart).

4- arterioles→ dilate –> decrease afterload (when heart contract it will pushes the blood to dilated arteriole not constricted ones).

5- kidneys → increase diuresis ; inhibits RAAS system.

Drugs for hypertension



we have two strategies to use antihypertensive drugs in patients:

1-The Monotherapy:

Its useful mainly in stage 1 hypertension.

2-combination Therapy:

Which is double or triple antihypertensive drugs used in stage 2 HTN.

1. Diuretics

↓ **BP by →** ↓ **Na store** (increase Na excretion)

↓ blood volume (by increase urine output)

& ↓ CO.

↑ H2O excretion.

- There site of actions in the Nephron.
- Used in mild to moderate HT→ alone
- In sever case → combination(sympathoplegic, Angiotensin antagonist & vasodilator drugs)
- Cause electrolyte imbalance.

1. Diuretics

Can be divided into 3 classes which are

1- Thiazide

Targets the transport system in the distal **convoluted tubule** which is responsible of the reabsorption of Na and Cl back into the body , the percentage of Na and Cl which is reabsorbed here is 5% so thiazide diuretics reduce the reabsorption by 5% .

2- loop diuretics

- ✓ Targets the co-transport system in **the thick ascending limp within the loop of henle** , which is responsible of the reabsorption of Na , 2Cl , K back into the body , and the percentage in here is 25% so it's more effective.

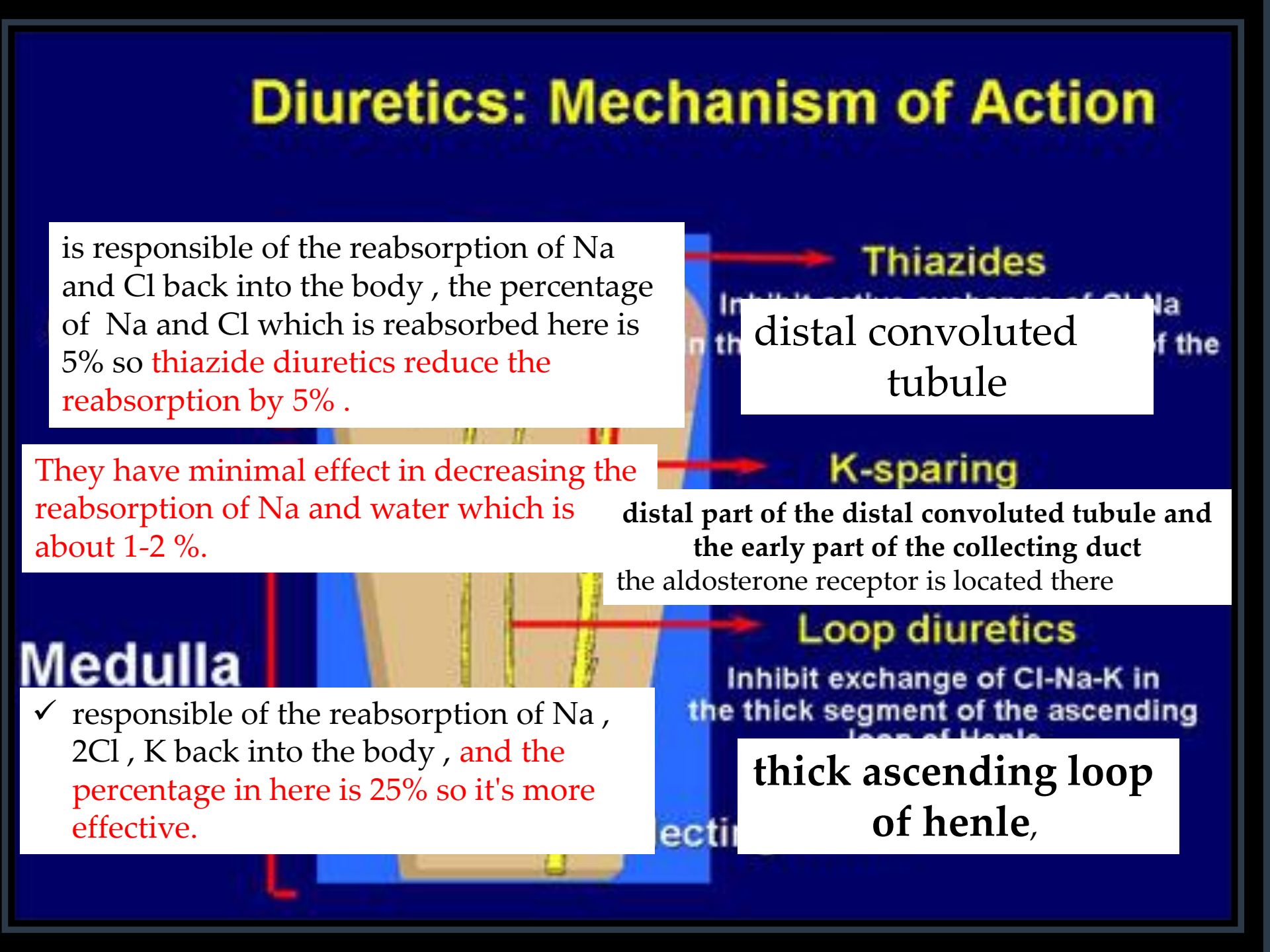
3- Potassium sparing diuretics

They target the aldosterone receptors within the distal convoluted tubule and the collecting duct.

_ They have minimal effect in decreasing the reabsorption of Na and water which is about 1-2 %.

Diuretics: Mechanism of Action

is responsible of the reabsorption of Na and Cl back into the body , the percentage of Na and Cl which is reabsorbed here is 5% so thiazide diuretics reduce the reabsorption by 5% .



They have minimal effect in decreasing the reabsorption of Na and water which is about 1-2 %.

- ✓ responsible of the reabsorption of Na , 2Cl , K back into the body , and the percentage in here is 25% so it's more effective.

Diuretics

1- Thiazide
Hydrochlorothiazide

USED for long treatment…

- (the most commonly used because it's extremely cheap)

- Also it has vasodilator effect→ reduce peripheral resistance

2- loop diuretics
furosemide

✓ Used in emergency(IV)

→very effective .

✓ Strongest diuretics

✓ Also it has effect on PG synthesis

3- Potassium sparing diuretics
spironolactone

✓ Weakest diuretics. Used in combination Not alone

✓ Aldosterone antagonist.

Loop diuretics :

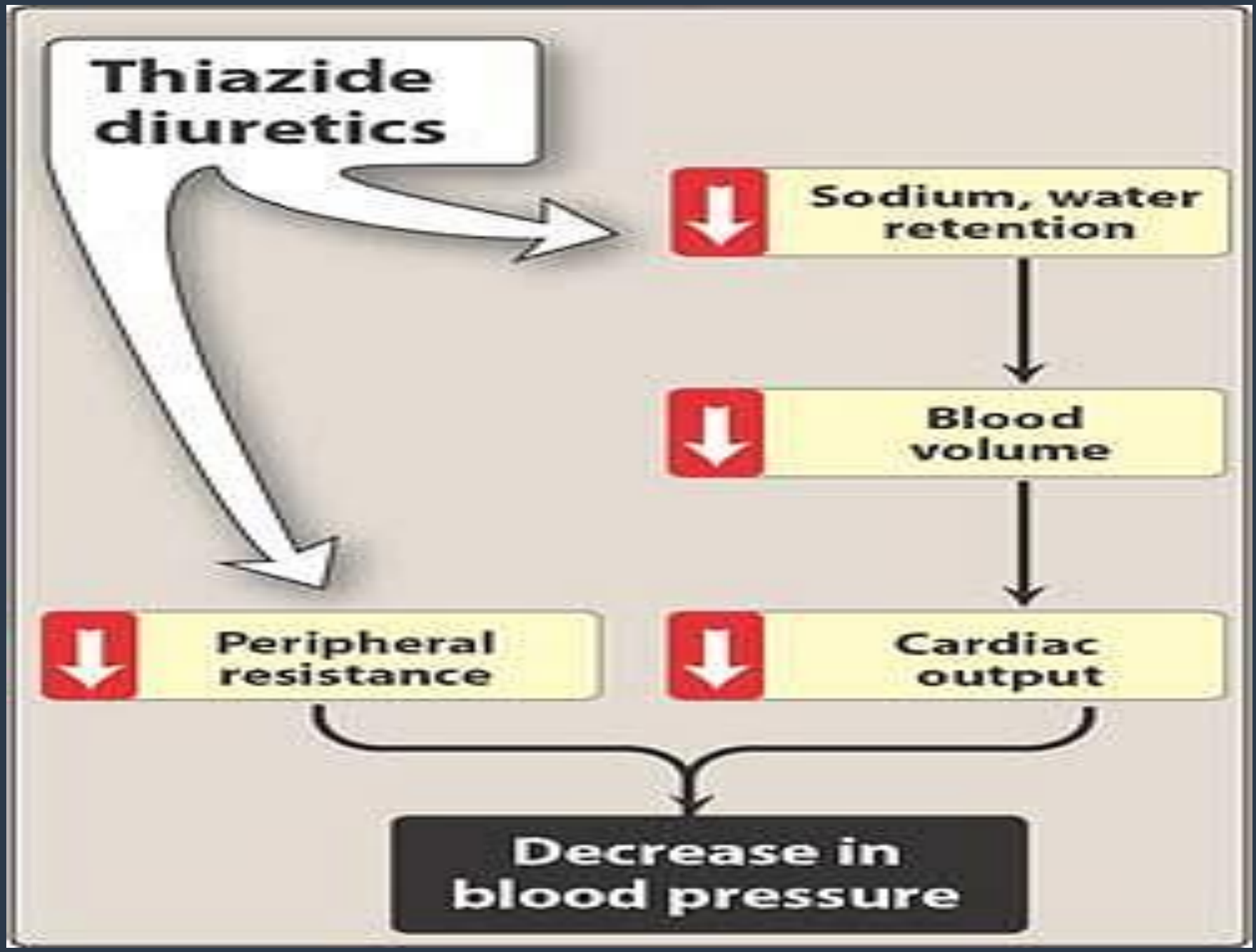
Note that **they are not the most commonly used** because they affect the life style and reduce the compliance of the patient (he won't be active socially and he will be going to the bathroom all the night so he can't sleep).

That's why they are used in emergency situations (heart failure, pulmonary edema)

Spironolactone

Has the additional benefit of diminishing the cardiac remodeling that occurs in heart failure

Now, how the diuretics achieve their function and reduce the blood pressure??


Thiazide diuretics
Sodium, water retention
Blood volume
Cardiac output
Peripheral resistance
Decrease in blood pressure

practical comments

- ***Loop and thiazide :***

  Safe, inexpensive, and effective drugs.

Remember : They are usually used in mild to moderate cases(alone)

And because of this they are considered as an integral part in combination therapy of HTN.

The major function of diuretics is to reduce the blood volume and CO.

But What would happen if we have a decrease in the mean arterial pressure?

there is something called fight back mechanism, we have the baroreceptor reflex and this will lead to the activation of both:

1. ***Sympathetic system.***
2. ***Renin angiotensin aldosterone system (RAAS system) .***

So, you will reach a point of balance between diuretics which reduces the reabsorption and sympathetic and RAAS system which increase it so you will have some sort of balance.

that's why We must combine the diuretics with either:

Sympathetic blockers or RAAS inhibitor

Loop diuretics increase prostaglandins synthesis

The major function of PG is a vasodilatation renal blood flow will increase, so the amount which can be cleared by the diuretics will be increased.

And this another cause why loop diuretics are more effective than thiazide diuretics because as we said:

---

it has the ability of decreasing reabsorption of Na and water by 25% - they increase the PG synthesis

NSAIDs interfere with response to diuretics

- ***NSAIDs inhibit the prostaglandins synthesis*** and particularly in the chronic use of diuretics, NSAIDs will reduce the effect of diuretics.

Thiazide diuretics *are the 1st line antihypertensive drugs (they are cheap and effective) particularly in: -*

- ***elderly.***
- ***diabetics.***

Loop diuretics are the first line in:

- ***Heart failure***
- ***Renal failure***

always think of **loop diuretics** because they have the ability to reduce the reabsorption by 25%, so there will be a great reduction of fluid in our body.

Side effects of diuretics thiazide & loop

1-Hypotension the 1st SE in any antihypertensive drug is hypotension.

2- Hyperuricemia Increase in the uric acid concentration. THUS, They are contra in gout patients

3-Hypokalemia : **Both are contra with digoxin bcoz it enhances the toxicity of digoxin**

Now there is SE particular for each class:

1. *Thiazide diuretics:*

hyperglycemia .

2. loop diuretics

ototoxicity They cause some defect in hearing.

3. K - sparing :

hyperkalemia

2. Sympathoplegics

Adrenergic blockers

Drugs that alter sympathetic NS function.

1- alpha-blockers: the major function is on the blood vessels.

2- beta-blocker: **effect on both B1 & B2**

3- central sympatholytics : which affect both of them and cause reduction in sympathetic activity.

I. Alpha-1-blockers.

Ex. Prazosin

- ❖ Are the major regulator of sympathetic tone in the blood vessels.

- block the sympathetic nerve supply to the small arteries and arterioles by Blocking α-receptors on vascular smooth muscle allows muscle relaxation, dilation of vessel, and reduced resistance.

- Its used in patient with H.T & Benign prostatic hyperplasia….why ???
- Very essential use in pheochromoctoma

It’s seldom used alone, it's always used in combination therapy with beta –blockers. Why??

Adverse effects:-

postural hypotension; reflex tachycardia→ **1st dose syncope**.

II. Beta Blockers

Non-selective (β1, β2):- Propranolol (prototype)

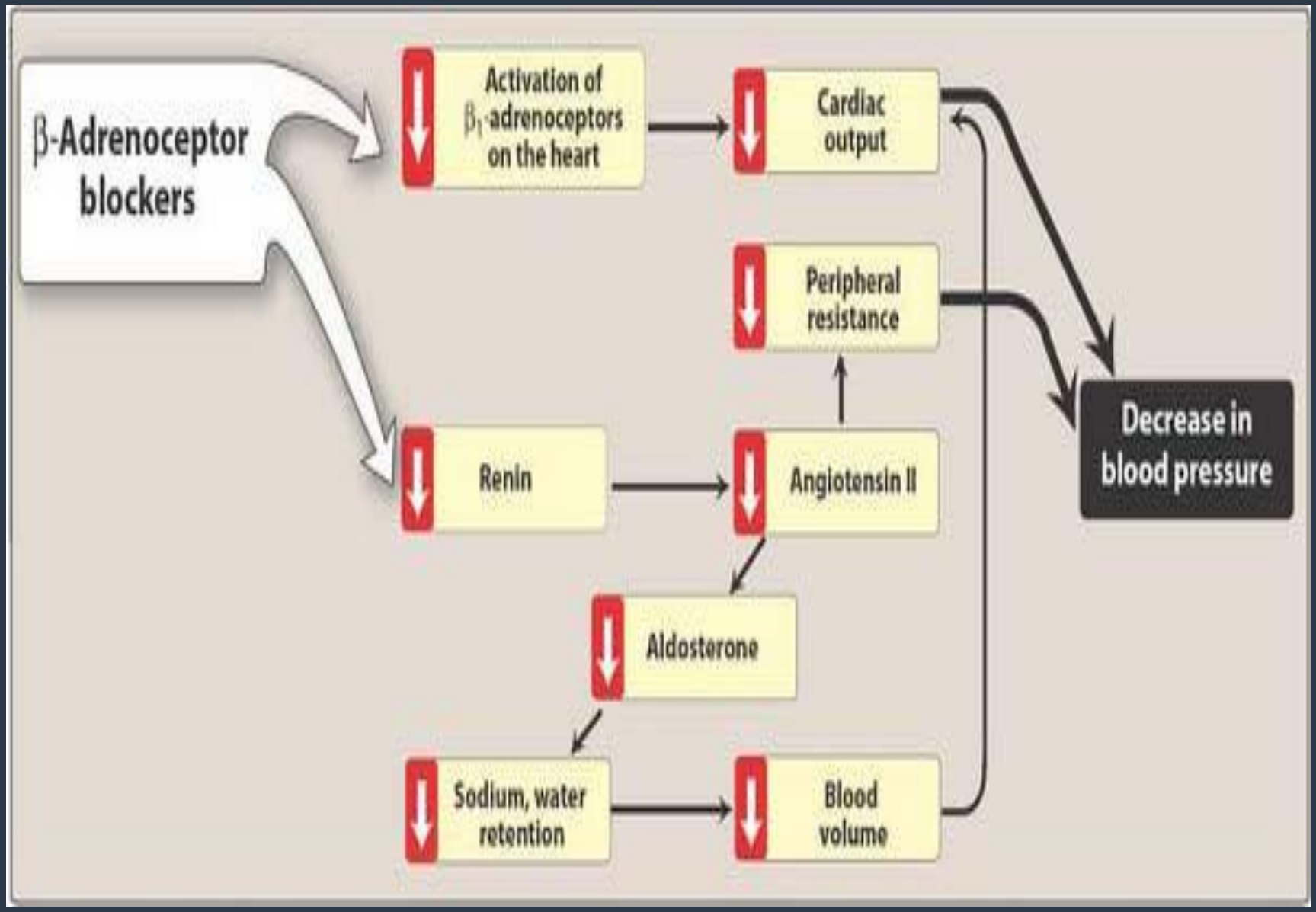
Selective(β1) :- Atenolol

Non selective (β & α1):- labetalol,carvedilol.

MOA:-

competitive antagonist at β- adrenergic receptors

- **Block cardiac β1 receptors** → ↓HR ,↓ contractility,↓ CO→ reduce BP.
- **Block renal β1 receptors (on chronic use)** → ↓ renin secretion → ↓ PVR → reduce BP.


β-Adrenoceptor blockers
Activation of β1-adrenoceptors on the heart
Cardiac output
Peripheral resistance
Renin
Angiotensin II
Aldosterone
Sodium, water retention
Blood volume
Decrease in blood pressure

Labetalol also used in pheochromocytoma , alternative to methyldopa in hypertensive pregnant women

&

In emergency hypertension

B-Blockers

Therapeutic use

- Hypertension.
- Angina.
- MI.
- Arrhythmias.
- Hyperthyroidism.
- Heart failure. (selective drug for selective pts)
- Glaucoma.
- migraine.

Adverse Effects

- Bradycardia.
- Hypotension.
- Bronchoconstriction **(non-selective).**
- Withdrawal syndrome.
- Cold extremities.

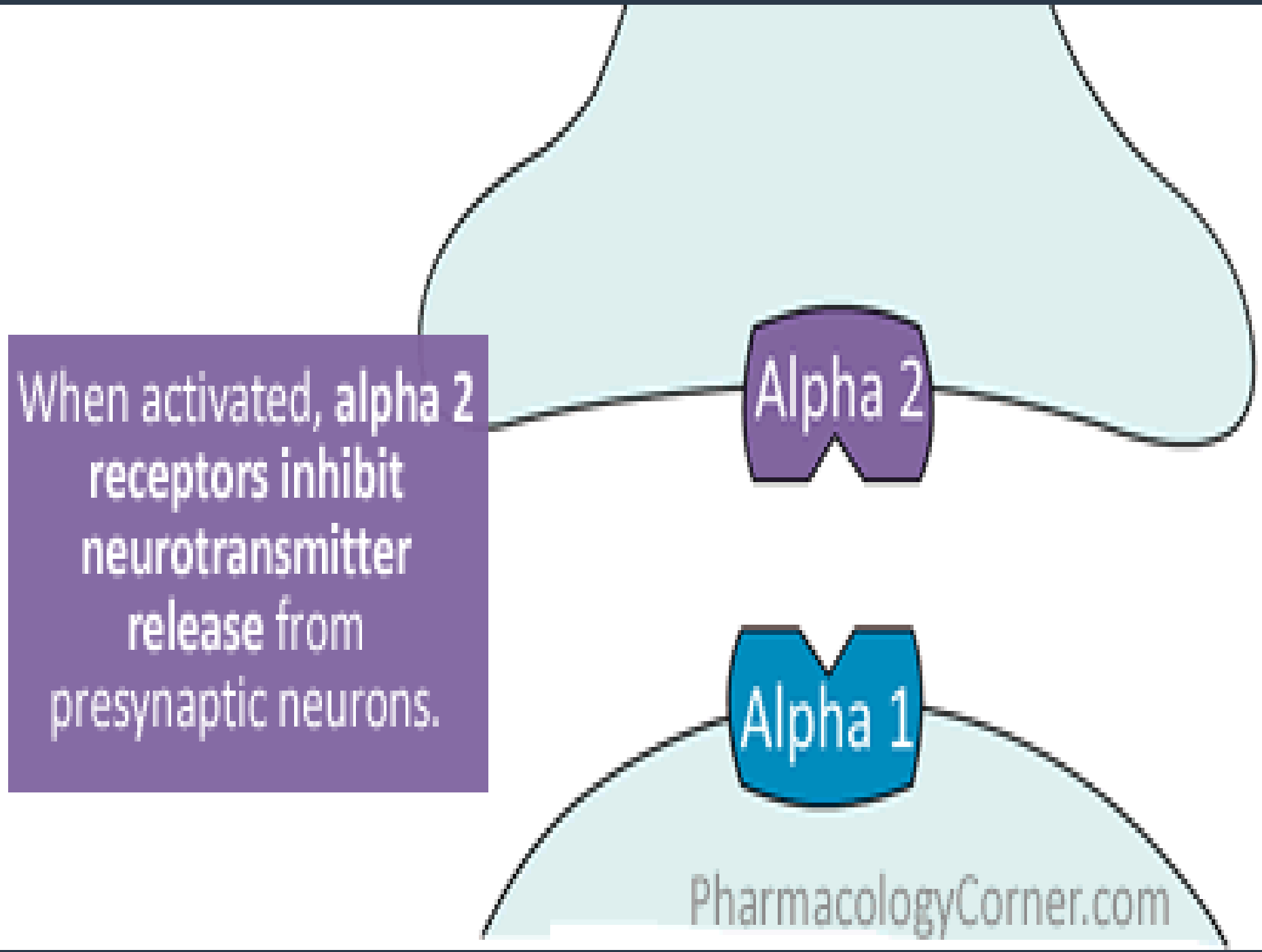
Contraindications

- Asthma (due toβ2 antagonist).
- Diabetes.
- Bradycardia.

III. Centrally acting sympatholytics
α-2 Agonists

MOA:-

- CNS α–2 adrenergic stimulation in the medulla → decreases peripheral sympathetic activity→ reduces tone → vasodilation and decreases TPR.


When activated, alpha 2 receptors inhibit neurotransmitter release from presynaptic neurons.
Alpha 2
Alpha 1
PharmacologyCorner.com

Methyldopa

Used primary in hypertension in pregnancy.

Clonidine

- **when the patient is having *resistant hypertension*** (which means that you are using all the conventional classes of antihypertensive drugs and there is no apparent response),

Suddenly withdrawn cause →hypertensive crisis (rebound HT)

3. DIRECT Vasodilators

Dilate(relax) blood vessels by acting directly on the smooth muscle of arterioles some them on veins→ ↓ PVR.

Example:

1. Hydralazine
2. Minoxidil
3. Nitroprusside

Primary acting on arteries and arterioles not veins

✓ Hydralazine → safe for pregnancy

→ given IV & oral.

Not given alone, usually combination… why??

Adverse Effects

✓ Fall in BP → Reflex tachycardia.

✓ Fall in BP→ renin release → Na/water retention.

} Combined with B-Blockers & diuretics

✓ Systemic lupus-Like syndrome → Hydralazine.

✓ Hypertrichosis (growth body hair) → Minoxidil. That's why now days used in this case

Parenteral

✓ Nitroprusside →dilates both arterial and venous vessels.

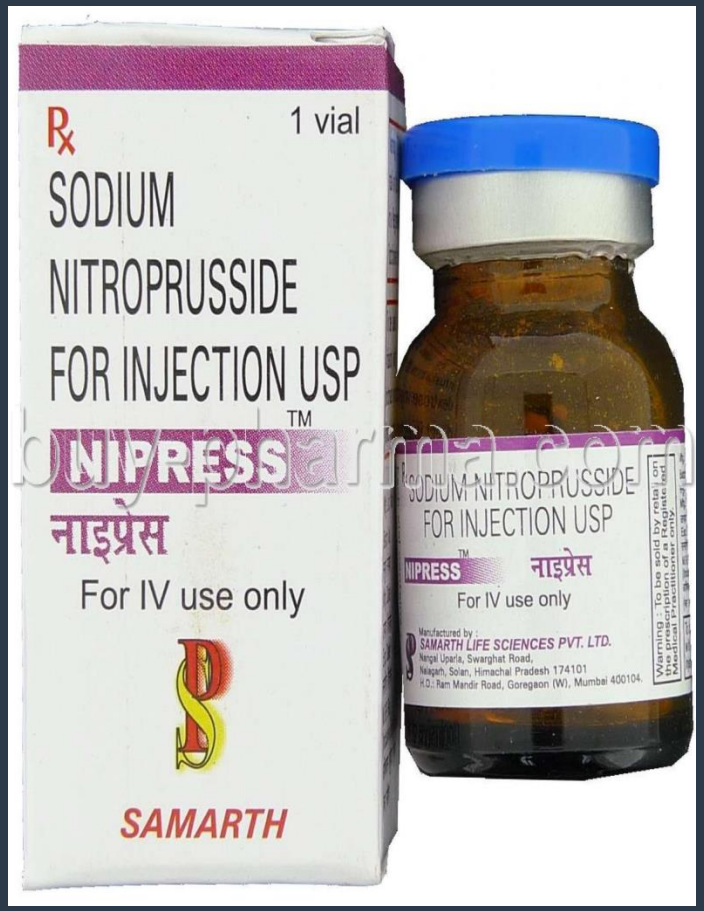
its powerful reduced BP→ reduced Peripheral resistance & venous return → **used in hypertensive emergencies (**comes with End Organ Damage)**.**

we have another drug which is Labetalol (used in emergency hypertensive control hypertensive crisis) and it is a combined alpha1 & beta blocker.

- *The onset of action* for Nitroprusside is immediate while it takes 5-10 minutes with labetalol

Nursing point

- ✓ Nitroprusside → the content of ampoule should be dissolved in 2 ml 5 % dextrose or saline .
- ✓ The infusion must be protected from the light (because it rabidly hydrolyze to cyanide) and discarded after 24 hr.
- ✓ It should also be discarded if the color changes from pale orange to dark brown or blue.
- ✓ Continues infusion to maintain hypotensive action.


Rx
1 vial
SODIUM
NITROPRUSSIDE
FOR INJECTION USP
NIPRESS
नाइप्रेस
For IV use only
SAMARTH
SODIUM NITROPRUSSIDE
FOR INJECTION USP
NIPRESS
नाइप्रेस
For IV use only
Manufactured by :
SAMARTH LIFE SCIENCES PVT. LTD.
Nangal Uparla, Swarghat Road,
Nalagarh, Solan, Himachal Pradesh 174101
H.O.: Ram Mandir Road, Goregaon (W), Mumbai 400104.

4. CCB

✓Very nice drugs

MOA : *they block the inward movement of calcium by binding to L-type calcium channels in the heart and in smooth muscle of the coronary and peripheral vasculature.*

This causes vascular smooth muscle to relax, dilating mainly arterioles.

Amlodipine Dihydropyridine	Verapamil Non-dihydropyridine,	Diltiazem Non-dihydropyridine,
Selective act on vascular smooth muscle or blood vessel (arterial side) ➢→ reduce peripheral resistance (reduce after load) → *cause relaxation thus decrease in BP.*	Act on cardiac muscle → inhibit lead to slow heart rate & delay of conduction. (-ve inotropic & dromotropic)	both cardiac and vascular smooth muscle
Cause reflex tachycardia due to hypotension	Cause bradycardia	bradycardia

- They have natriuretic action that's why we don't prescribe with diuretics drugs.

- useful in the treatment of hypertensive patients who also have asthma, diabetes, angina, and/or peripheral vascular disease.

Calcium-Channel Blockers

Cardiac effects

- Decrease contractility
  (negative inotropy)
- Decrease heart rate
  (negative chronotropy)
- Decrease conduction velocity
  (negative dromotropy)

Vascular effects

- Smooth muscle relaxation
  (vasodilation)

Therapeutic Use of Calcium-Channel Blockers

- Hypertension
  (systemic & pulmonary)
- Angina
- Arrhythmias

Adverse effect

1. **(amlodipine)** → **Postural hypotension ,vertigo and** reflex tachycardia.

   usually combine with B-blocker

   ankle edema (dihydropyridine edema)

2. **(Verapamil , Diltiazem).** → **bradycardia**

3. **Constipation.** occurs in 10 percent of patients treated with verapamil.

4. **Headache.**

5. *The RAAS inhibitors*

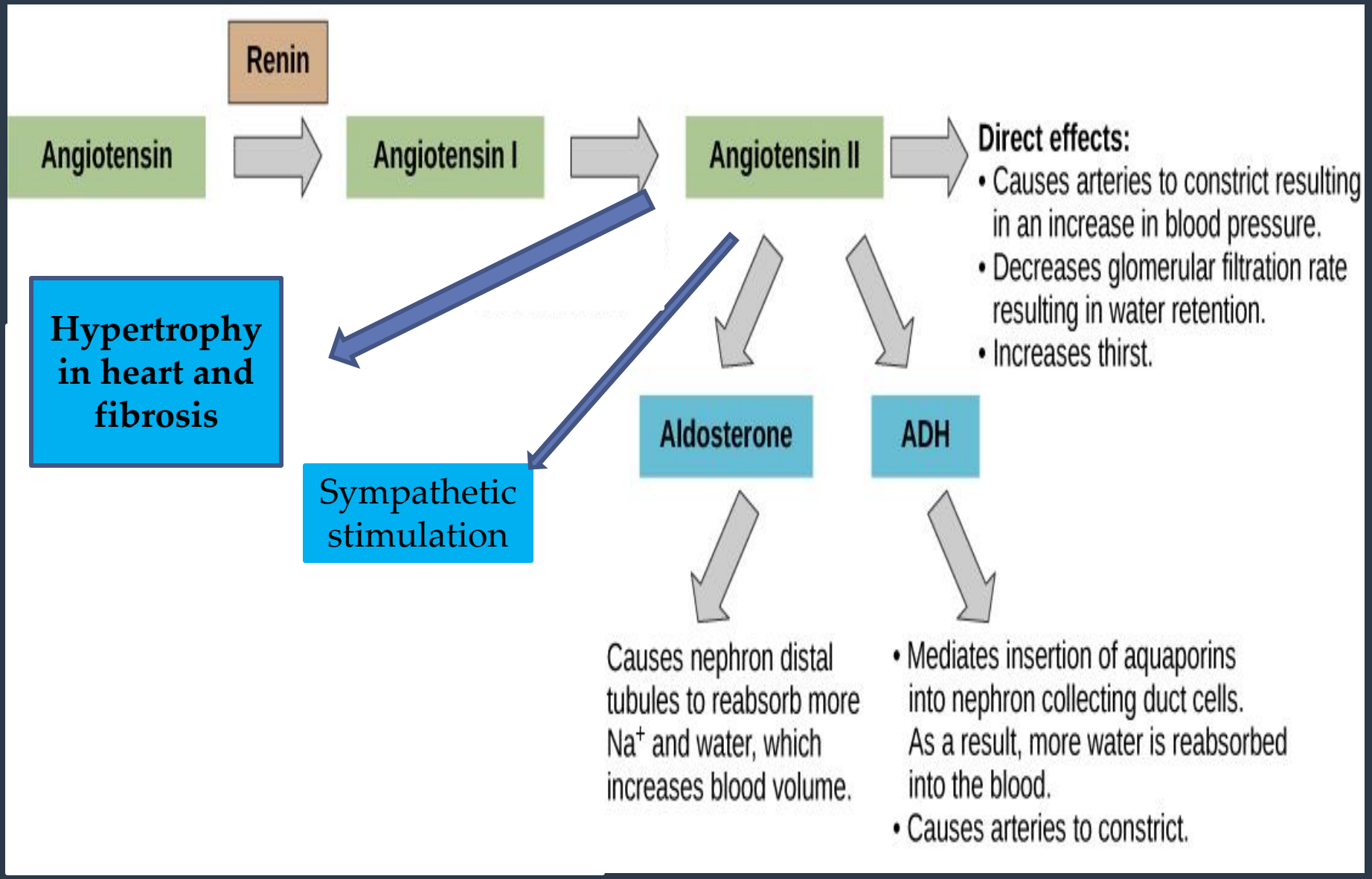
Prevent the synthesis of angiotensin II.

I. Angiotensin Converting Enzyme-Inhibitors (ACEI)

- Enalo**pril**
- Captopril

II. Angiotensin II Receptor Antagonists (ARB)

- Lo**sartan**
- Candesartan
- Valsartan


Renin
Angiotensin
Angiotensin I
Angiotensin II
Direct effects:
• Causes arteries to constrict resulting in an increase in blood pressure.
• Decreases glomerular filtration rate resulting in water retention.
• Increases thirst.
Hypertrophy in heart and fibrosis
Sympathetic stimulation
Aldosterone
ADH
Causes nephron distal tubules to reabsorb more Na^+ and water, which increases blood volume.
• Mediates insertion of aquaporins into nephron collecting duct cells. As a result, more water is reabsorbed into the blood.
• Causes arteries to constrict.

I. ACEI

ACEI *action:*

1. Inhibit Convert angiotensin I to angiotensin II

2. Inhibit breakdown of **bradykinin** (endogenous vasodilator).

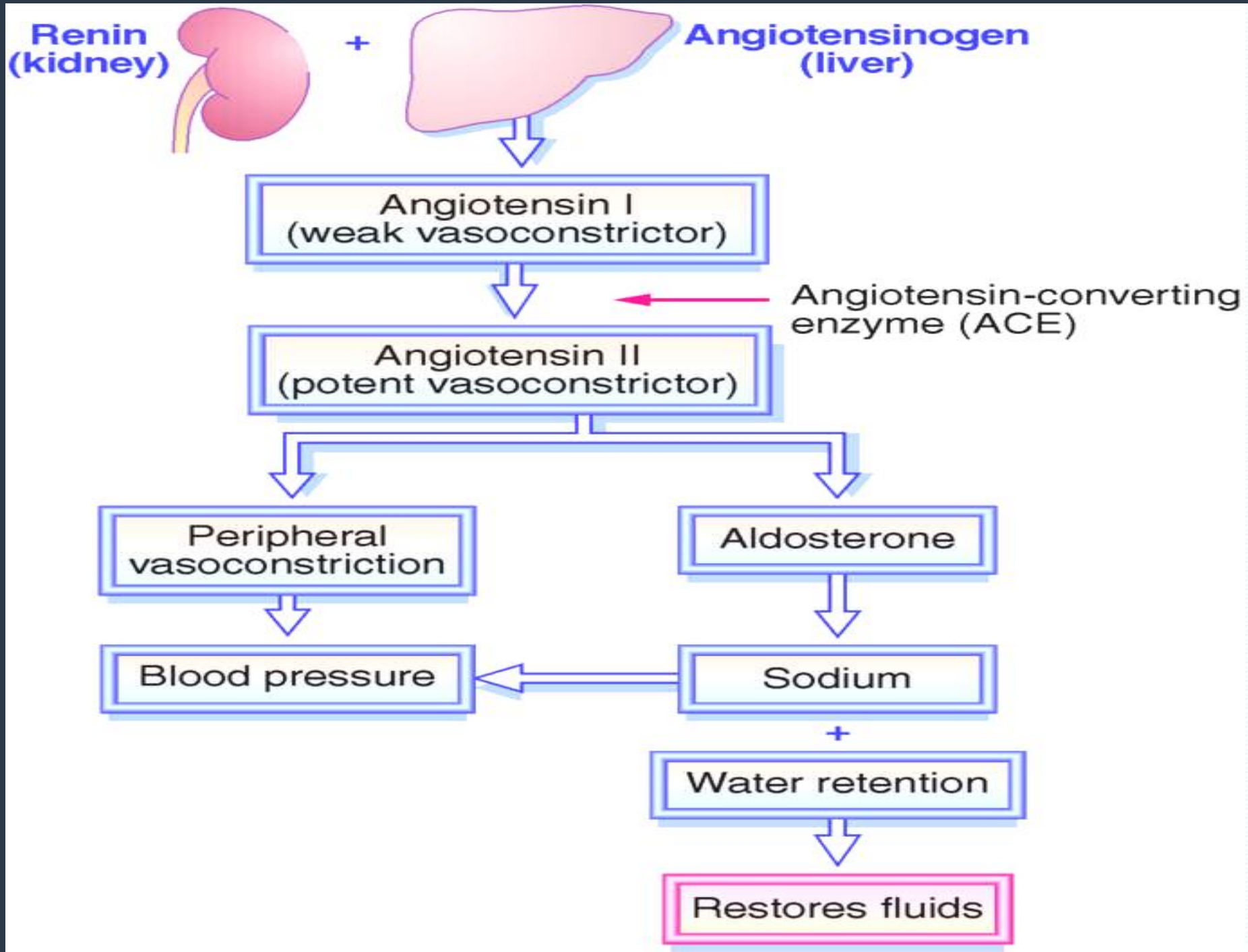
3 - Reduce sympathetic activity→ decreased vasoconstriction.

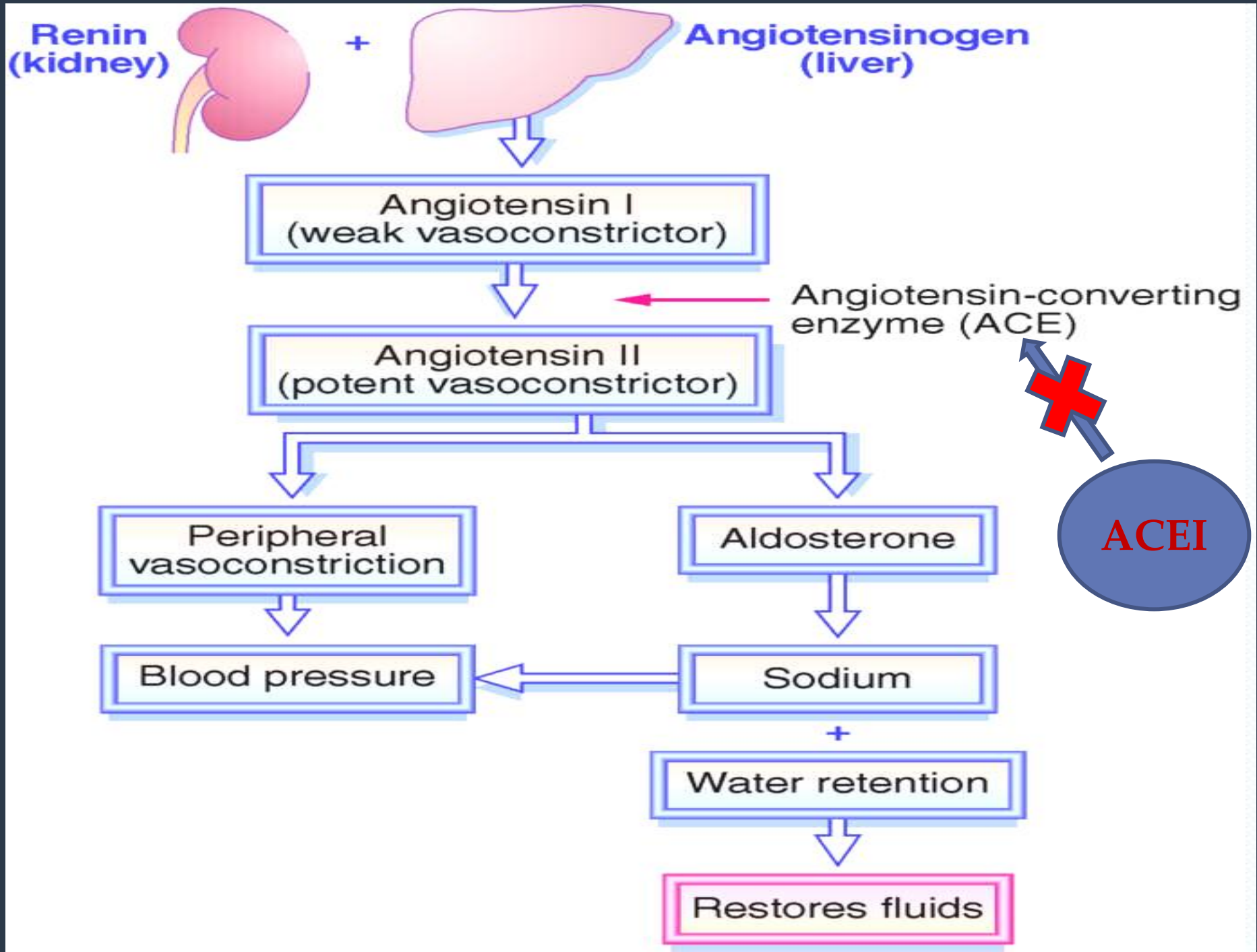
Vasodilation occurs as a result of the combined effects of lowering angiotensin II and increasing bradykinin

Reduction in sympathetic stimulation & aldosterone excretion

Decrease Peripheral Resistance

Reduce C.O & H.R


Renin
(kidney)
+
Angiotensinogen
(liver)
Angiotensin I
(weak vasoconstrictor)
Angiotensin-converting
enzyme (ACE)
Angiotensin II
(potent vasoconstrictor)
Peripheral
vasoconstriction
Aldosterone
Blood pressure
Sodium
+
Water retention
Restores fluids


Renin
(kidney)
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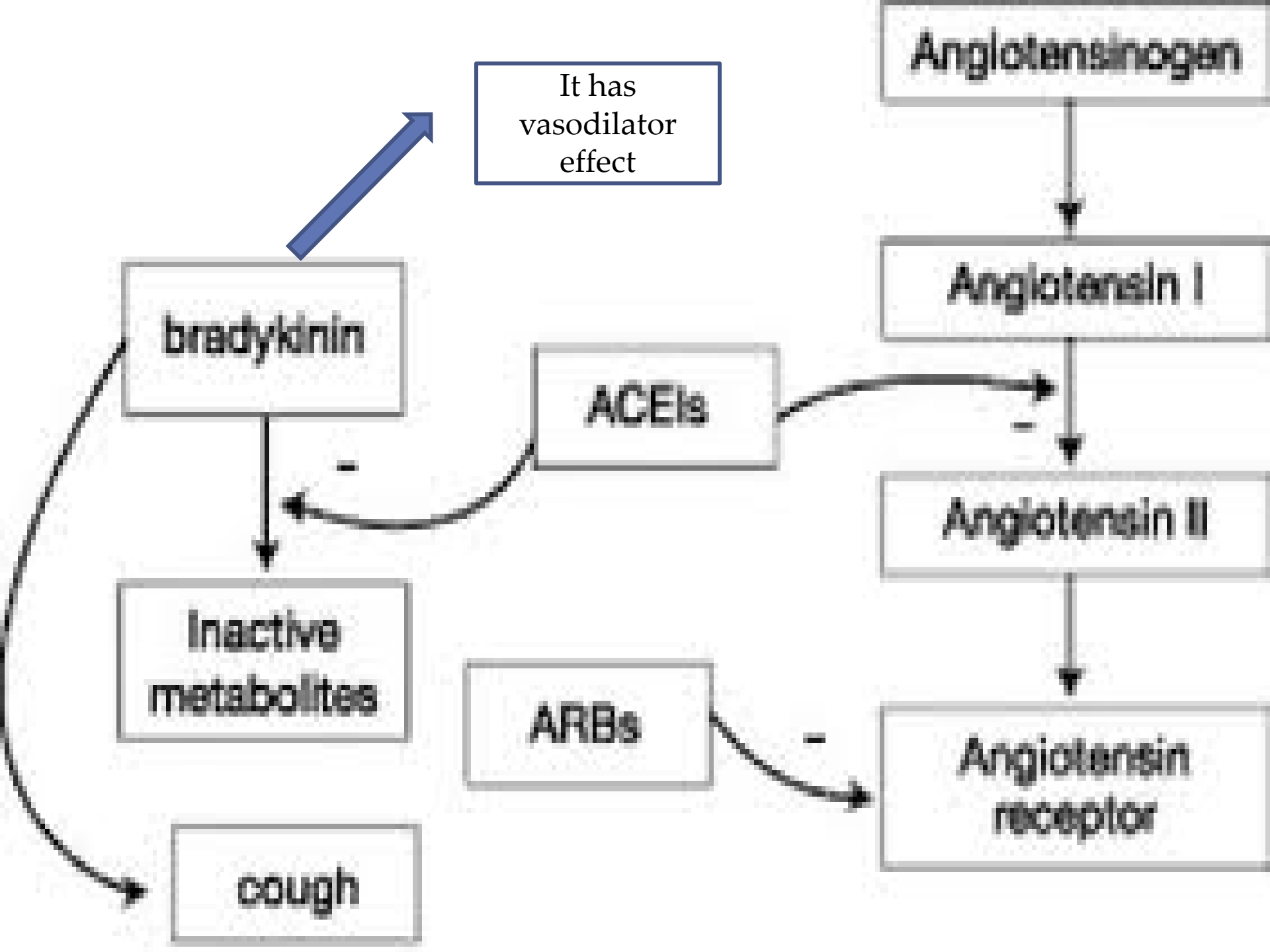
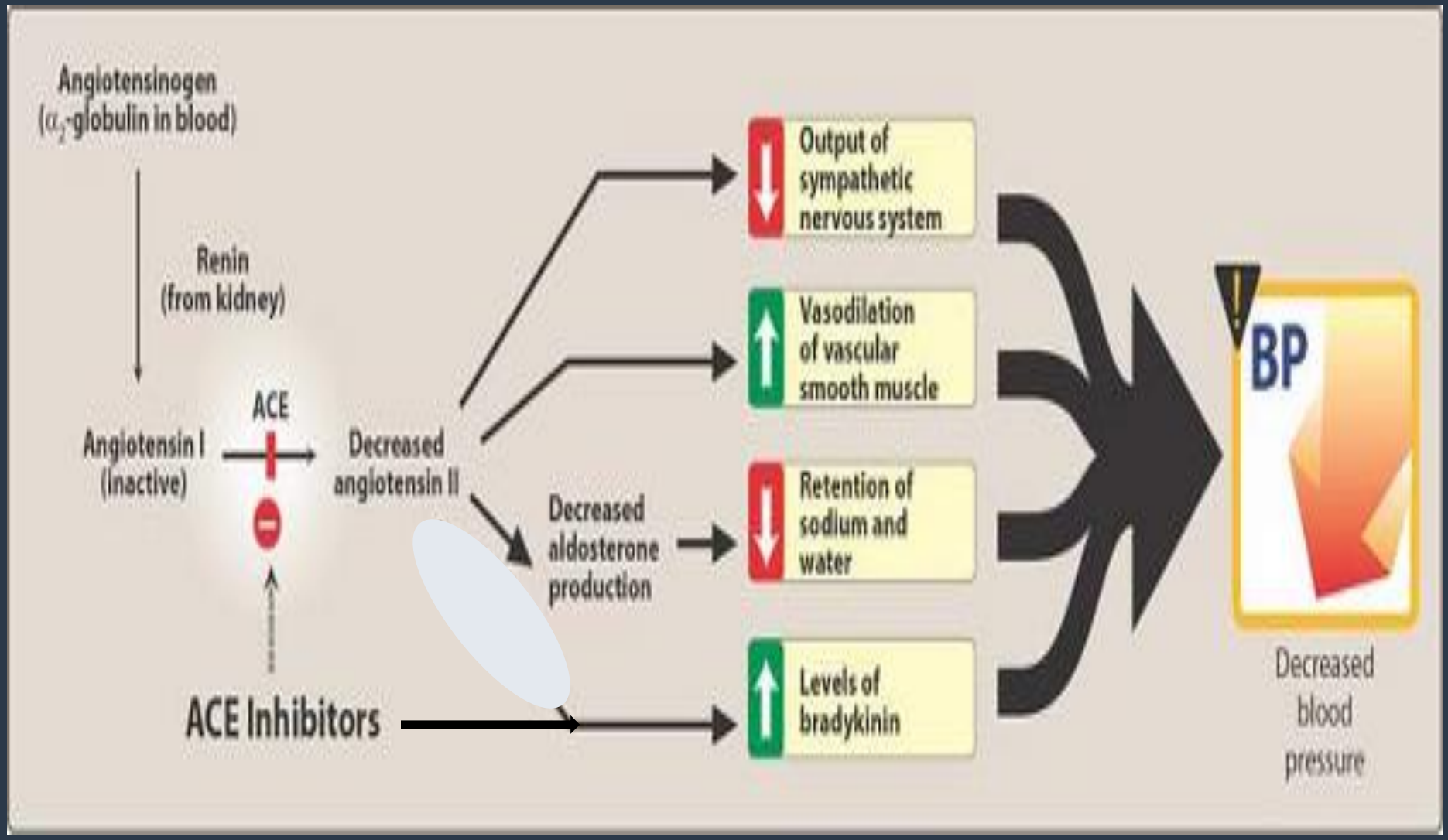
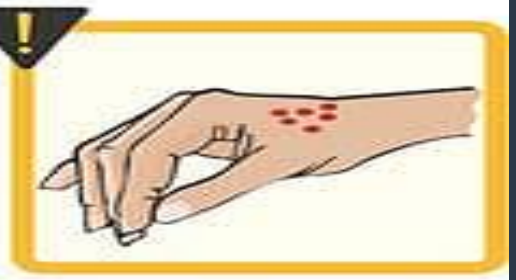

It has vasodilator effect
Angiotensinogen
Angiotensin I
Angiotensin II
bradykinin
ACEIs
Inactive metabolites
ARBs
Angiotensin receptor
cough


Angiotensinogen
(α_2-globulin in blood)
Renin
(from kidney)
Angiotensin I
(inactive)
ACE
Decreased
angiotensin II
Decreased
aldosterone
production
ACE Inhibitors
Output of
sympathetic
nervous system
Vasodilation
of vascular
smooth muscle
Retention of
sodium and
water
Levels of
bradykinin
BP
Decreased
blood
pressure

Dry cough

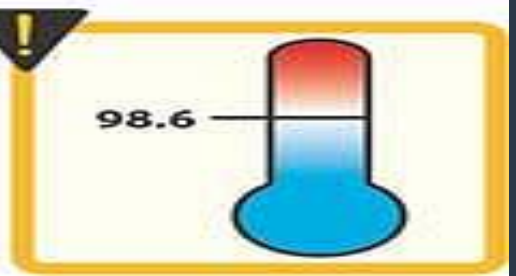
Hyperkalemia

Skin rash



Hypotension

Fever



Indications

1- Hypertension.

2- chronic Heart Failure

3- **Drug of choice**

In progressive renal insufficiency, diabetic nephropathy.

slow the progression of diabetic nephropathy and decrease albuminuria.(first-line in hypertensive type1diabetes)

➢ Adverse effect:-

1- Dry cough, angioedema (due to bradykinin)

2- hyperkalemia .

3- first dose syncope (hypotension).

➢ Contraindication

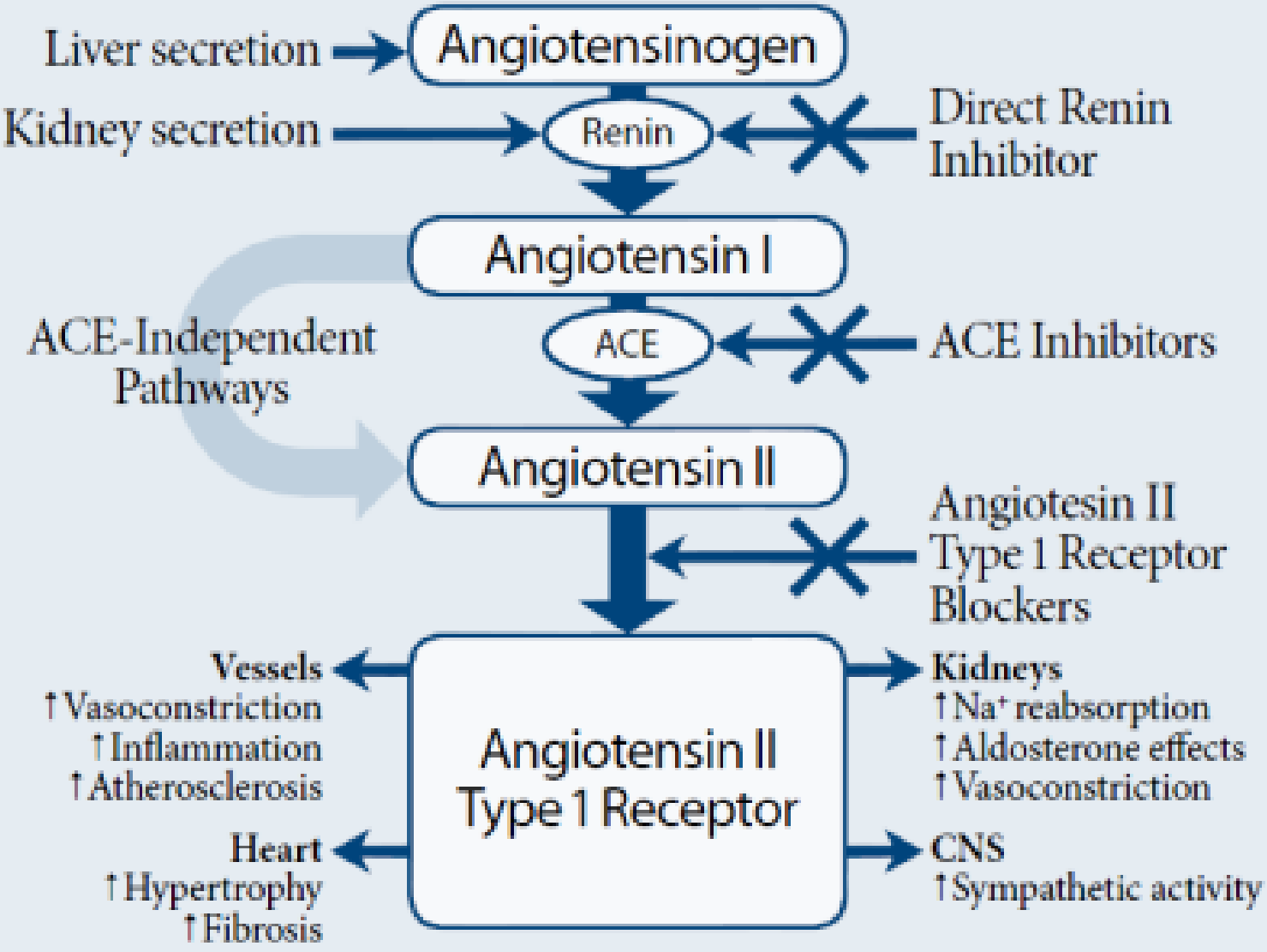
1- Pregnant women(they are fetotoxic drugs).

2- bilateral renal stenosis.

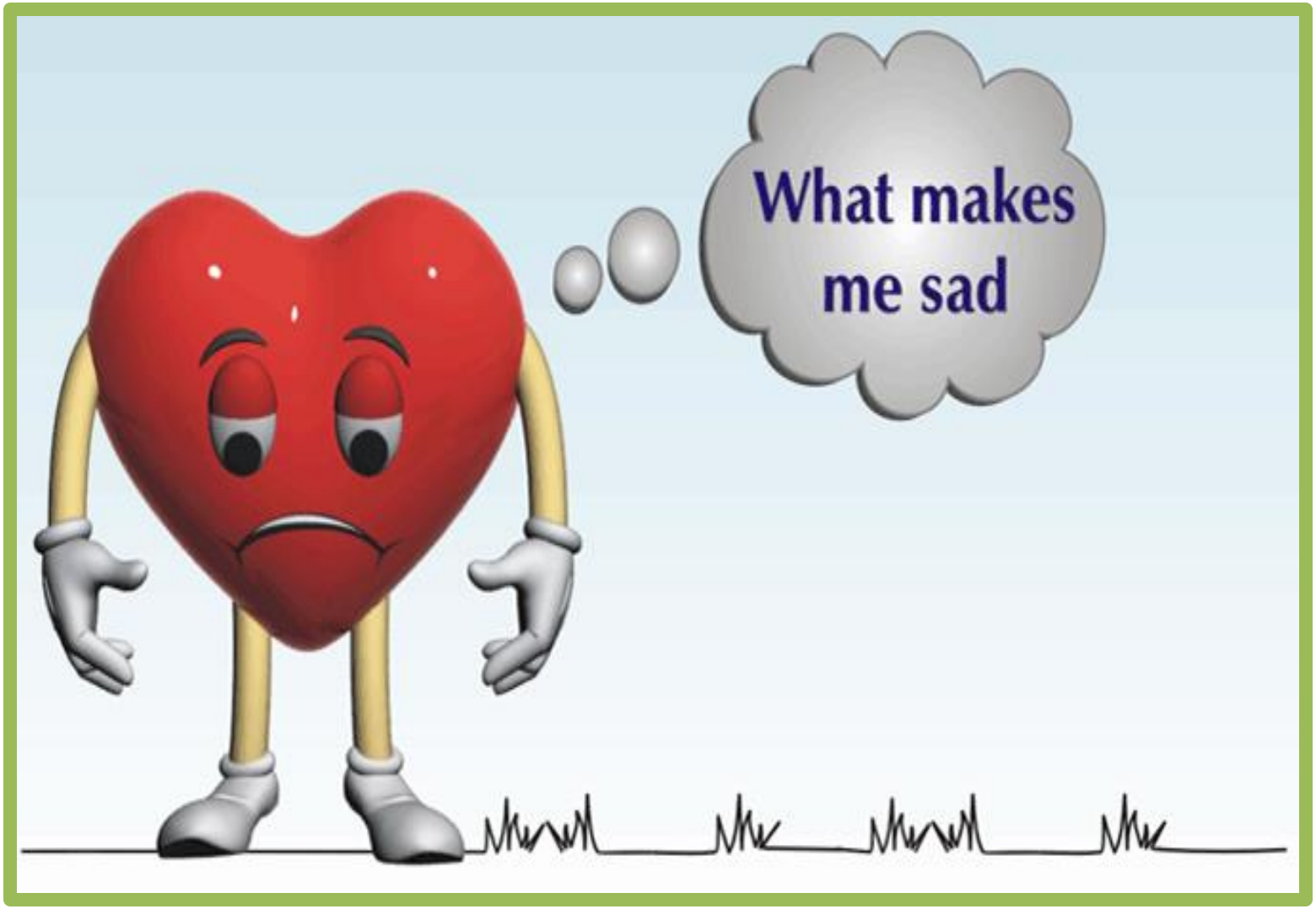
II. **AT2 receptor blockers** (Angiotensin II receptor blockers) **ARBs**

- Block the AT1 receptors .
- They carry NO advantage over ACE inhibitors, **they actually much more expensive, EXCEPT for one advantage : they don`t produce dry cough**, because it won`t cause accumulation of bradykinin, and this is important for the patients who are complaining of dry cough to consider switch them to AT2 receptor blockers but they have to have insurance or enough money.

Figure 1. Different mechanisms of pharmacological blockade of the renin-angiotensin system



Anti-Anginal drugs



Angina Pectoris

- Definition
- Types of Angina
- Management of Angina
- Antianginal drugs

Angina

Or Angina pectoris……

Or coronary artery disease……..

Or arteriosclerosis…….

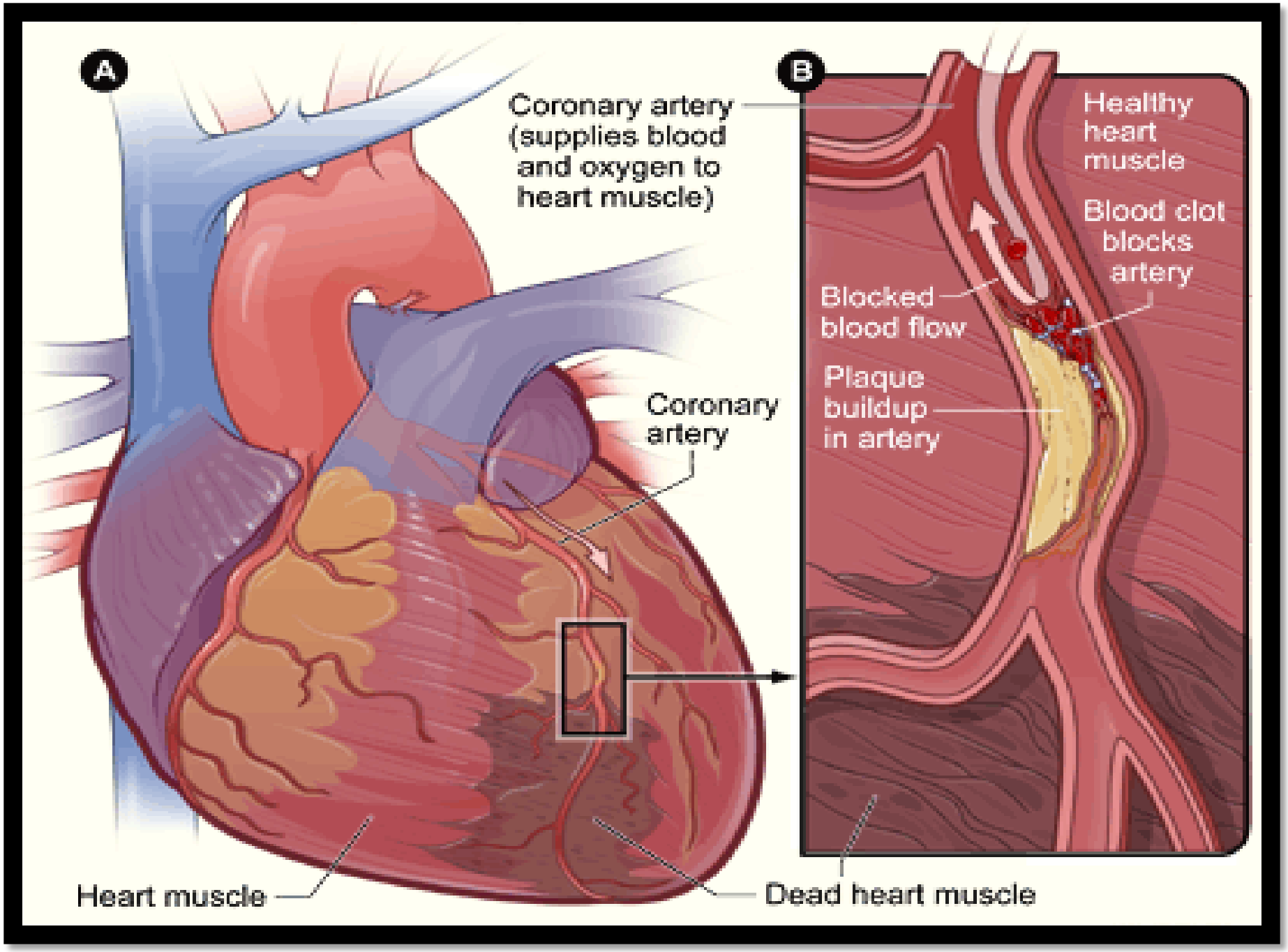
Are closely related…….

A chronic disease of CVS or ischemic heart disease.

What Is It?

- Angina occurs in people who have some form of blockage in the coronary arteries.

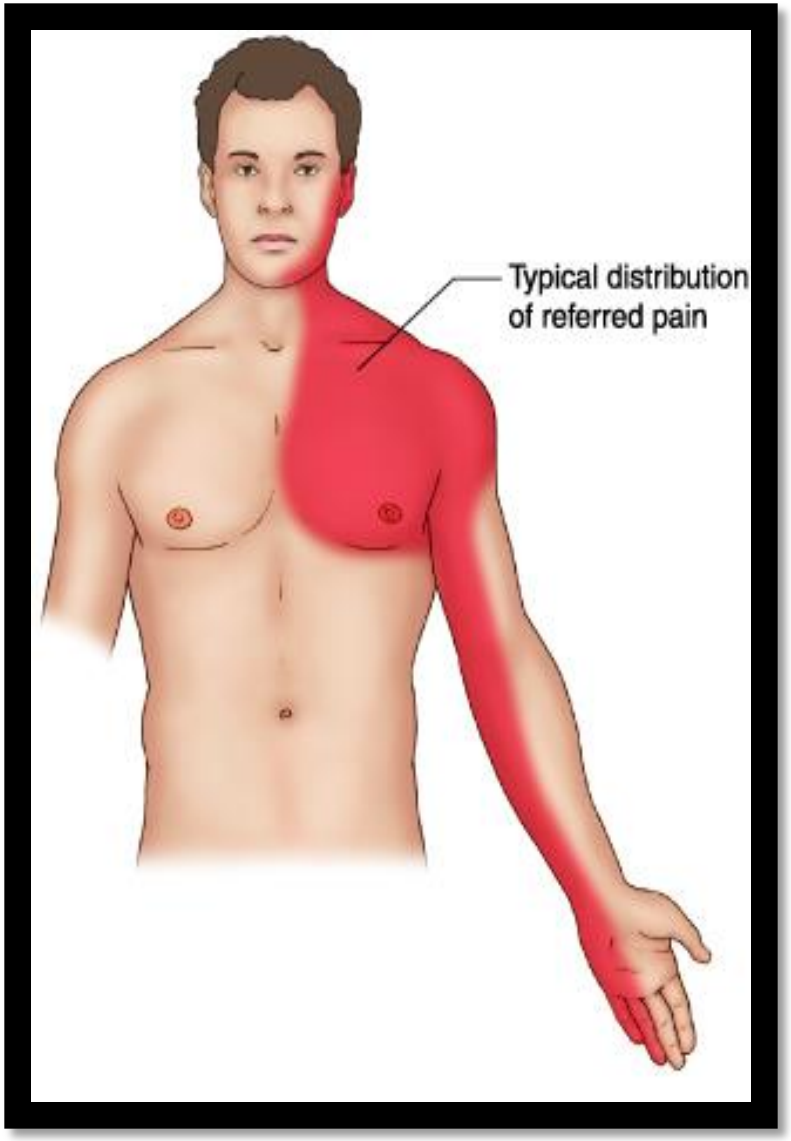
- **Angina pectoris**: a heart condition marked by paroxysms of chest pain due to reduced oxygen to the heart.
- Site of pain :behind sternum (substernally).


A
B
Coronary artery (supplies blood and oxygen to heart muscle)
Coronary artery
Heart muscle
Dead heart muscle
Healthy heart muscle
Blood clot blocks artery
Blocked blood flow
Plaque buildup in artery

What Does It Feel Like?

- ***May feel like*** sudden, severe ***pressure or a squeezing pain in chest.***
  - ***Pain could also occur in the shoulders, arms, neck, jaw, or back.***
  - ***Could also feel like indigestion.***

- Occur with intermittent chest pain spread along the chest and arms.



Angina occurs when the coronary arteries (the heart's primary source of oxygen) supply insufficient oxygen to the myocardium for it's need (due to a narrowed coronary artery)

In other word:-

Is an imbalance between myocardial oxygen demand and oxygen supplied by coronary vessels

This increases

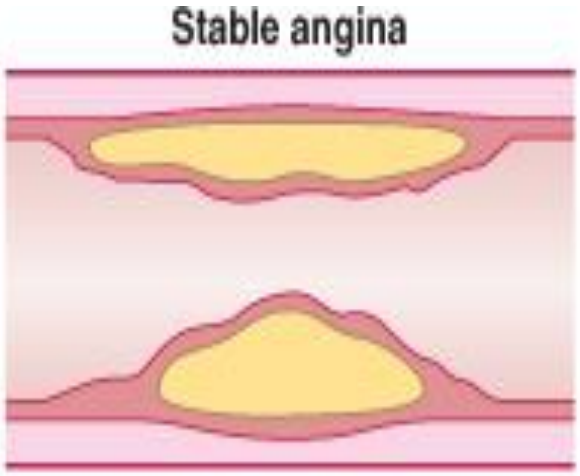
I. The heart's workload.
II. Heart rate.
III. Preload.
IV. Afterload.
V. Force of myocardial contractility.

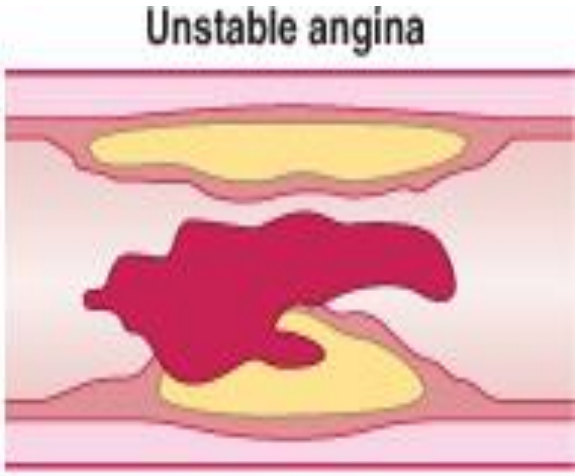
Types of Angina pectoris

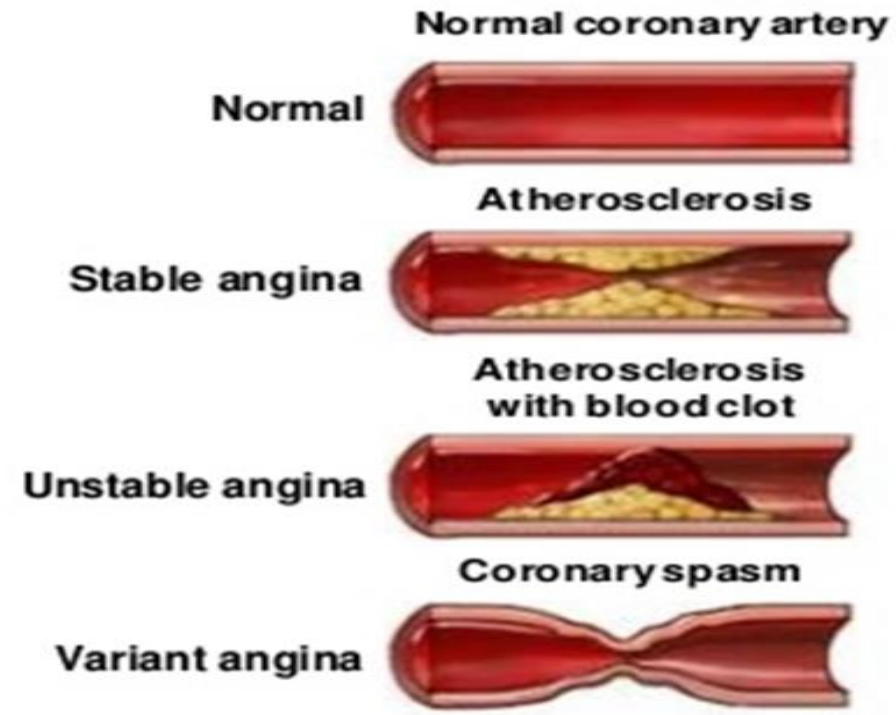
1- Stable angina.

2- Unstable angina.

3- Variant angina.


Stable angina


Unstable angina


Normal coronary artery
Normal
Atherosclerosis
Stable angina
Atherosclerosis
with blood clot
Unstable angina
Coronary spasm
Variant angina

1. Stable Angina .

Exertional angina, Typical or classic angina, Angina of effort, Atherosclerotic angina.

The most common cause is

ADVANCED ATHEROSCELEROSIS

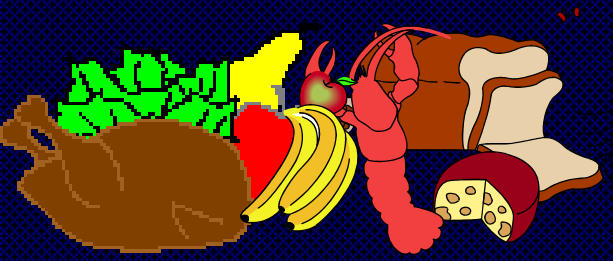
increase demand of the heart and by
a fixed narrowing of coronary vessels.

Lasting less than 15 min.

Stable Angina

Predisposing factors

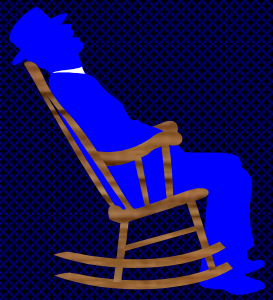
Exertion



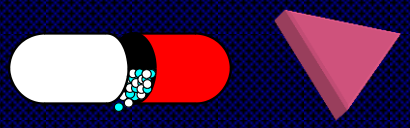
Heavy meals

Cold Weather

Relieving factors



Rest



sublingual nitroglycerin

- Lead to incr. cardiac work, oxygen requirements ,coronaries cannot supply the increased requirements.

- Therapeutic goals:
  - Dilating coronary arteries and arterioles in order to increase myocardial blood flow & coronary supply to the heart. Lead to *increase oxygen delivery*.

  - Decreasing cardiac load (preload and afterload)

II. Unstable Angina

It is pre-infarction.

- Very dangerous condition that requires emergency treatment → Not relieved by rest or medicine.

- Myocardial infarction may occur in 10-20% of patients.

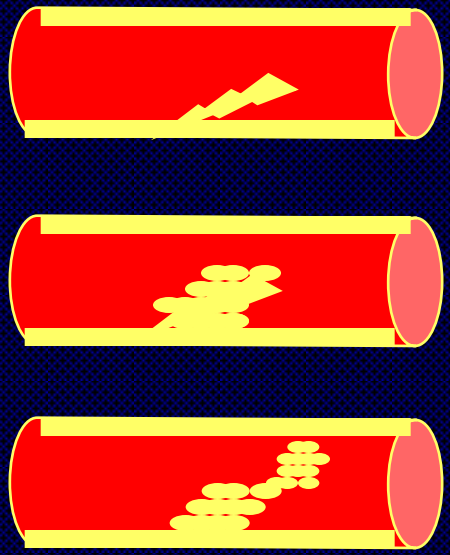
- Pain occurs with less exertion or at rest

The underlying cause is

Fissuring of atherosclerotic plaques

Platelets aggregation

Thrombosis



•Atheroscelerotic changes

Therapeutic goal

- ✓ **Inhibit platelet aggregation and thrombus formation.**

  (aspirin, heparin, clopidogrel)

- ✓ **Decrease cardiac load .**

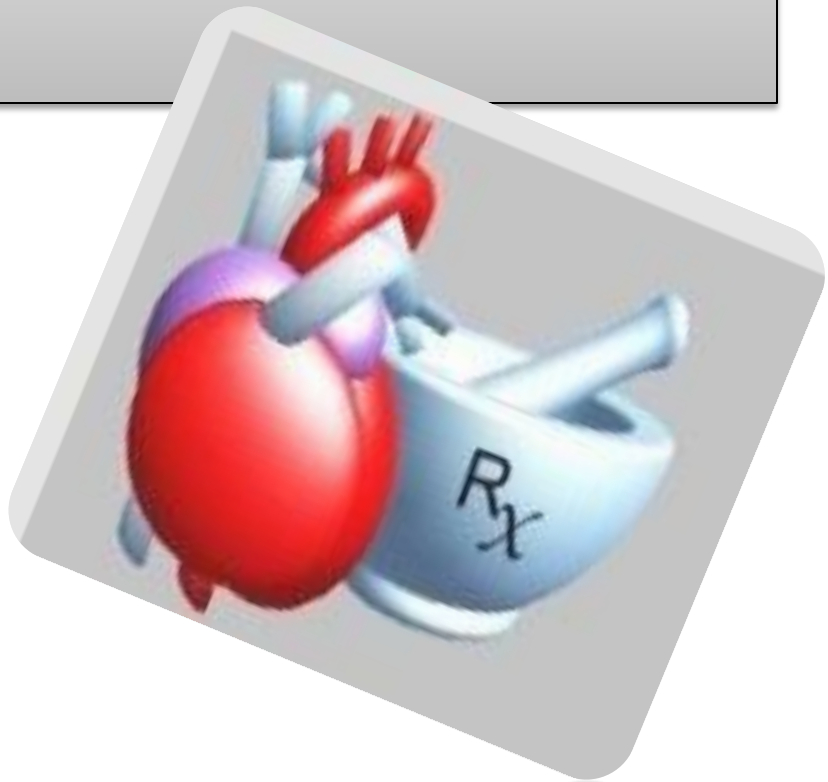
- ✓ **vasodilate coronary arteries.**

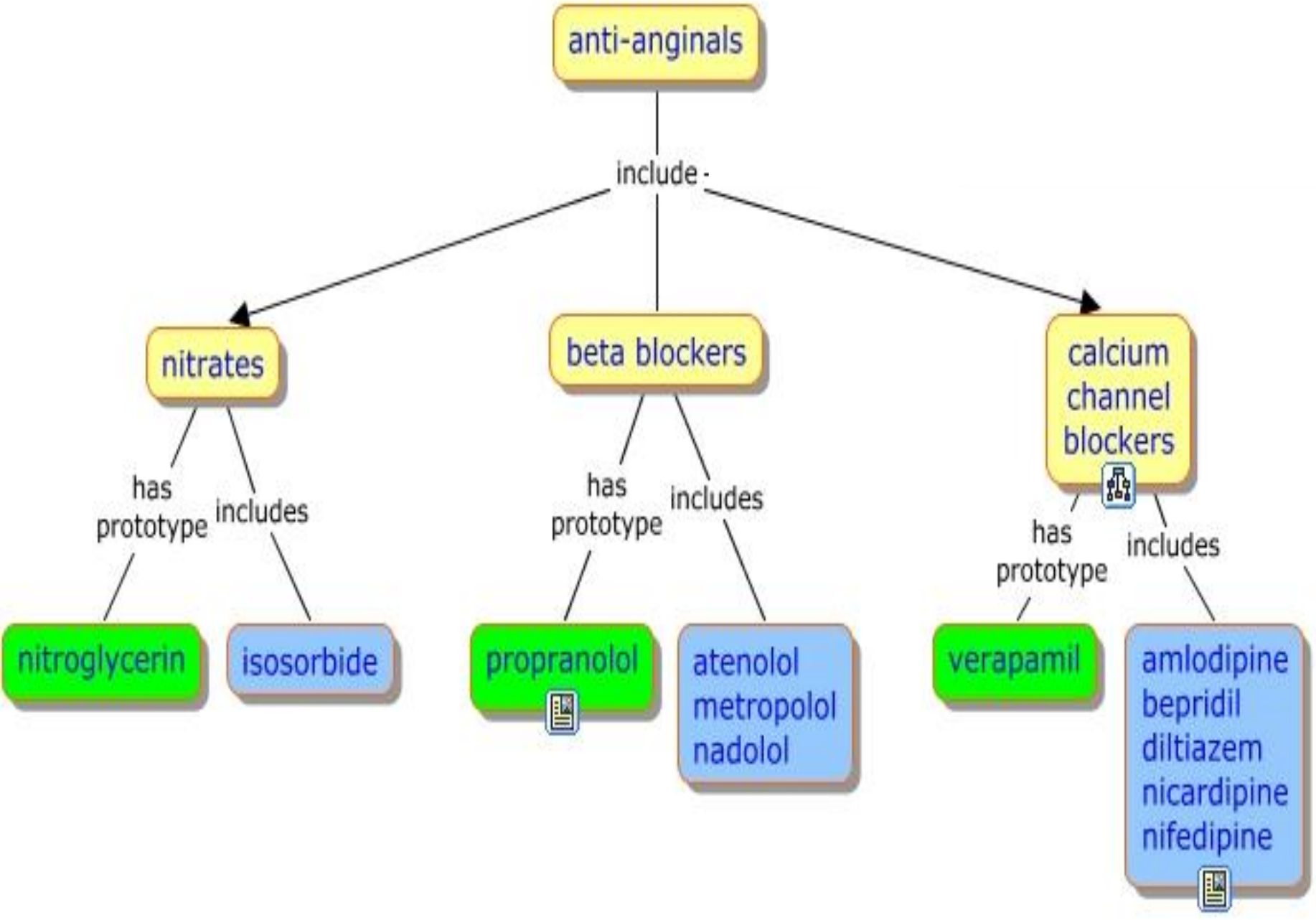
3. Variant Angina . (Prinzmetal's)

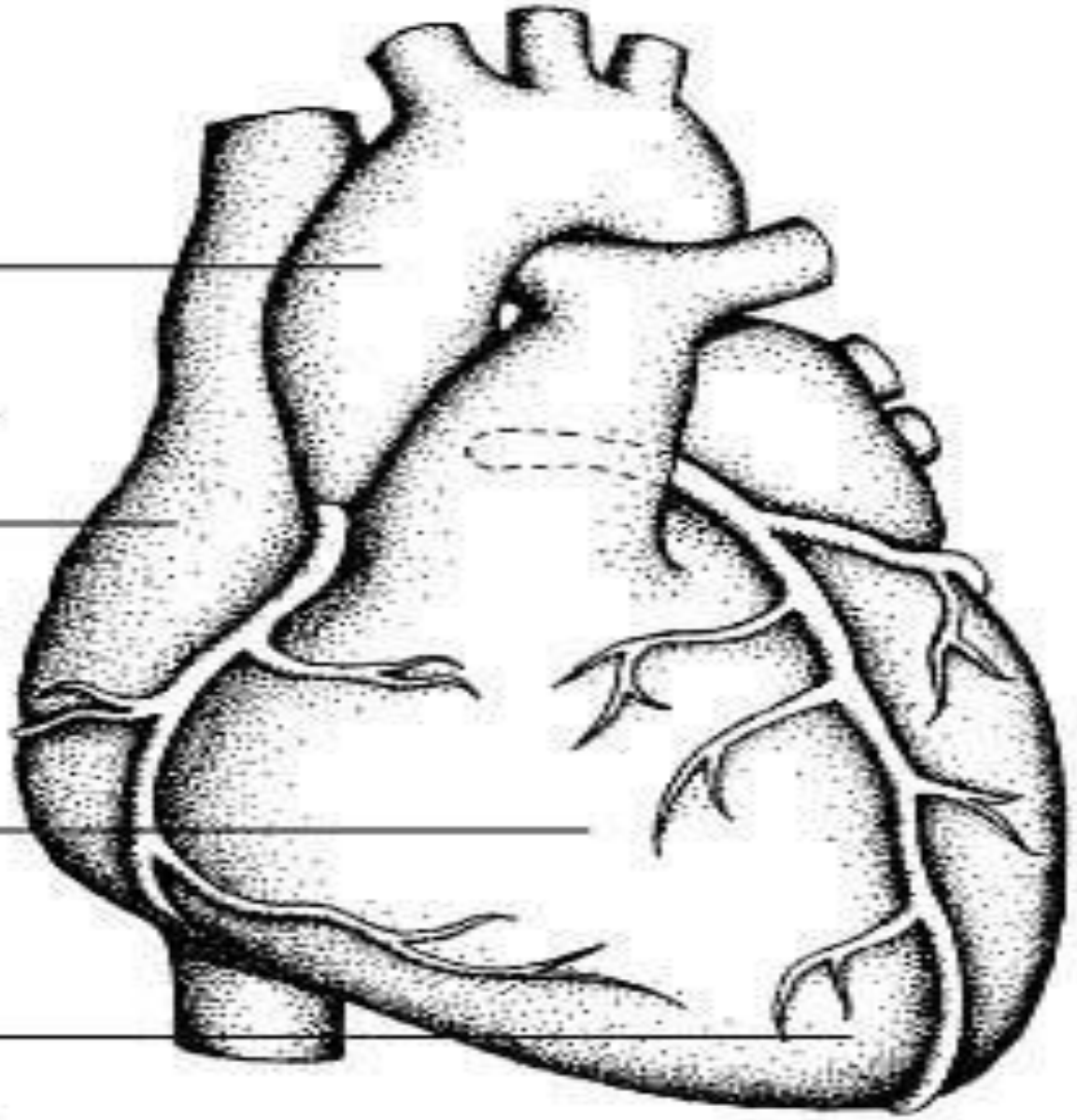
- Very rare.
- ***Chest pain at rest due to coronary artery spasm(decreased blood flow to the heart muscle)***
- ***pain Usually occurs when one is at rest between midnight and in the early morning).***
- **Relieved by medicine (NG & CCB).**

Drugs aimed at preventing & relieving Coronary Spasm.

Anti-Anginal drugs




anti-anginals
include -
nitrates
has prototype
includes
nitroglycerin
isosorbide
beta blockers
has prototype
includes
propranolol
atenolol
metropolol
nadolol
calcium channel blockers
has prototype
includes
verapamil
amlodipine
bepridil
diltiazem
nicardipine
nifedipine



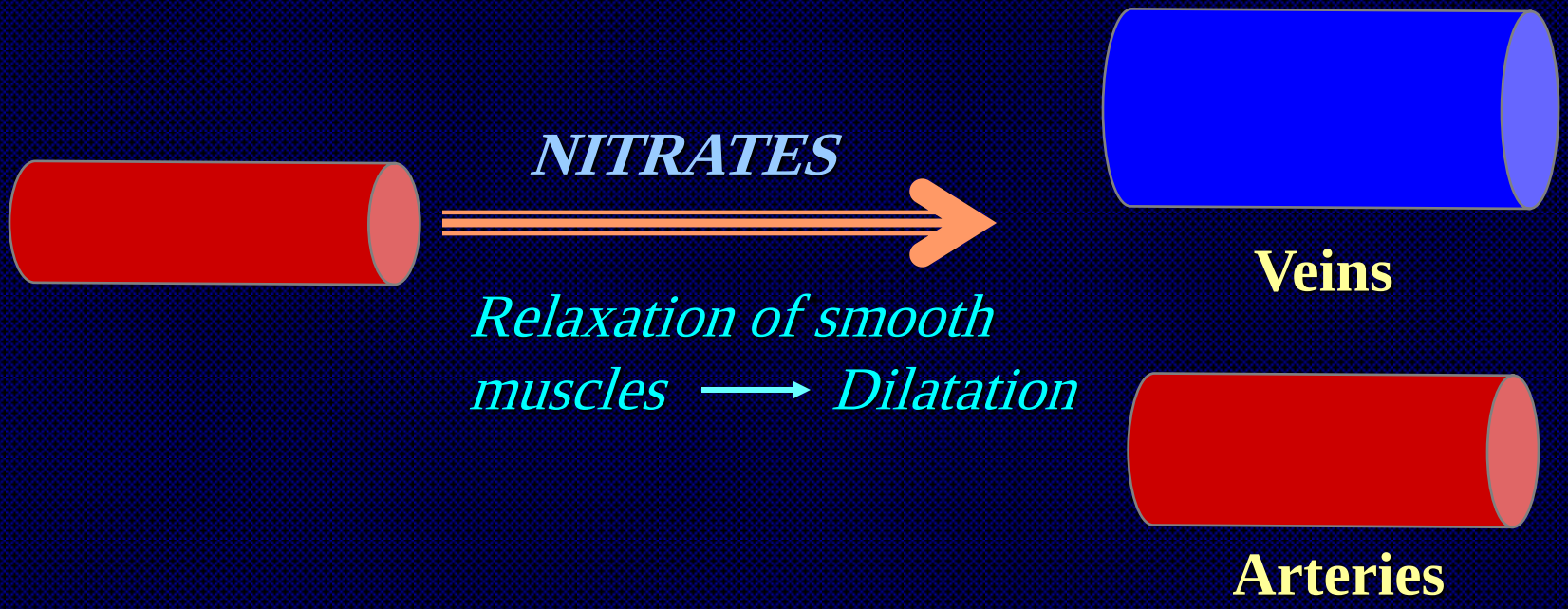
Afterload
Decreased by calcium channel blockers and nitrates

Heart rate
Decreased by beta-adrenergic blockers and some calcium channel blockers

Preload
Decreased by nitrates

Contractility
Decreased by beta-adrenergic blockers and calcium channel blockers

1- Organic Nitrates



Cellular Mechanism of Vasodilatation

Nitrates → Formation of Nitric oxide (NO)

Formation of Nitric oxide (NO) → Activation of Guanylate cyclase

Activation of Guanylate cyclase → Synthesis of cyclic GMP

Synthesis of cyclic GMP → Relaxation of Vascular smooth muscles

Effect of Nitrates :

On Stable Angina :

1- Venodilatation → Preload

Arteriolar dilatation → Afterload

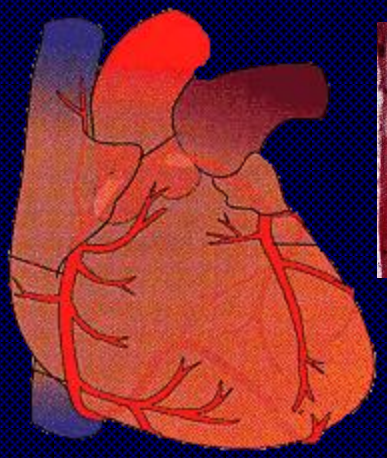
↓ Myocardial Oxygen demand

2- Redistribution of coronary flow towards subendocardium

3- Dilatation of coronary collateral vessels.

On Variant Angina :

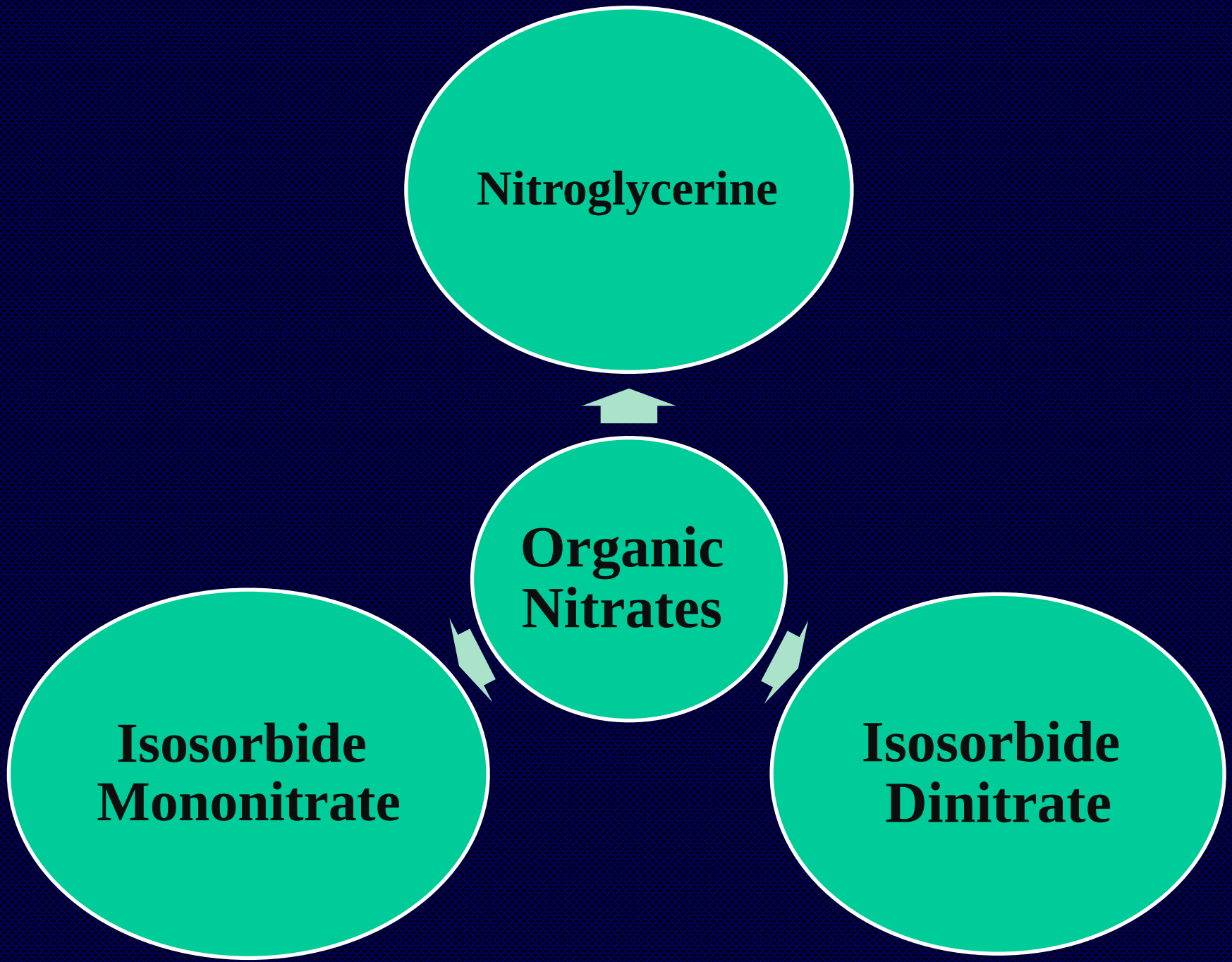
Relax smooth muscles of the epicardial coronaries → relieve coronary artery spasm



On Unstable Angina :

Dilatation of epicardial coronary arteries + reducing O_2 demands

Also they have Antiplatelet and antithrombotic effects.


Nitroglycerine
Organic Nitrates
Isosorbide Mononitrate
Isosorbide Dinitrate

Organic Nitrates

Nitrates are the drugs of choice for relieving acute angina.

EX:-

i. Isosorbide dinitrate.

ii. Isosorbide mononitrate.

iii. **Nitroglycerin (GTN).** life saving drug.

All of them are able to release nitric oxide in the vascular smooth muscle.

(They are Generalized vasodilators).

Used in all type (stable,unstable,varient)

Pharmacokinetic Properties of Organic Nitrates

1- Sublingual (rapid onset of action) (GTN) will avoids the first-pass effect →

used in acute attack (pain) it has rapid onset of action.

2- Oral route: Hepatic first-pass metabolism is high and oral bioavailability is low for nitroglycerin (GTN) and isosorbide dinitrate (ISDN).

3- **Transdermal patches :** Nitroglycerin .

Both not for acute cases, for maintenance of treatment against angina they have continues sustained supply of the drug.

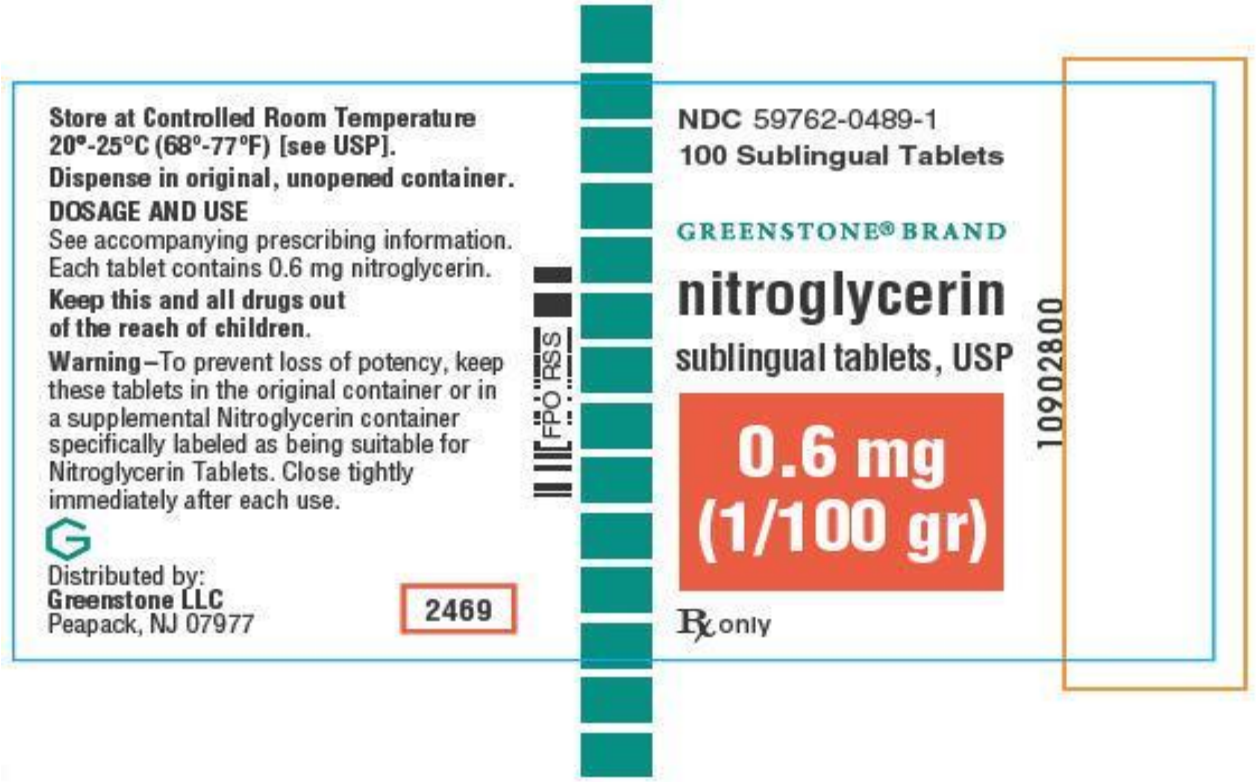
Routes of Administration

- GTN and ISDN have a rapid onset of action (1-3 min) when administered sublingually, but the short duration of action (20-30 min) is not suitable for maintenance therapy.

- IV Nitrogylcerin can be used to treat severe recurrent unstable angina.

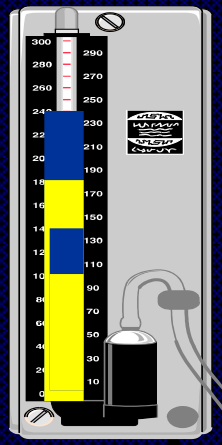
Acute anginal pain →

Relief by NG sublingual is the drug of choices.

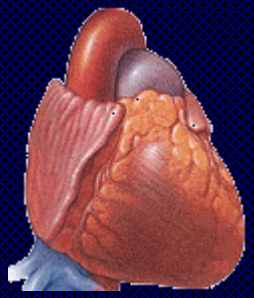


Adverse Reactions :

1- Postural Hypotension & Syncope



2-Reflex Tachycardia



3- Facial Flushing

4- Throbbing Headache

2- B-Blockers

Used in stable and unstable angina, While **Contraindication in Variant angina**??

Also, contraindication in :-

- Asthma(non-selective).
- bradycardia.

It is important **not to discontinue B -blocker therapy abruptly**. The dose should be gradually tapered off over 5 to 10 days to avoid rebound angina or hypertension.

Beta- blockers (for long-term prevention of angina).

- Decrease heart rate and contractility
- Decrease afterload due to a decrease in cardiac output
- Improve myocardial perfusion due to a decrease in heart rate

Result in reducing the demand of the cardiac muscle.

Hypotension

Bradycardia

Fatigue

Insomnia

Sexual dysfunction

3- Calcium Channel-Blockers

Used in treatment of all types of angina.

- Calcium channel blockers are used for long-term prevention of angina only, not short-term relief of chest pain.

Block

Voltage -dependent calcium channels (L-type) in cardiac and smooth muscles.

Mechanism of Ca++ blocker action :

1 - Coronary artery dilatation and relief of coronary spasm (variant angina)

2 -Decrease myocardial O_2 demand due to:

•Arteriolar dilatation → ↓ Vascular resistance → ↓ Afterload

Verapamil & Diltiazem:

•Decrease HR.

•Decrease contractility

•Decrease AV conductivity

Therapeutic Use of Calcium-Channel Blockers

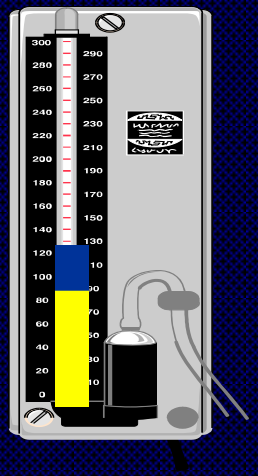
- Hypertension
  (systemic & pulmonary)
- Angina
- Arrhythmias

Adverse reactions :

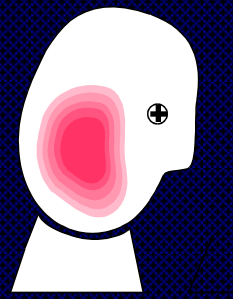
Dizziness

Ankle edema

Headache



Hypotension



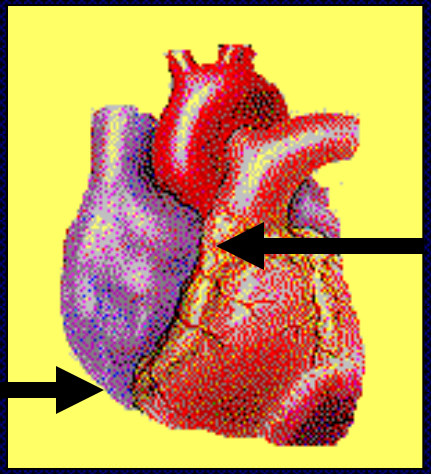
Flushing

Constipation

Bradycardia with verapamil &diltiazem.

Reflex Tachycardia with Nifedipine

Contraindications of Verapamil & Diltiazem:



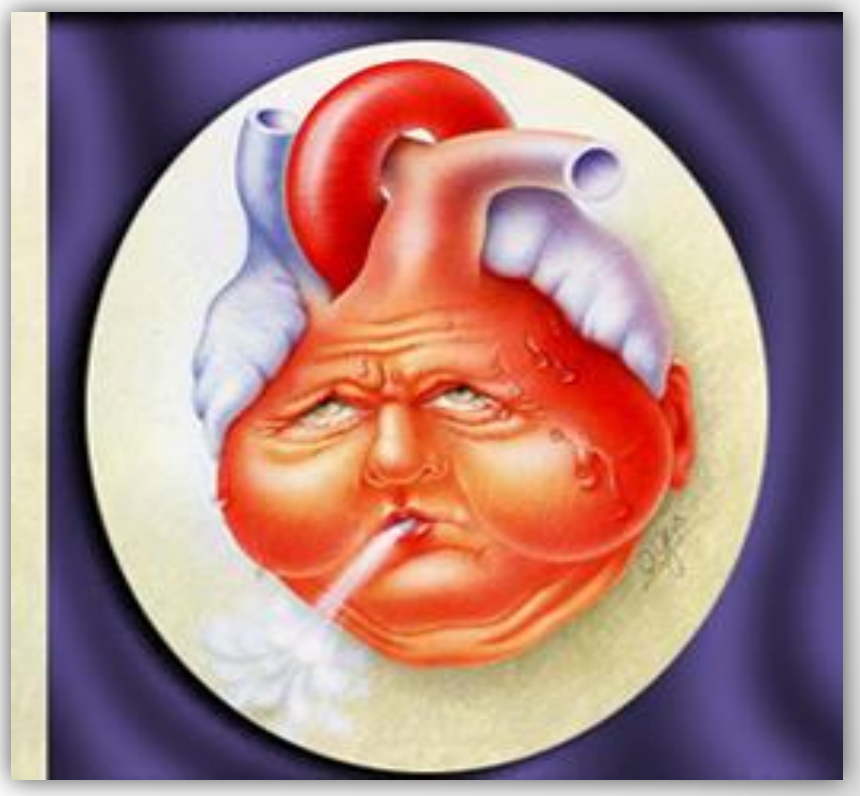
1 - HF

2 - Sinus or A-V node disease.

3 - Bradycardia.

Any Questions
????

Congestive heart failure



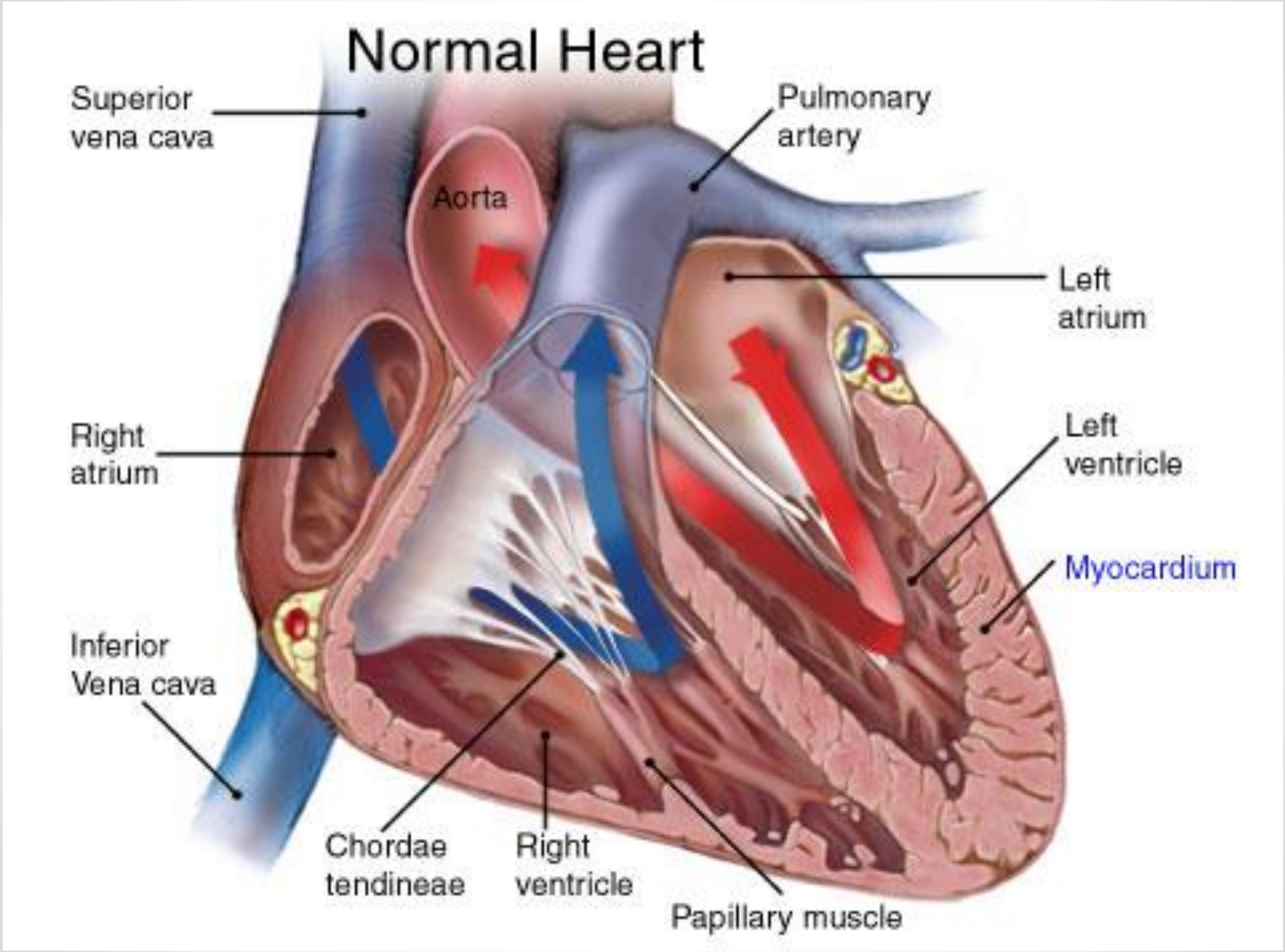
What is Heart Failure?

Heart failure is **NOT** a heart attack

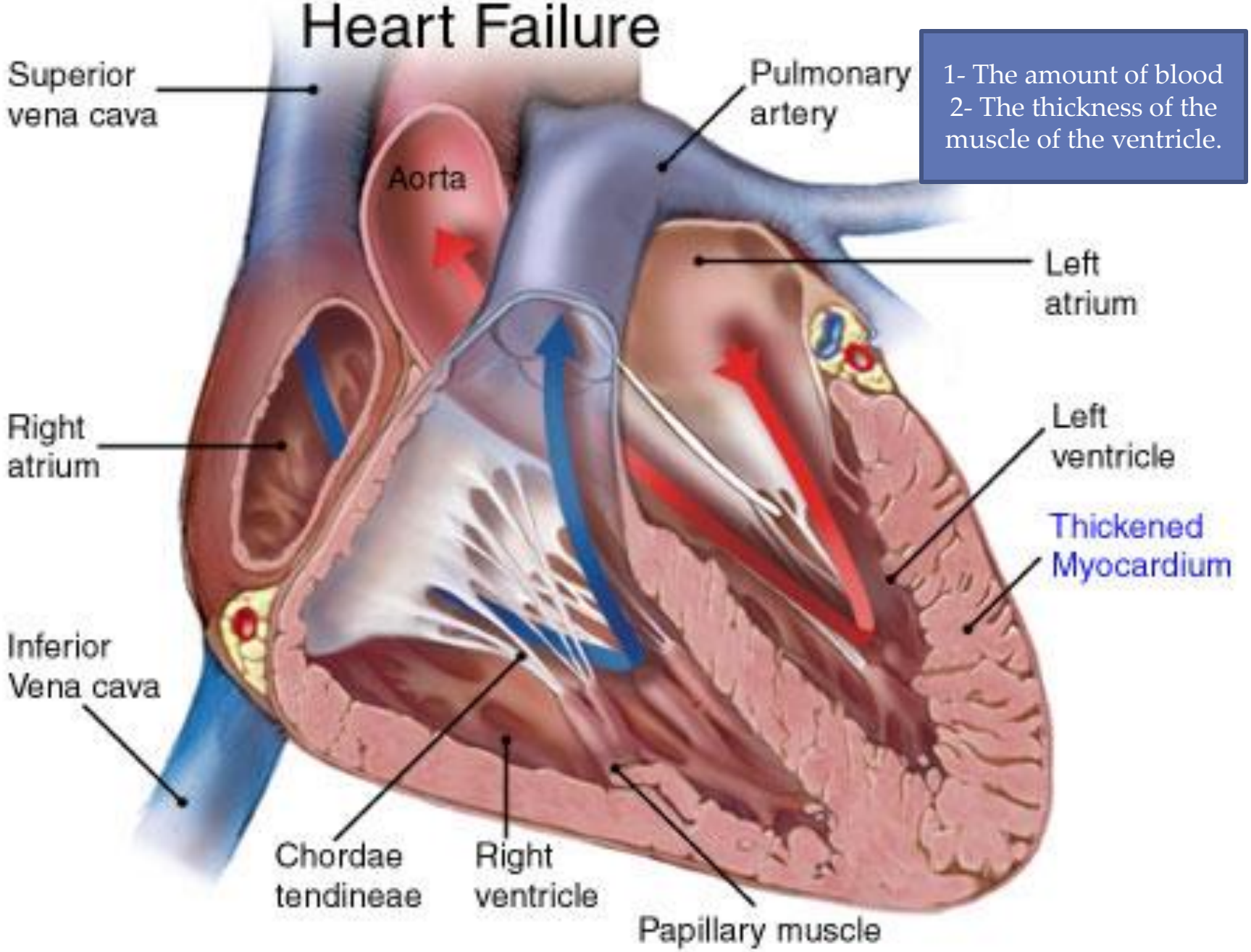
- Heart failure **is** a complex, progressive disorder in which the heart is unable to pump sufficient blood to meet the needs of the body.

- Heart failure means the heart is:
  - Weakened.
  - Cannot pump enough blood to supply the body's needs.

❑ abnormal increases in blood volume and interstitial fluid, hence the term **congestive**.


Normal Heart
Superior vena cava
Pulmonary artery
Aorta
Left atrium
Right atrium
Left ventricle
Myocardium
Inferior Vena cava
Chordae tendineae
Right ventricle
Papillary muscle

Heart Failure

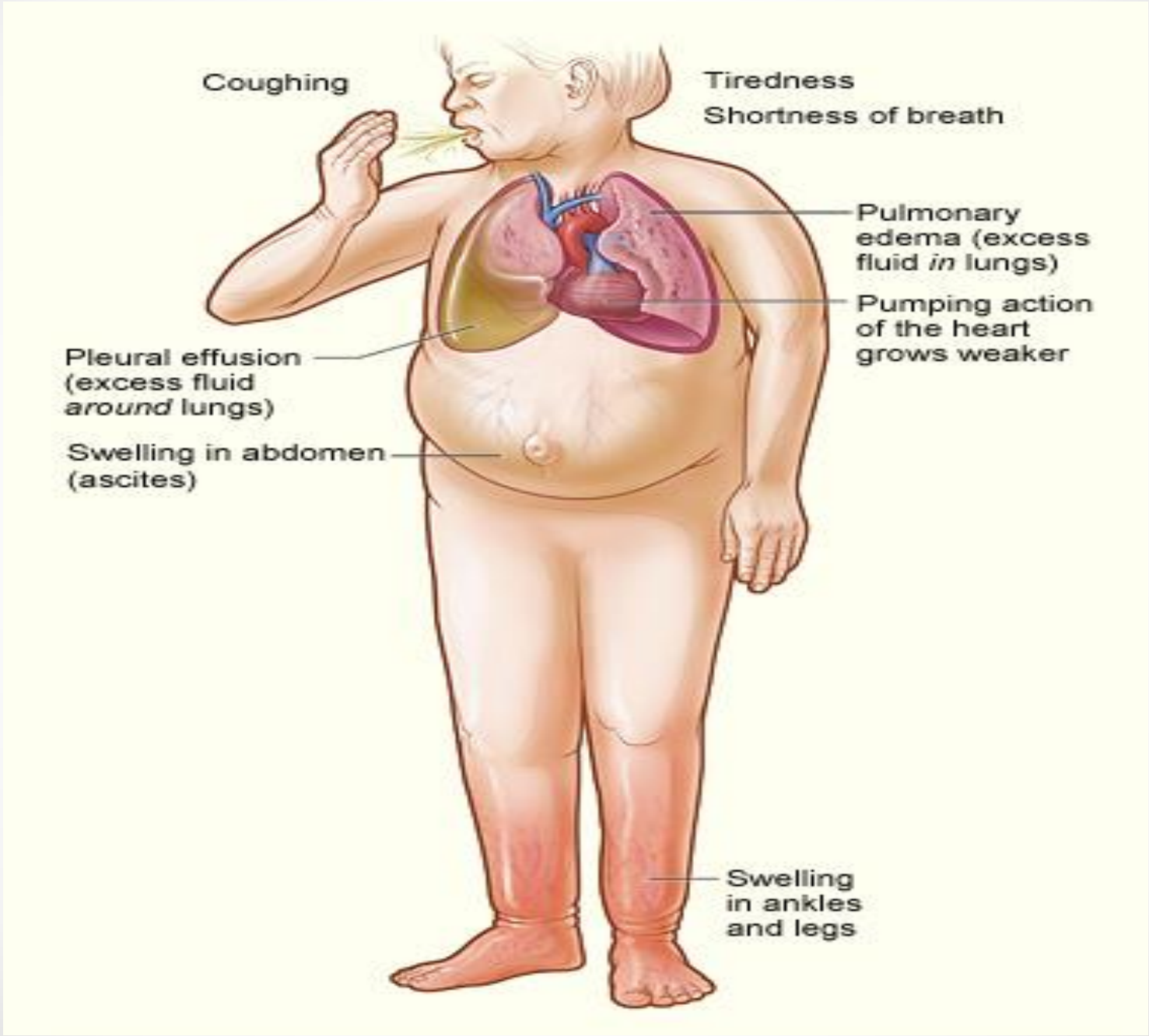


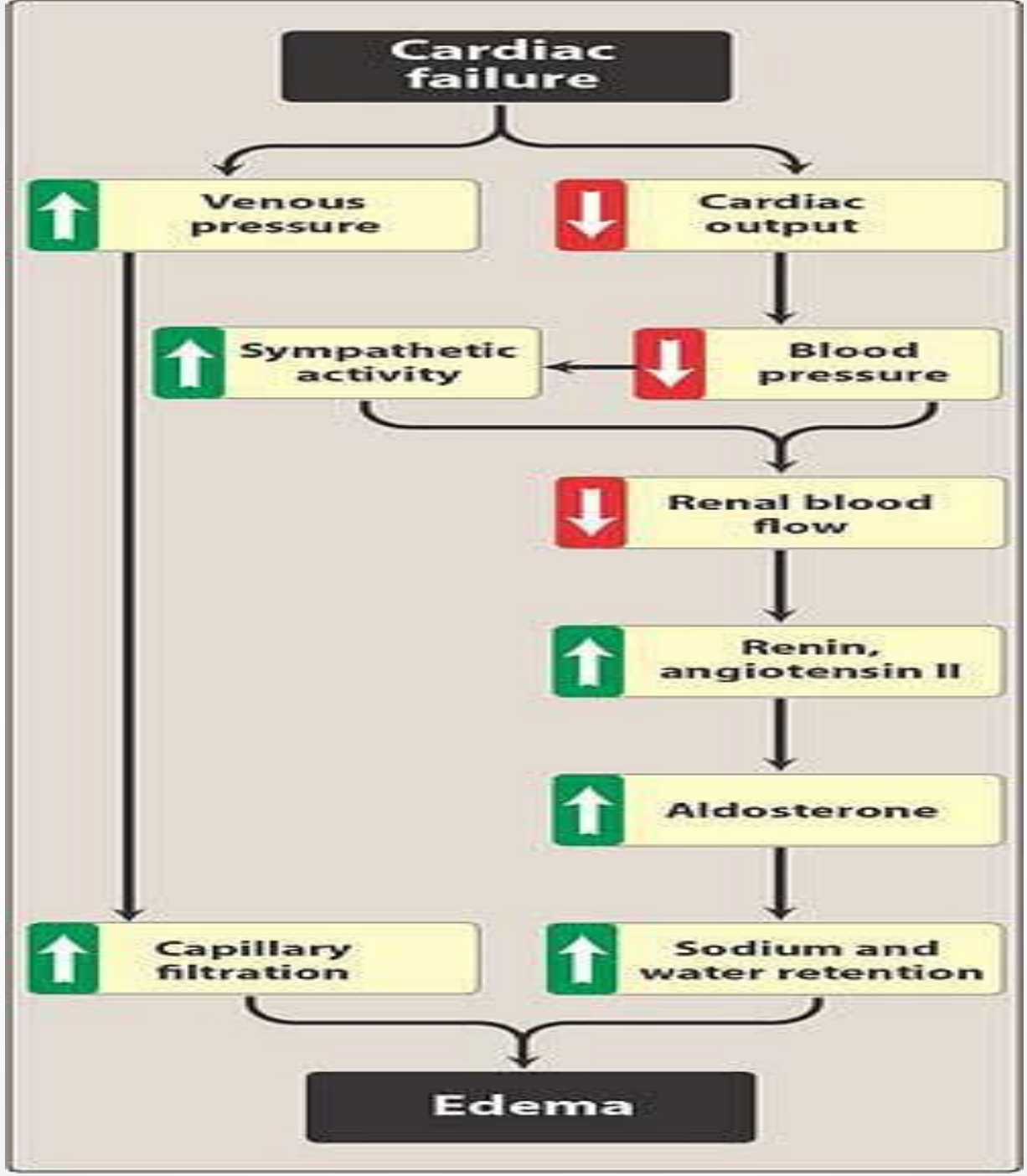
1- The amount of blood
2- The thickness of the muscle of the ventricle.

What Are The Symptoms of Heart Failure?

Think **FACES**...

- **F**atigue
- **A**ctivities limited
- **C**hest congestion
- **E**dema or ankle swelling
- **S**hortness of breath


Coughing
Tiredness
Shortness of breath
Pulmonary edema (excess fluid *in* lungs)
Pumping action of the heart grows weaker
Pleural effusion (excess fluid *around* lungs)
Swelling in abdomen (ascites)
Swelling in ankles and legs


Cardiac failure
Venous pressure
Cardiac output
Sympathetic activity
Blood pressure
Renal blood flow
Renin, angiotensin II
Aldosterone
Capillary filtration
Sodium and water retention
Edema

Reduced CO is compensated by

Chronic activation of

1- the sympathetic NS (Tachycardia and Increased contractility).

2-Active RAAS .

3- Chronic activation of the sympathetic nervous system and the renin-angiotensin-aldosterone axis is associated with **remodeling** of cardiac tissue, characterized by **hypertrophy**, and **fibrosis**.

- The geometry of the heart becomes less elliptical and more spherical, interfering with its ability to efficiently function as a pump.

Angiotensin II:

1- Constricts blood vessels (vasoconstriction).

2- increase the secretion of ADH → increase water reabsorbed from the filtrate (in the kidney) back into the bloodstream (water retention).

3- increase the secretion aldosterone ,hormone which cause the conservation of sodium.(salt retention)

→ we have lung congestion & edema occurs

Goal of management

- Improve oxygenation ,ventilation.
- Decrease venous return to the heart.
- Decrease cardiac work and O2 demand.
- Improve cardiac output by:-
  - Reduce after load
  - Increase myocardial contractility

Medicines to Control Symptoms…

1-Diuretics or "water pills":

decrease fluid retention and reduce swelling

- Deal with excess fluid contents in the circulation

2- Digoxin:

improves blood circulation

Medicines That Save Lives…

3- ACE Inhibitors: dilate or widen blood vessels, increase blood flow,

4- Beta blockers: help strengthen the heart's pumping ability, block the body's response to substances which can damage the heart

ANOTHER AGENTS

5- ARB.

6- Inotropic agent:-

Dobutamine , digitoxin.

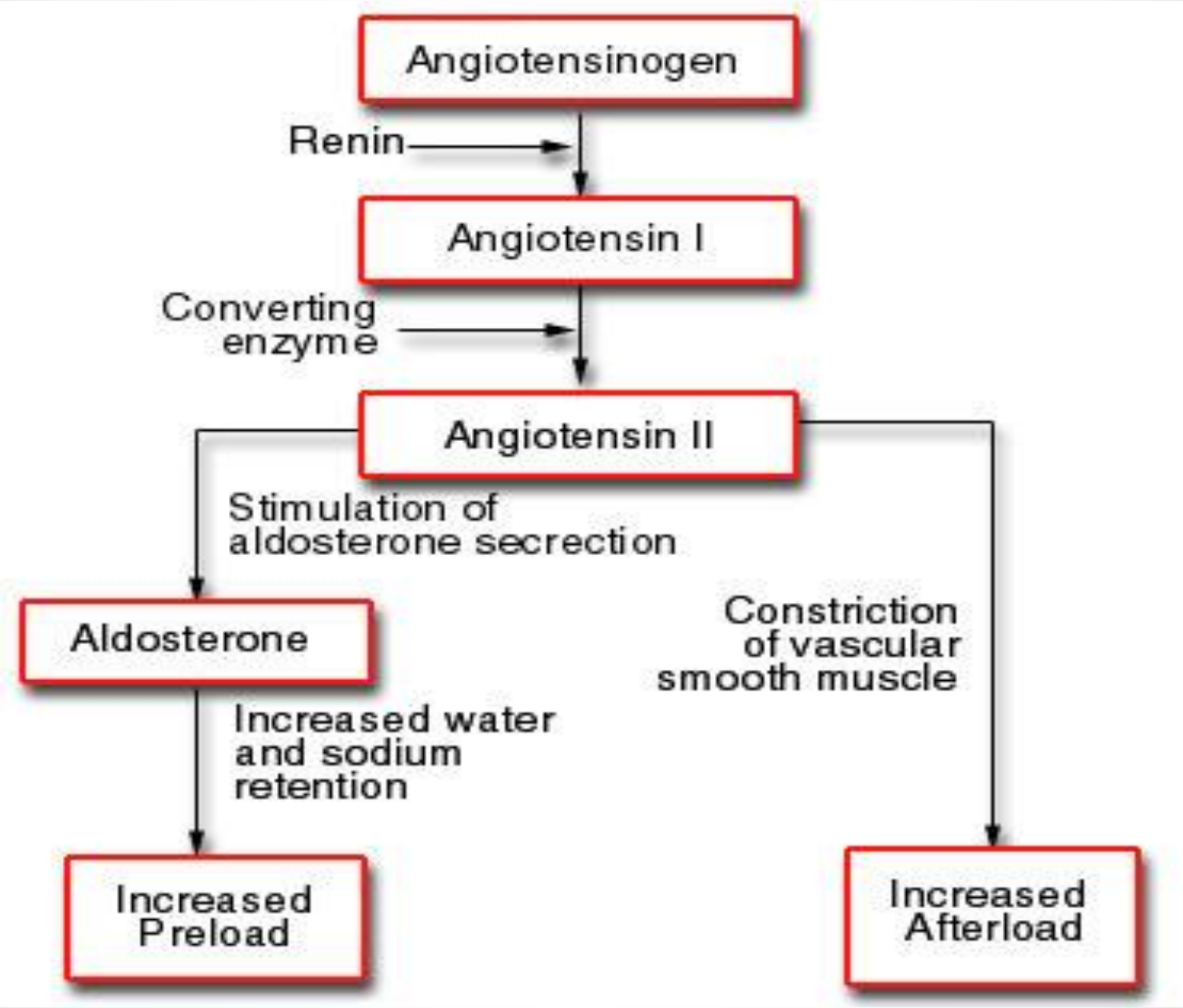
7- Aldosterone antagonist :

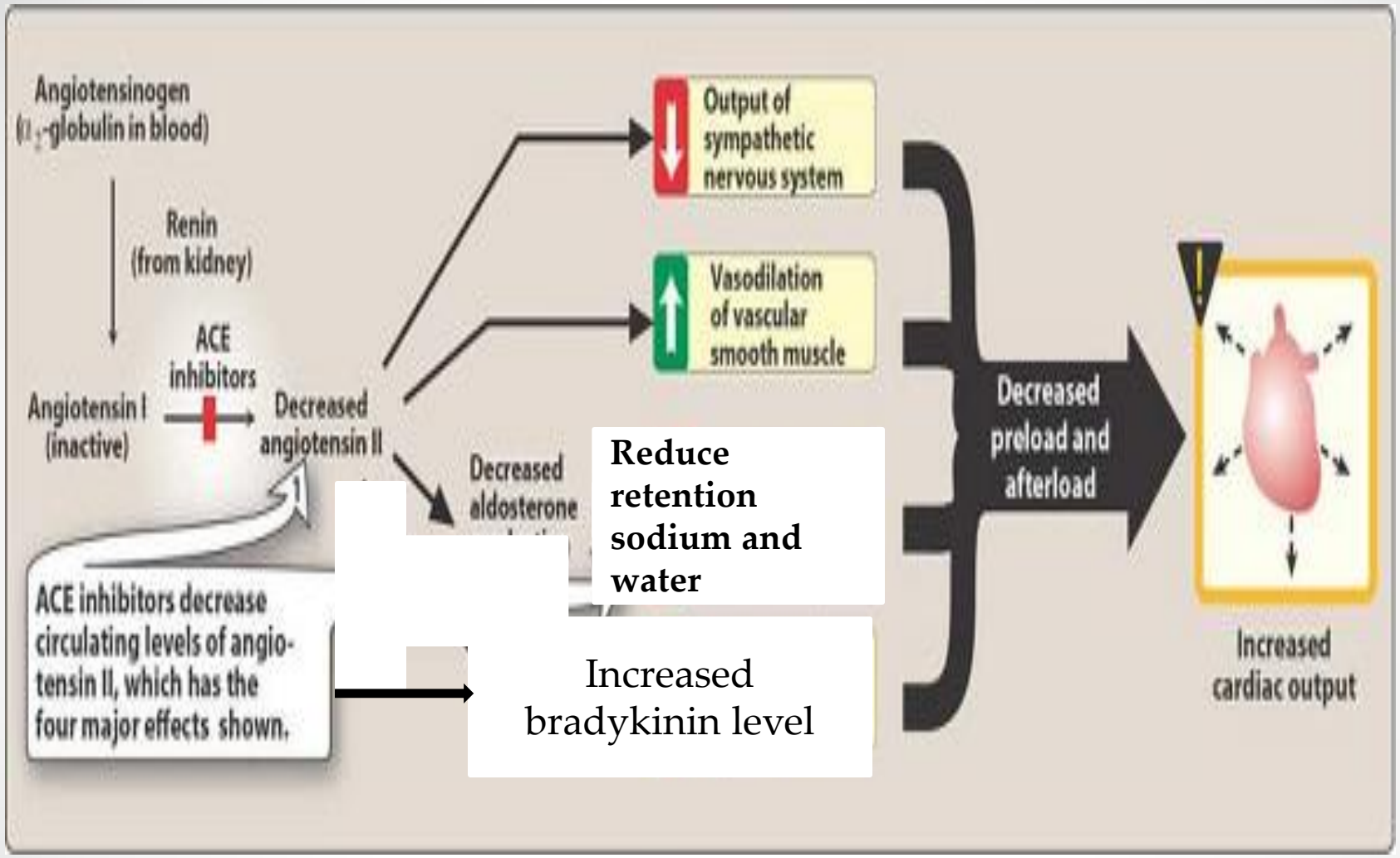
spiranolactone.

1. Angiotensin Converting Enzyme (ACE) Inhibitors

Captopril, Lisinopril, Enalapril, Ramipril, Quinapril

- (ACE) inhibitors are the **agents of choice in HF**.
- ACE inhibitors decrease vascular resistance, venous tone, and blood pressure, resulting in an increased cardiac output.
- ACE inhibitors the only drugs that reduce mortality, morbidity, and prolong the patients life)


Angiotensinogen
Renin
Angiotensin I
Converting enzyme
Angiotensin II
Stimulation of aldosterone secretion
Aldosterone
Increased water and sodium retention
Increased Preload
Constriction of vascular smooth muscle
Increased Afterload


Angiotensinogen
(α2-globulin in blood)
Renin
(from kidney)
ACE
inhibitors
Angiotensin I
(inactive)
Decreased
angiotensin II
Output of
sympathetic
nervous system
Vasodilation
of vascular
smooth muscle
Decreased
aldosterone
Reduce
retention
sodium and
water
Decreased
preload and
afterload
Increased
cardiac output
ACE inhibitors decrease
circulating levels of angio-
tensin II, which has the
four major effects shown.
Increased
bradykinin level

Angiotensin Converting Enzyme (ACE) Inhibitors :

- Reduction in arterial resistance (afterload)
- Reduction in venous tension (preload)
- Reduction in aldosterone secretion
- Inhibition of cardiac and vascular remodeling

2- Angiotensin Receptor AT-1 blockers (ARB)

Losartan, Irbesartan, Candesartan

Potent competitive antagonists of the Angiotensin II (AT-1).

- **No effect** on bradykinin level.
- **Contra** in pregnancy.

3- Direct Vasodilators

- Dilation of venous blood vessels → decrease in cardiac preload.
- Arterial dilators → decrease after load.

- **Nitrates , Isosorbide dinitrate** & **hydralazine** used specially in patients who cannot tolerate ACE inhibitors.

- **Amlodipine :** was the 1st choice in CHF in the past but now its was replaced by other agents

4- Diuretics

These are useful in reducing the symptoms of volume overload by:

- decreasing the extra cellular volume.
- decreasing the venous return (preload).. This decreases the cardiac workload and the oxygen demand.

→ Relieve pulmonary congestion and peripheral edema.

- Loop diuretics →are the most effective and commonly used.
- Thiazides → are effective in mild cases only.

5- Beta blockers

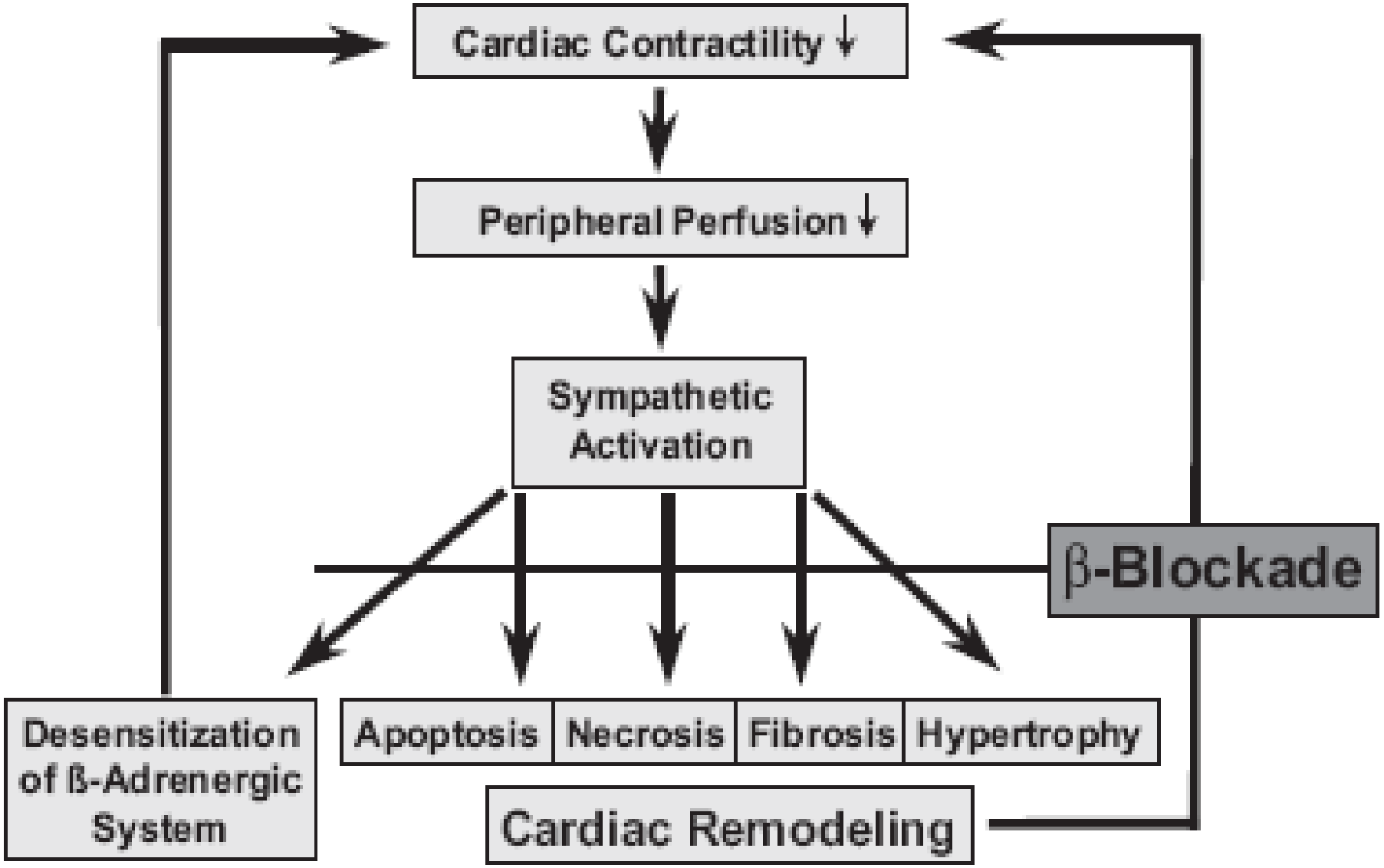
Carvedilol (non-selective β and α), metoprolol (β1 selective), Bisoprolol

Are the most commonly used for CCF

- **B-blockers prevent the changes that occur because of the chronic activation of the sympathetic nervous system.**
- **B-blockers decrease HR .**
- **B-blockers inhibit the release of renin.**
- **B-blockers decrease remodeling, hypertrophy and cell death.**

✓ Reduce mortality, morbidity.

Beta blockers in CCF



6- Inotropic drugs

Ex:

1. **Digitalis** (cardiac glycoside)
2. **Dobutamine** (β-adrenergic agonist)

- Positive inotropic → enhance cardiac muscle contractility→ increase cardiac out put.

- By different mechanism → All increase intracellular cardiac Ca^{++} concentration

1- Digoxin

Cardiac glycosides(digitalis)

- They are positive inotropic agent(increase heart contractility)
- Inhibition of Na/K ATPase pump increase intracellular sodium concentration – eventually increase cytosolic calcium→ increase heart muscle contractility.
- Decrease the propagation and the generation of impulses in SA & AV node.
- Restores the vagal tone stimulation (parasympathetic) ,that it will abolish the sympathetic activity.

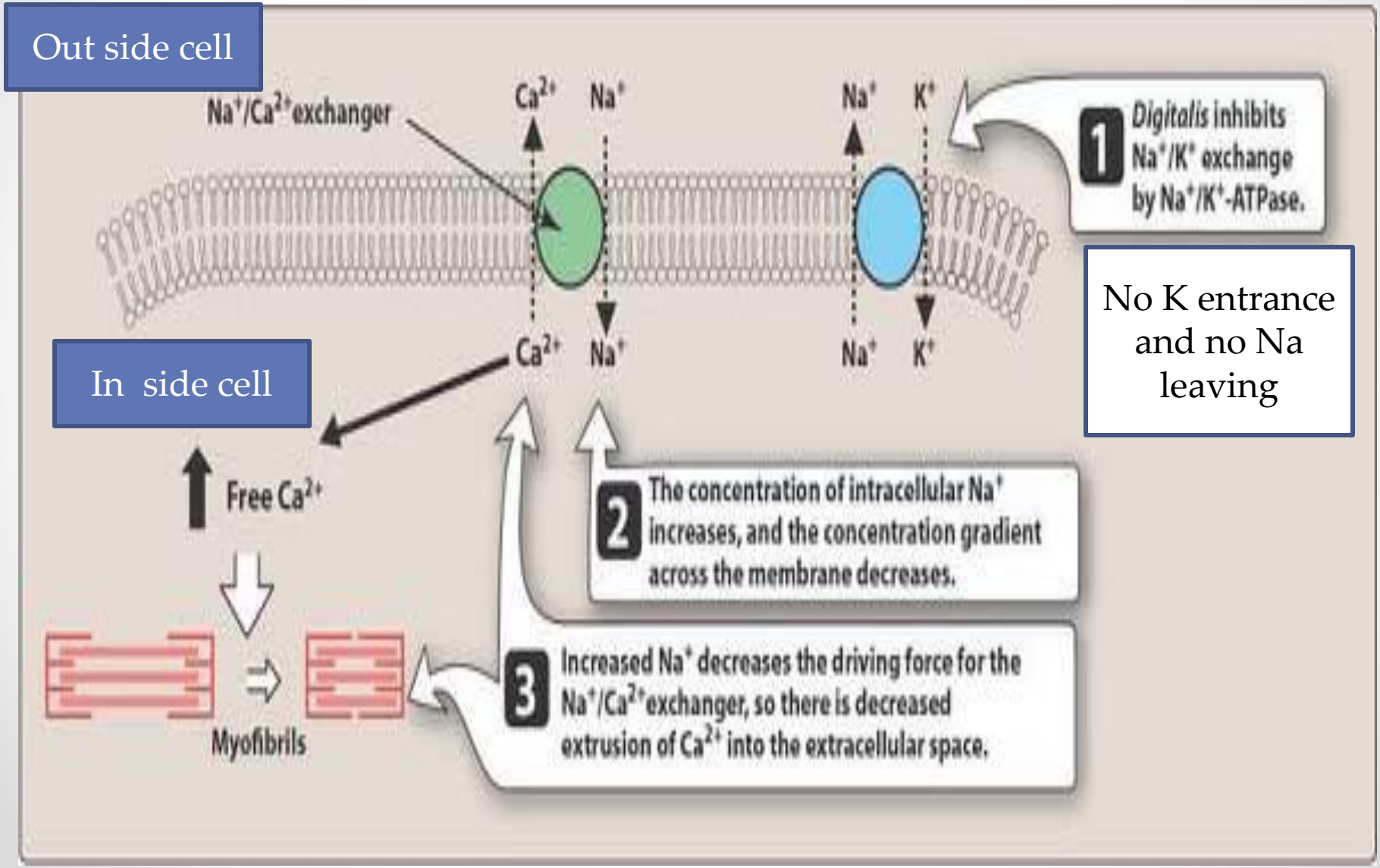
- at present digitalis reserved for patients who don't respond to diuretic, ACE inhibitors, B blockers.

- Digoxin is used as a first-line drug in patients with congestive heart failure who are in atrial fibrillation.

- has long half-life of around 36 hours→ give it as loading dose → is employed when acute HF & AF.

- given orally or parentally especially IV

Mechanism of action



Adverse effects / Precautions

Digoxin has very narrow therapeutic index

- Nausea, vomiting, visual disturbances (red –green blindness) , gynecomastia (early signs of intoxication).
- confusion and Arrhythmia(due to hypokalemia).
- Bradycardia.

Drug-Drug Interaction

- verapamil can increase the plasma concentration of digoxin by displacing *digoxin* from tissue protein-binding sites and by competing with *digoxin* for renal excretion.

- Digoxin cause bradycardia thus should not be combined with the drugs with -ve inotropic effect

  (B-blocker ,verapamil)

Digoxin toxicity

Treatment:

- Toxicity can be treated with higher than normal doses of potassium
- Digoxin antibody (digibind) is used specifically to treat life-threatening digoxin overdose.

Cardiac Inotropes

2- Dobutamine:- is a beta-1 agonist .

- ✓ - It improves cardiac performance by causing positive inotropic effects increases contractility , cardiac output and vasodilation.
- ✓ Dobutamine must be given by intravenous infusion and is primarily used in the treatment of **acute HF** in a hospital setting.

Thank you