Drugs for Angina Pectoris

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Reference

Basic & Clinical Pharmacology

BG Katzung, SB Masters, AJ Trevor

McGraw Hill LANGE

13th edition, Chapter 12.

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Thursday 10-11

Angina Pectoris

a retrosternal pain.. occures mainly due to myocardial ischemia

- **It is chest pain caused by accumulation of metabolites, resulting from myocardial ischemia.**
- **A clinical syndrome resulting from an imbalance between myocardial O_2 supply and demand. Coronary blood flow does Not increase in proportion to the increase in demand.**

Angina Pectoris

irreversible but manageable

Causes: most common cause is atherosclorosis, as it reduces myocardial blood flow with any effort.

1. **Coronary artery atherosclerosis leading to obstruction in coronary blood vessels: typical angina, classic angina, stable angina, angina of effort.**
2. **Vasospasm in large epicardial coronary arteries (variant angina, vasospastic angina, or Prinzmetal's angina). Reversible.** in young people with genetic predespstion

first scientist who described it

Angina Pectoris

Coronary artery disease ranges from stable angina to MI, unstable angina is located midway between them

3. **In certain patients, "angina at rest" or "unstable angina" may result from a combination of:**

   A. Vasoconstriction.

   B. Platelet aggregation.

   C. Atherosclerotic plaque rupture.

   D. Severe increase in O_2 demand.

Angina Pectoris

- **Manifested as an increase in the severity, frequency, and duration of chest pain in patients with previously stable angina.**
- **This subset of acute coronary syndrome is associated with a high risk of myocardial infarction and death and is considered a medical emergency.**

unstable angina is considerd as an acute coranary syndrdrome

Treatment of Angina Pectoris

- **The imbalance between oxygen delivery and myocardial oxygen demand can be corrected by decreasing oxygen demand or by increasing coronary flow.**

1. **In effort angina, oxygen demand can be reduced by decreasing cardiac work.**
2. **In variant angina, spasm of coronary vessels can be reversed by nitrate or calcium channel-blocking vasodilators.**

by dec. TPR, and thus afterload

treatment is by relaxants/ Vasodilators

TABLE 12–1 **Determinants of myocardial oxygen consumption.**

Wall stress
Intraventricular pressure
Ventricular radius (volume)
Wall thickness
Heart rate
Contractility

Treatment of Angina Pectoris

3. Lipid-lowering drugs, especially the "statins," have become extremely important in the long-term treatment of atherosclerotic disease.
4. In unstable angina, vigorous measures are taken to achieve both increased oxygen delivery, and decreased oxygen demand.

We may give aspirin also

We have also to modify risk factors ..

Treatment of Angina Pectoris

1. **Reduction of overall myocardial O_2 demand:**

   Organic nitrates: reduce preload and afterload, decreasing oxygen demand

   Calcium channel blockers

   β- Adrenoceptor blockers

   Reduce work done by the heart, decreasing oxygen demand

2. **Increase of blood flow, and thus, O_2 supply, in the coronaries:**

   Organic nitrates → these drugs relax coronary vascular smooth muscles in vasospastic ischemia, but Not in stable in stable angina as the vessels are already dilated maximally as a result of atherosclerosis

   Calcium channel blockers

   But not β-adrenoceptor blockers (not vasodilators)

Nitrates & Nitrites

all relase nitrate .. then produce NO

all given sublingually, why ??
see next page

Classification:

1. ~~Extremely volatile liquids: Amyl nitrite~~
2. Moderately volatile liquids: Nitroglycerin
3. Solids: Isosorbide dinitrate, Isosorbide mononitrate

- A high-capacity organic nitrate reductase in the liver removes nitrate groups in a stepwise fashion from the parent molecules and inactivates these drug.

Nitrates & Nitrites

- They undergo extensive first-pass metabolism → bioavailability of nitroglycerin and isosorbide dinitrate is 10-20%, t½ ~ 2-8 min.
- There duration of action is 15-30 min.
- The t½ of denitrated compound is ~ 3 hours.
- The sublingual route avoids first-pass metabolism.

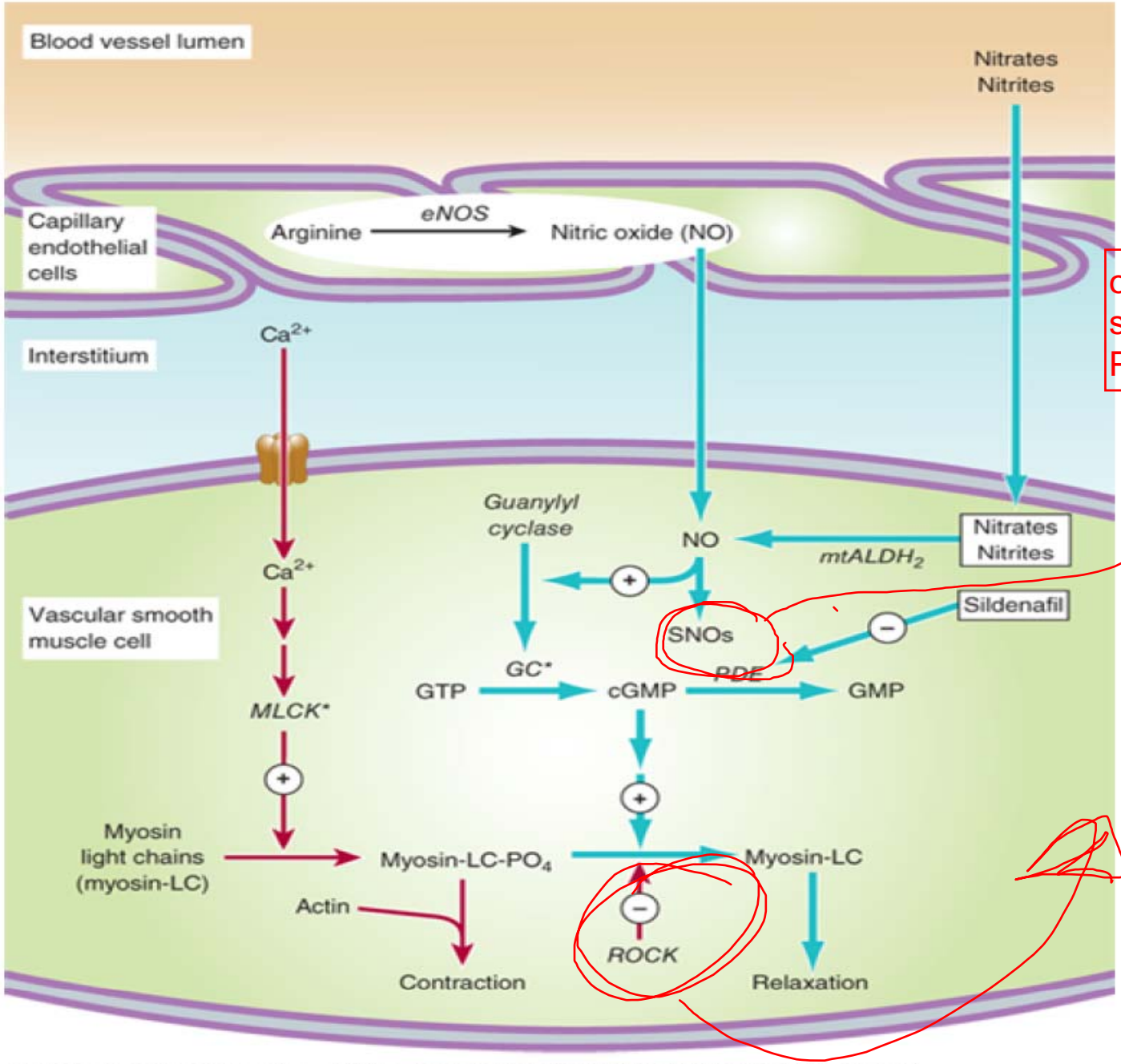
Nitrates & Nitrites

- **Most of the therapeutic effect of nitroglycerin is due to its dinitro metabolite, and most of the effect of isosorbide dinitrate is due to its 5-mononitrate metabolite.**
- **Isosorbide 5-mononitrate has a bioavailability of 100%.**

Nitrates & Nitrites

Mechanism of Action:

- Nitroglycerin can be denitrated to free nitrite by glutathione-S-transferase and/or mitochondrial aldehyde dehydrogenases, with an ultimate conversion to nitric oxide (NO).
- Nitric oxide (probably complexed with cysteine) combines with the heme group of soluble guanylyl cyclase, activating it and causing an increase in cGMP.

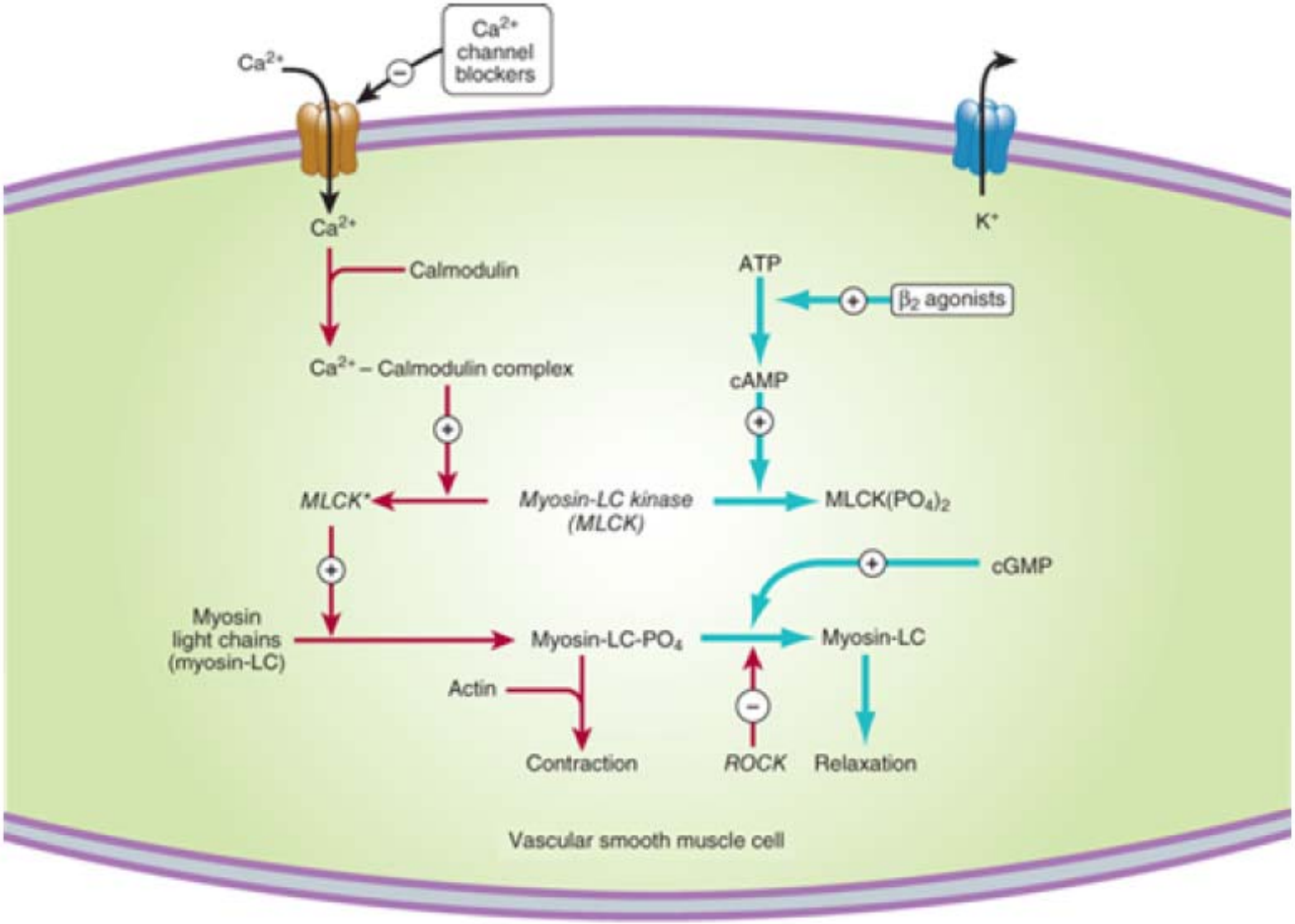


open K channel, so it stimulates Prostaglandins

it inhibits dephosphorylation of myosin, causing vasoconstriction. if you blocked it, you may cause vasodilation

FIGURE 12–2

Mechanism of action of nitrates, nitrites, and other substances that increase the concentration of nitric oxide (NO) in vascular smooth muscle cells. Steps leading to relaxation are shown with blue arrows. MLCK*, activated myosin light-chain kinase (see Figure 12–1). Nitrosothiols (SNOs) appear to have non-cGMP-dependent effects on potassium channels and Ca^{2+}-ATPase. GC*, activated guanylyl cyclase; PDE, phosphodiesterase; eNOS, endothelial nitric oxide synthase; $mtALDH_2$, mitochondrial aldehyde dehydrogenase-2; ROCK, Rho kinase.



Source: Bertram G. Katzung, Anthony J. Trevor: Basic & Clinical Pharmacology, 13th Ed.
www.accesspharmacy.com

FIGURE 12–1

A simplified diagram of smooth muscle contraction and the site of action of calcium channel-blocking drugs. Contraction is triggered (red arrows) by influx of calcium (which can be blocked by calcium channel blockers) through transmembrane calcium channels. The calcium combines with calmodulin to form a complex that converts the enzyme myosin light-chain kinase to its active form (*MLCK**). The latter phosphorylates the myosin light chains, thereby initiating the interaction of myosin with actin. Other proteins, including calponin and caldesmon (not shown), inhibit the ATPase activity of myosin during the relaxation of smooth muscle. Interaction with the Ca^{2+}-calmodulin complex reduces their interaction with myosin during the contraction cycle. $Beta_2$ agonists (and other substances that increase cAMP) may cause relaxation in smooth muscle (blue arrows) by accelerating the inactivation of MLCK and by facilitating the expulsion of calcium from the cell (not shown). cGMP facilitates relaxation by the mechanism shown in Figure 12–2. ROCK, Rho kinase.

Nitrates & Nitrites

cGMP → dephosphorylation of myosin light chain → smooth muscle relaxation.

- **Production of PGE and PGI_2 and membrane hyperpolarization may also be involved.**

Nitrates & Nitrites

Pharmacodynamics:

1. **Relaxation of all segments of the vascular system from large arteries through large veins. Veins respond at low concentration while arteries need higher concentration.**

- **Arterioles and precapillary sphincters are affected least due to less ability to release NO or due to reflex responses.**

this decrease preload --> less contraction --> less stroke volume --> decrease O2 demand

Nitrates & Nitrites

- **The epicardial coronary arteries are sensitive, but concentric atheromas can prevent significant dilation.**
- **Eccentric lesions permit an increase in flow when nitrates relax the smooth muscle on the side away from the lesion.**

Nitrates & Nitrites

2. **Increase venous capacitance, reduce venous return, decrease ventricular preload, reduce pulmonary vascular pressure and heart size and → Reduce myocardial O_2 requirement.**

- **In the absence of heart failure, cardiac output is reduced, while in HF is increased, because preload is originally high.**

Nitrates & Nitrites

but we don't depend on it as an antiplatelet.. so in long term management of angina, we have to give antiplatelet ..

3. **Relaxation of all other types of smooth muscle, but not cardiac or skeletal muscles.**
4. **cGMP reduces platelet aggregation.**
5. **Formation of methemoglobin (Fe^{3+}) → pseudocyanosis, tissue hypoxia, and death.**

تستخدم النترات بشكل غير قانوني لجعل اللحوم تبدو طازجة و حمراء في المحلات التجارية.
إن تناول مثل هذه المنتجات قد يؤدي الى methemoglobinemia خاصة عند الأطفال

Nitrates & Nitrites

Adverse Effects:

1. **Orthostatic hypotension.**
2. **Throbbing headache due to temporal and meningeal artery pulsations.**
3. **Reflex sympathetic discharge, tachycardia.**
4. **Sodium and water retention.**
5. **Increased intracranial pressure.**

as a result of arterial vasodilation, so each pulse causes stretching in these arteries, leading to throbbing headache

increase perfusion-->
increase blood volume in the cranial cavity-->
increase intracraneal pressure

Nitrates & Nitrites

6. **Tolerance:**

Proposed causes:

A. **A decrease in tissue sulfhydryl groups (cysteine). Tolerance can be partially prevented or reversed with a sulfhydryl-regenerating agent.**

B. **Increased generation of oxygen free radicals during nitrate therapy. Treatment with antioxidants that protect ALDH2 appears to prevent or reduce tolerance.**

Nitrates & Nitrites

C. Recent evidence suggests that diminished availability of calcitonin generelated peptide (CGRP, a potent vasodilator) is also associated with nitrate tolerance.

- Tolerance can also be prevented by an 8-hour nitrate-free period.

important

TABLE 12–2 Beneficial and deleterious effects of nitrates in the treatment of angina.

Effect	Result
Potential beneficial effects	
Decreased ventricular volume Decreased arterial pressure Decreased ejection time	Decreased myocardial oxygen requirement
Vasodilation of epicardial coronary arteries	Relief of coronary artery spasm
Increased collateral flow	Improved perfusion to ischemic myocardium
Decreased left ventricular diastolic pressure	Improved subendocardial perfusion
Potential deleterious effects	
Reflex tachycardia	Increased myocardial oxygen requirement
Reflex increase in contractility	Increased myocardial oxygen requirement
Decreased diastolic perfusion time due to tachycardia	Decreased coronary perfusion

Nitrates & Nitrites

Therapeutic Uses:

1. Typical angina.
2. Prinzmetal's angina.
3. Unstable angina.
4. Myocardial infarction.
5. Congestive heart failure.
6. Hypertension.

are not antihypertensive .. but could be used in hypertensive patients that suffer from angina ...
لتضرب عصفورين بحجر واحد

Nitrates & Nitrites

Routes of administration:

1. Sublingual: immediate relief
2. IV: severe, recurrent, rest angina and MI
3. Oral: prevention
4. Transdermal patch: prevention and maintenance
5. Topical ointment; prevention and maintenance

read only

Nitrates & Nitrites

Drug	Route	Duration of action
Nitroglycerin	SL	10-30 min
	PO	6-8 hours
	TD patch	8-10 hours
	Oint	3-6 hours
Isosorbide dinitrate	SL- short acting	10-60 min
	SL- long acting	1.5-2 hours
	PO	4-6 hours
Isosorbide mononitrate	PO	6-10 hours

Nicorandil

it affects veins, like Nitrates

- It is a nicotinamide nitrate ester.
- It dilates normal coronary arteries, by activating potassium channels.
- It reduces both preload and after-load.
- May be associated with a significant reduction in relative risk of fatal and nonfatal coronary events (myocardial protection).

Molsidomine

- It is a prodrug that is converted to a nitric oxide-releasing metabolite.
- It may have efficacy comparable to that of the organic nitrates without development of tolerance.

Ranolazine

- **It reduces late sodium current (I_{Na}) that facilitates calcium entry via the sodium-calcium exchanger .** less work .. less oxygen demand
- **Thus it reduces intracellular calcium concentration → reduction of diastolic tension, cardiac contractility, and work.**
- **It is effective in stable angina, but it does not reduce the incidence of death in acute coronary syndromes.**

Ranolazine

- **It prolongs the QT interval in patients with coronary artery disease (but shortens it in patients with long QT syndrome, LQT3).**
- **It has <u>NOT</u> been associated with *torsades de pointes*.** polymorphic ventricular tachycardia.. different QRS ..leads to ventricular fibrillation
- **It may inhibit the metabolism of digoxin and simvastatin.**

Trimetazidine

- **Because metabolism shifts to oxidation of fatty acids in ischemic myocardium, the oxygen requirement per unit of ATP produced increases.**
- **pFOX inhibitors (trimetazidine) partially inhibit the fatty acid oxidation pathway in myocardium.**

Trimetazidine

- **Partial inhibition of the enzyme required for fatty acid oxidation (long-chain 3-ketoacyl thiolase, LC3KAT) appears to improve the metabolic status of ischemic tissue.**
- **It is effective in stable angina.**

Fasudil

- **The Rho kinases (ROCK) comprise a family of enzymes that inhibit vascular relaxation, leading to coronary spasm, pulmonary hypertension, apoptosis, and other conditions.**
- **Fasudil is an inhibitor of smooth muscle Rho kinase and reduces coronary vasospasm and has improved performance in stress tests.**

β-Adrenoceptor Blockers

- **Reduce heart rate, blood pressure and myocardial contractility → Reduce myocardial O_2 requirement, and increase cardiac perfusion (reduced HR prolongs diastole).**
- **Decrease mortality in patients with recent MI.**
- **Reduce infarct size.**
- **Not useful in variant angina.**

So, beta blockers must be used for this effect

Ca^{+2} channel Blockers

- **Reduce heart rate, blood pressure and myocardial contractility → reduce myocardial O_2 requirement, and increase cardiac perfusion (↓HR). (verapamil & diltiazem).**
- **Produce vasodilation → reduce afterload, BP, and thus myocardial O_2 requirement. (All).**
- **Useful in variant angina.**

Ivabradine

- **Bradycardic drug.**
- **It is relatively selective I_f sodium channel blockers, reduces cardiac rate by inhibiting the hyperpolarization-activated sodium channel in the sinoatrial node.**
- **Ivabradine appears to reduce anginal attacks with an efficacy similar to that of calcium channel blockers and β blockers.**
- **Used in angina and heart failure.**

Ivabradine

- **The funny current (I_f) is a mixed sodium–potassium current that activates upon hyper-polarization at voltages in the diastolic range (normally from −60/−70 mV to −40 mV).**

Modification of risk factors is an integral part of management of ischemic heart disease.

Statins

irrespective to cholesterol levels .. we have to give statins .. why?

A: for these 5 functions .. لازم تحفظهم زي اسمك

- **They reduce oxidative stress and vascular inflammation, stabilize atherosclerotic lesions and improve the microcirculation.** → thus relieve ischemia
- **They also inhibit proliferation of arterial wall smooth muscle and improve endothelial cell function.**

→ production of NO and prostaglandins

Statins

- They are indicated after myocardial infarction irrespective of cholesterol level in the plasma.
- Started immediately after MI with antiplatelets and ACEIs.
- Reduce myocardial events and reduce mortality after MI.