PATHOPHYSIOLOGY & DRUGS USED IN THE TREATMENT OF ANGINA PECTORIS

(ISCHEMIC HEART DISEASE)

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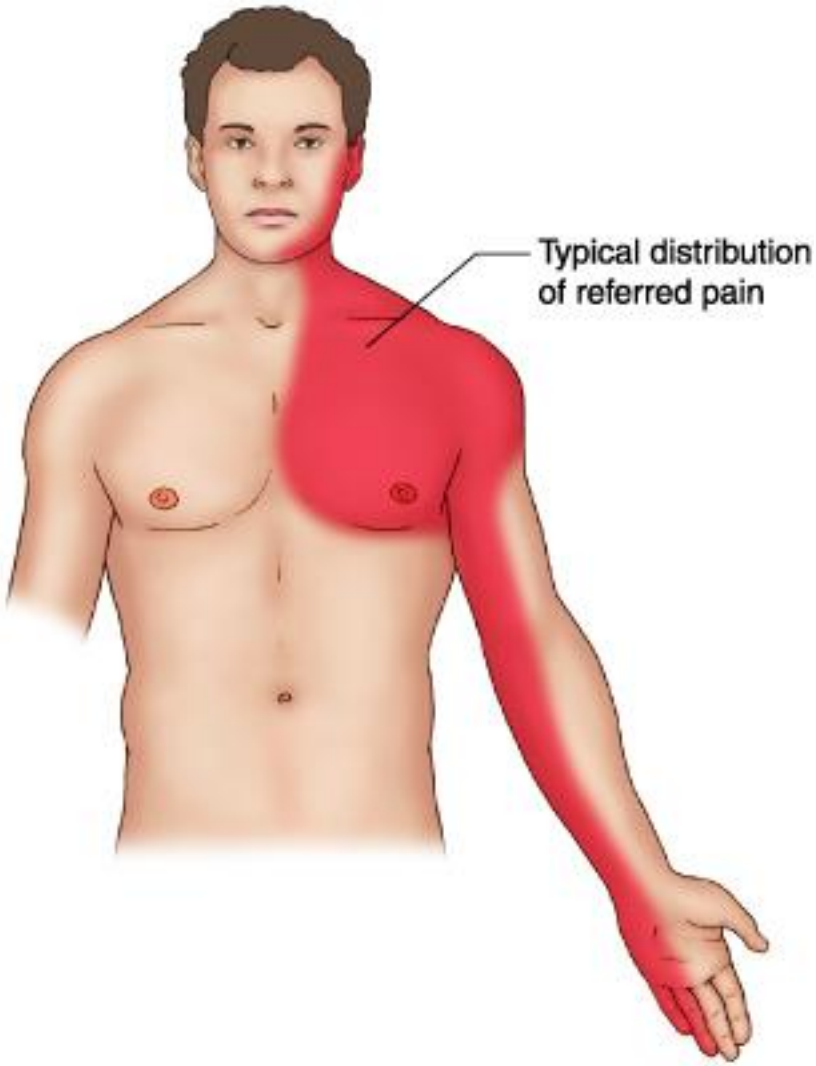
DRUGS USED IN THE TREATMENT OF ANGINA PECTORIS

- Strangling (*Latin: Angina*) or pressure-like pain in chest *(Latin: pectos)* caused by cardiac ischemia
- Located substernally but sometimes perceived in the neck, shoulder or epigastrium



Usually pain is in the chest but
Might radiate to other regions as
Shown in the figure

Classification of severity of Angina

Class	Description
I	Able to perform ordinary physical activity (e.g., walking and climbing stairs) without symptoms. Strenuous, rapid, or prolonged exertion causes symptoms.
II	Symptoms slightly limit ordinary physical activity. Walking rapidly or for more than two blocks, climbing stairs rapidly or climbing more than one flight of stairs causes symptoms.
III	Symptoms markedly limit ordinary physical activity. Walking less than two blocks or climbing one flight of stairs causes symptoms.
IV	Angina may occur at rest. Any physical activity causes symptoms.

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PATHOPHYSIOLOGY OF ANGINA

A. TYPES OF ANGINA

1. Atherosclerotic angina

- Angina of effort or classic angina
- Associated with atheromatous plaques that partially occlude one or more of the coronaries
- 90% of cases

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PATHOPHYSIOLOGY OF ANGINA

A. TYPES OF ANGINA

1. Atherosclerotic angina

- When cardiac work increases (eg, exercise), obstruction of flow results to accumulation of acidic metabolites and ischemic changes that stimulate myocardial pain endings
- Rest leads to relief of pain in 5-15 minutes

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PATHOPHYSIOLOGY OF ANGINA

A. TYPES OF ANGINA

2. Vasospastic angina

- Rest angina, variant angina or Prinzmetal's angina
- Reversible spasm of coronaries, usually at the site of an atherosclerotic plaque
- Main cause is ISCHEMIA
- Spasm may occur anytime, even during sleep
- May deteriorate to unstable angina

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PATHOPHYSIOLOGY OF ANGINA

A. TYPES OF ANGINA

3. Unstable angina

- Crescendo angina, acute coronary syndrome
- Increased frequency and severity of attacks that result from atherosclerotic plaques, platelet aggregation at fractured plaques and vasospasm
- Immediate precursor of myocardial infarction (MI)
- Medical emergency

DRUGS USED IN THE TREATMENT OF ANGINA PECTORIS

DETERMINANTS OF CARDIAC OXYGEN REQUIREMENT

- Treatment is based on physiologic factors that control myocardial O_2 requirement
- Myocardial fiber tension is a major determinant (the higher the tension, the higher the O_2 requirement)

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DETERMINANTS OF CARDIAC OXYGEN REQUIREMENT

A. PRELOAD AND AFTERLOAD

- PRELOAD (diastolic filling pressure)
  - Function of blood volume and venous tone
  - Venous tone is mainly controlled by sympathetic outflow

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DETERMINANTS OF CARDIAC OXYGEN REQUIREMENT

A. PRELOAD AND AFTERLOAD

- AFTERLOAD
  - Determined by arterial blood pressure and large artery stiffness
  - Systolic determinant of O_2 requirement

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DETERMINANTS OF CARDIAC OXYGEN REQUIREMENT

B. HEART RATE

- Contributes to time-integrated fiber tension
- At fast heart rates
  - Fibers spend more time in systolic tension levels
  - Diastole is abbreviated (diastole constitutes the time available for coronary blood flow)

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DETERMINANTS OF CARDIAC OXYGEN REQUIREMENT

B. HEART RATE

- SYSTOLIC BP X HR = DOUBLE PRODUCT
  - Measure of cardiac work (O_2 requirement)
  - In patients with atherosclerotic angina, effective drugs reduce the double product

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DETERMINANTS OF CARDIAC OXYGEN REQUIREMENT

c. CARDIAC CONTRACTILITY

- **Force of cardiac contraction**
- Systolic factor controlled mainly by sympathetic outflow to the heart

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DETERMINANTS OF CARDIAC OXYGEN REQUIREMENT

c. CARDIAC CONTRACTILITY

- **Ejection time** for ventricular contraction is inversely related to force of contraction
- Also influenced by impedance to outflow
  - Increased ejection time increases O_2 requirement

DRUGS USED IN THE TREATMENT OF ANGINA PECTORIS

THERAPEUTIC STRATEGIES

- The defect that causes anginal pain is inadequate O_2 delivery relative to myocardial oxygen requirement
- Corrected in 2 ways

1. Increasing O_2 delivery
2. Reducing O_2 requirement

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ALTERNATIVE THERAPEUTIC STRATEGIES

3. Efficiency of O_2 utilization

- Newer investigational approach
- Shifting the energy substrate reference of the heart from fatty acid to glucose
- Partial fatty acid oxidation inhibitors (eg, ranolazine, trimetazidine)

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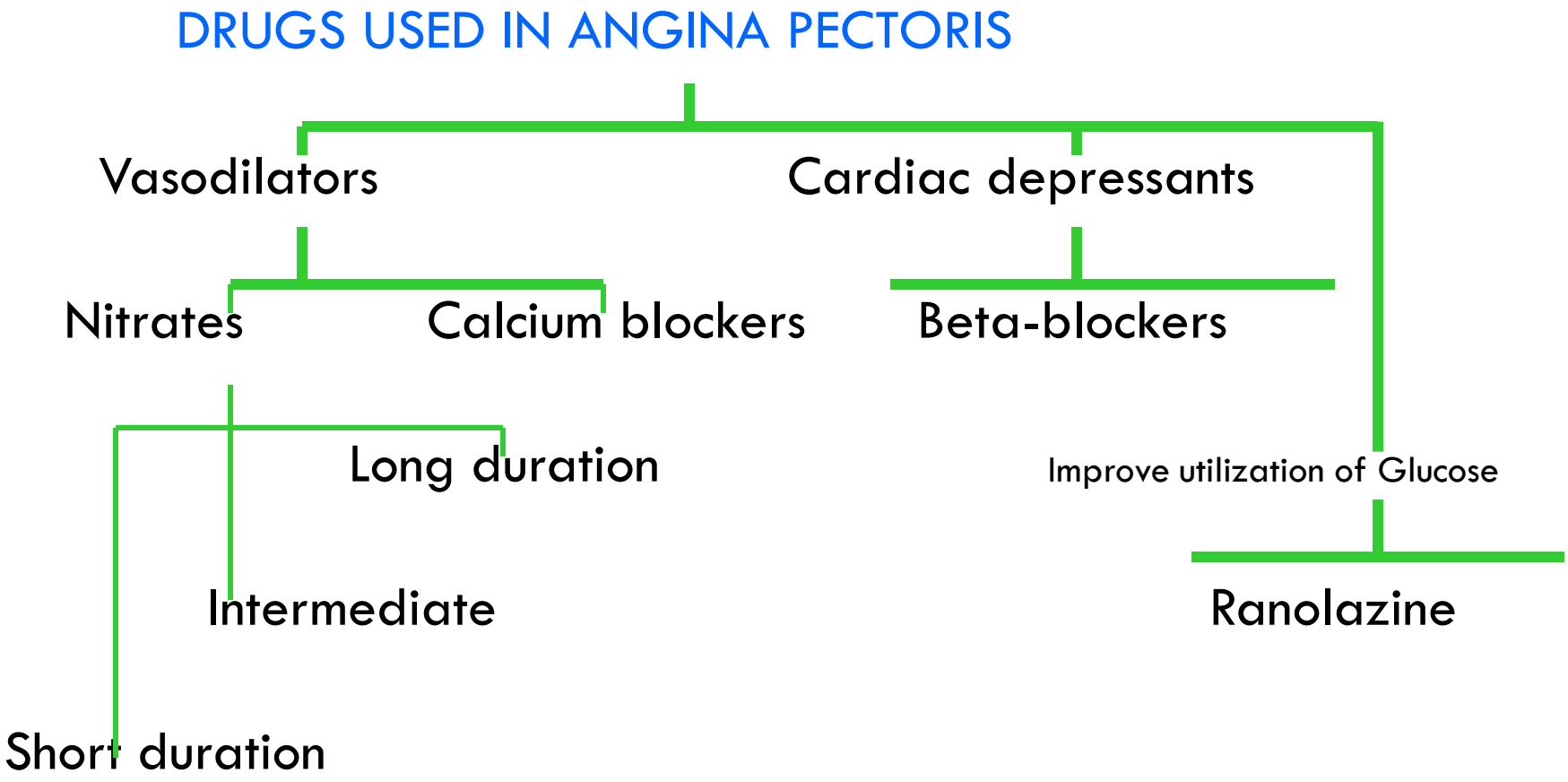
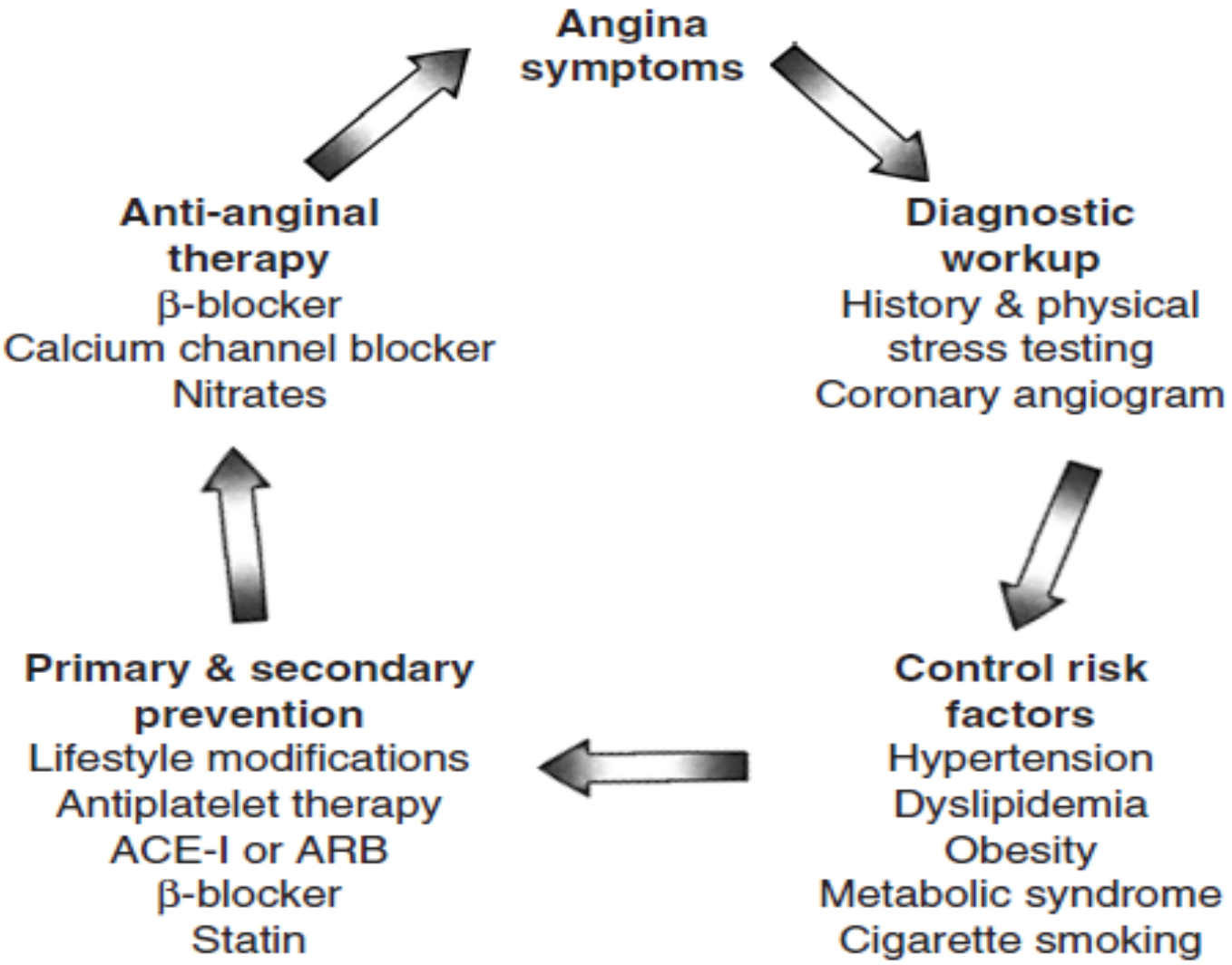


Management of Angina



DRUGS USED IN THE TREATMENT OF ANGINA PECTORIS

THERAPEUTIC STRATEGIES

- Nitrates, calcium blockers and beta-blockers all reduce the O_2 requirement in atherosclerotic angina
- Nitrates and calcium blockers (but not beta-blockers) can increase O_2 delivery by reducing vasospasm (only in vasospastic angina)

DRUGS USED IN THE TREATMENT OF ANGINA PECTORIS

THERAPEUTIC STRATEGIES

- Myocardial revascularization corrects coronary obstruction either by bypass grafting or angioplasty
- Therapy for unstable angina differs from stable angina because treatment is urgent angioplasty and platelet clotting is major target of drug therapy

DRUGS USED IN THE TREATMENT OF ANGINA PECTORIS

NITRATES

A. CLASSIFICATION AND PHARMACOKINETICS

NITROGLYCERINE (NTG)

- Active ingredient in dynamite
- Most important of the nitrates
- Available forms
  - Sublingual (10-20 min)
  - Transdermal (8-10 h)

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NITRATES

B. MECHANISM OF ACTION

- Denitration causes release of nitric oxide (NO) within smooth muscle cells stimulate guanyl cyclase increase → in cGMP → smooth muscle relaxation

DRUGS USED IN THE TREATMENT OF ANGINA PECTORIS

NITRATES

C. ORGAN SYSTEM EFFECTS

1. CARDIOVASCULAR

- Smooth muscle relaxation → peripheral venodilation
  reduced cardiac size and CO → reduced preload
- Reduced afterload because of arteriolar dilation →
  increase in ejection → decrease in cardiac size

DRUGS USED IN THE TREATMENT OF ANGINA PECTORIS

NITRATES

c. ORGAN SYSTEM EFFECTS

1. CARDIOVASCULAR

- Venodilation ⟶ decreased diastolic heart size and fiber tension
- Arteriolar dilation ⟶ reduced peripheral resistance and BP
- Overall reduction in myocardial fiber tension, O_2 consumption and double product

DRUGS USED IN THE TREATMENT OF ANGINA PECTORIS

NITRATES

D. CLINICAL USES

- Sublingual tablet
  - Standard form for treatment of acute anginal pain

DRUGS USED IN THE TREATMENT OF ANGINA PECTORIS

NITRATES

E. TOXICITY OF NITRATES AND NITRITES

- Most common toxic effects are responses evoked by vasodilation
  - Tachycardia (baroreceptor reflex)
  - Orthostatic hypotension (direct extension of venodilator effect)
  - Throbbing headache from meningeal artery vasodilatation

"Monday Morning Sickness"

- Nitrates are metabolized by sulfhydryl containing compounds to form Nitrosothiols

- Depletion of –SH groups
- Decreased metabolism to active metabolites
- Replenished after a Sunday in workers working in nitrate production factories
- Increased metabolism
- Headaches, etc might occur

DRUGS USED IN THE TREATMENT OF ANGINA PECTORIS

NITRATES

E. TOXICITY OF NITRATES AND NITRITES

- Interact with *sildenafil (Viagra)* and similar drugs promoted for erectile dysfunction
- Synergistic relaxation of vascular smooth muscle with potentially dangerous hypotension and hypoperfusion of critical organs

DRUGS USED IN THE TREATMENT OF ANGINA PECTORIS

NITRATES

E. TOXICITY OF NITRATES AND NITRITES

- Cause methemoglobinemia at high blood concentration
- Potential antidote for cyanide poisoning

DRUGS USED IN THE TREATMENT OF ANGINA PECTORIS

NITRATES

CYANIDE POISONING

DRUGS USED IN THE TREATMENT OF ANGINA PECTORIS

NITRATES

CYANIDE POISONING

- Cyanide ion complexes with iron in cytochrome oxidase block of oxidative metabolism → cell death
- Iron in methemoglobinemia has a → higher affinity for cyanide

DRUGS USED IN THE TREATMENT OF ANGINA PECTORIS

NITRATES

CYANIDE POISONING

Can be treated by a 3-step procedure

1. Immediate exposure to amyl nitrite, followed by
2. Intravenous administration of sodium nitrite which rapidly increases methemoglobin level necessary to remove significant amount of cyanide

DRUGS USED IN THE TREATMENT OF ANGINA PECTORIS

NITRATES

CYANIDE POISONING

Can be treated by a 3-step procedure

3. Intravenous sodium thiosulfate which converts cyanmethemoglobin resulting from step 2 to thiocyanate (excreted by the kidney) and methemoglobin

- Excessive methemoglobin is fatal because it is a very poor O_2 carrier

DRUGS USED IN THE TREATMENT OF ANGINA PECTORIS

CALCIUM CHANNEL BLOCKERS

A. CLASSIFICATION AND PHARMACOKINETICS

Nifedipine, Diltiazem, Verapamil

- Differ markedly in structure but all are orally active with half-lives of 3-6 hours

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CALCIUM CHANNEL BLOCKERS

B. MECHANISM OF ACTION

- Block voltage-gated "L-type" calcium channels (channel most important in cardiac and smooth muscle)
- Reduce intracellular calcium concentration and muscle contractility

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CALCIUM CHANNEL BLOCKERS

c. EFFECTS

- Relax blood vessels, and to a lesser extent, the uterus, bronchi and the gut
- Nifedipine and other dihydropyridines evoke greater vasodilation
- All drugs reduce BP and reduce the double product in angina

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CALCIUM CHANNEL BLOCKER

D. CLINICAL USE

- Prophylactic therapy in effort and vasospastic angina
- Nifedipine has also been used to abort acute anginal attacks

DRUGS USED IN THE TREATMENT OF ANGINA PECTORIS

CALCIUM CHANNEL BLOCKER

E. TOXICITY

- Constipation, pretibial edema, nausea flushing and dizziness
- Heart failure, AV blockade and sinus node depression (verapamil)

DRUGS USED IN THE TREATMENT OF ANGINA PECTORIS

BETA-BLOCKING DRUGS

A. CLASSIFICATION AND MECHANISM OF ACTION

- Prophylaxis of atherosclerotic anginal attacks

DRUGS USED IN THE TREATMENT OF ANGINA PECTORIS

BETA-BLOCKING DRUGS

B. EFFECTS

BENEFICIAL EFFECTS

- Decreased heart rate
- Decreased cardiac force
- Decreased BP

DETRIMENTAL EFFECTS

- Increased heart size
- Longer ejection period

DRUGS USED IN THE TREATMENT OF ANGINA PECTORIS

BETA-BLOCKING DRUGS

c. CLINICAL USE

- Only for prophylactic therapy
- No value for acute attacks
- Prevents exercise-induced angina but not the vasospastic form

DRUGS USED IN THE TREATMENT OF ANGINA PECTORIS

BETA-BLOCKING DRUGS

c. CLINICAL USE

- Combination with nitrates reduces the undesirable compensatory effects like tachycardia and increased cardiac force

DRUGS USED IN THE TREATMENT OF ANGINA PECTORIS

BETA-BLOCKING DRUGS

D. TOXICITY

CNS

- Sedation
- Fatigue
- sleep alteration
- Depression
- Psychosis

DRUGS USED IN THE TREATMENT OF ANGINA PECTORIS

BETA-BLOCKING DRUGS

D. TOXICITY

CVS

- Bradycardia
- AV blockade
- Heart failure

RESPIRATORY

- Worsen the asthma