angina pectoris = ischemic heart disease (IHD)
**Definition**

*ankhon* = strangling  
*pectis* = chest

**basic cause:**
coronary blood flow fails to meet myocardial oxygen requirements (myocardial ischemia):

- ↑ $O_2$ demand (physical activity)
- ↓ $O_2$ supply (blood flow obstructed)
Pathophysiology

\[ O_2 \text{ supply} \quad \text{versus} \quad O_2 \text{ demand} \]

angina pectoris
Clinical presentation

- **chest discomfort:**
  - pressure/tightness
  - burning
  - choking/breathlessness
  - pain

- **discomfort at other sites:**
  - epigastrum
  - shoulders/arms
  - neck/jaw

- **nausea**

- **diaphoresis**

**duration:**
- typically 1-5 minutes
- range 15sec-15min
Angina classification

1. stable (typical) angina
   - the most common form of angina
   - consequence of coronary atherosclerosis
   - presents in physical activity, emotional stress etc.
   - predictable, reproducible (exertion)
   - worse in cold conditions and after meals
2. unstable angina (crescendo/pre-infarction angina)

- intermediate state between stable angina and MI
- a presentation of “acute coronary syndromes” (ACS)
- may appear unexpectedly, at rest
- often not associated with physical activity
- usually a consequence of severe coronary atherosclerosis possibly complicated by a rupture and thrombus formation
- management similar to that of MI
Angina classification

3. Prinzmetal angina (variant/vasospastic angina)
   - an uncommon form of angina
   - consequence of coronary artery spasm
   - occurs at rest
   - patients may be younger, with lower risk
   - typical ECG profile
Angina classification

<table>
<thead>
<tr>
<th>coronary artery obstruction</th>
<th>angina</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>potential</td>
</tr>
<tr>
<td>70%</td>
<td>stable (exercise-induced)</td>
</tr>
<tr>
<td>90%</td>
<td>unstable (at rest)</td>
</tr>
</tbody>
</table>
Angina classification

Risk factors

• smoking
• HTN
• hyperlipidemia
• diabetes
• overweight
• sedentary lifestyle
• family history
• male gender
Non-pharmacological Tx

**lifestyle modifications**
- increased, controlled physical activity (exercise training)
- smoking cessation
- weight management, balanced diet

**invasive interventions**
- PCI - percutaneous coronary intervention:
  - balloon angioplasty
  - stent placement
- CABG - coronary artery bypass grafting
- EECP - enhanced external counter-pulsation
Pharmacotherapy

Three major drug classes:

- β-blockers
- organic nitrates
- CCBs
Pharmacotherapy

Three major drug classes:

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- CCBs
Pharmacotherapy

β-blockers

cardiac $\beta_1$ receptor antagonism

- blood pressure
- myocardial contractility

myocardial O2 demand

relief of angina symptoms
Pharmacotherapy

\(\beta\)-blockers - clinical considerations

- 1\textsuperscript{st} line in stable angina
- long-acting \(\beta_1\)-selective preferred (atenolol, metoprolol)
- anti-anginal effect is dose-dependent
- titrate dose to alleviate symptoms and HR=50-60, considering ADEs
- very effective in prevention of exertional angina
- reduce morbidity and mortality (post-MI)
- ineffective, \textbf{potentially harmful} in Prinzmetal angina (induction of vasospasms)
Pharmacotherapy

Three major drug classes:

• β-blockers
• organic nitrates
• CCBs
Pharmacotherapy

Organic nitrates:

• nitroglycerin (NTG)
Pharmacotherapy

Organic nitrates:

- nitroglycerin (NTG)
- isosorbide dinitrate (ISDN)
- isosorbide mononitrate (ISMN)
Pharmacotherapy

Organic nitrates - mechanism of action

Endogenous sources:
- arginine + O₂

Nitric oxide (NO)
- vascular smooth muscle relaxation
- venous and coronary vasodilation
- small hypotensive effect

Nitrite
- minor effect on arteries

Nitrate
- nitrite

ISDN  →  NTG  →  nitrate
ISMN  →  nitrate

angina pectoris
Pharmacotherapy

Organic nitrates:

- nitroglycerin (NTG):
  
  *Nitroderm®, Deponit®, Nitrolingual®, Nitrocin®*

- isosorbide dinitrate (ISDN):
  
  *Isoket® (spray), Cordil®, Isolong®*

- isosorbide mononitrate (ISMN):
  
  *Monolong®, Mononit®, Monocord®*
Pharmacotherapy

Organic nitrates - ADEs:

• headache
• facial flushing
• hypotension
• bradycardia

Organic nitrates - DDIs:

• PDE-5 inhibitors (sildenafil = Viagra®, severe hypotension)
• alcohol (hypotension)
# Pharmacotherapy

## Organic nitrates - use:

<table>
<thead>
<tr>
<th>nitrate</th>
<th>clinical use</th>
<th>mode of administration</th>
<th>onset of effect</th>
<th>duration of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTG</td>
<td>acute angina</td>
<td>sublingual/IV</td>
<td>rapid</td>
<td>short</td>
</tr>
<tr>
<td></td>
<td>chronic angina</td>
<td>transdermal</td>
<td>rapid</td>
<td>long</td>
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<tr>
<td></td>
<td>chronic angina</td>
<td>oral</td>
<td>delayed</td>
<td>medium</td>
</tr>
<tr>
<td>ISMN</td>
<td>chronic angina</td>
<td>oral</td>
<td>delayed</td>
<td>long</td>
</tr>
</tbody>
</table>
Pharmacotherapy

Organic nitrates - tolerance:

presentation:

• reduced effect following long-term use
• effect restored after “nitrate-free interval”

proposed mechanisms:

• decrease in NO formation
• decrease in NO effect
• activation of vasoconstricting RAAS
Pharmacotherapy

Organic nitrates - tolerance:

prevention:

• asymmetrical dosing allowing for 8-12hr “nitrate-free intervals”:

<table>
<thead>
<tr>
<th>nitrate</th>
<th>dosage form</th>
<th>recommended dosing regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISDN</td>
<td>IR</td>
<td>BID: 7/12; TID: 7/12/17</td>
</tr>
<tr>
<td></td>
<td>SR</td>
<td>BID: 8/14; OD: morning</td>
</tr>
<tr>
<td>ISMN</td>
<td>IR</td>
<td>BID: 8/15</td>
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IR/SR: immediate/sustained release; OD - ×1/d; BID - ×2/d; TID - ×3/d
Pharmacotherapy

Organic nitrates - clinical considerations:

- sublingual NTG/ISDN for acute angina and for prophylaxis (prior to physical activity known to induce acute angina)
- ISDN/ISMN for chronic angina: daytime for exertional angina, nighttime for nocturnal angina
- prevention of nitrate tolerance
- improve exercise duration; not shown to ↓ mortality
Pharmacotherapy

Three major drug classes:

• β-blockers

• organic nitrates

• CCBs
Pharmacotherapy

**Ca^{++} in ischemia**

- peripheral vasodilation
- coronary vasodilation
- negative chronotropic effect
- negative inotropic effect
Pharmacotherapy

CCBs - subclasses

Dihydropyridines (nifedipine, amlodipine)

- arterial vasodilation
- minimal effect on cardiac rate/conduction
- avoid short acting (BP drop, reflex tachycardia, ↑ mortality)

<table>
<thead>
<tr>
<th>relative affinity to</th>
<th>nifedipine</th>
<th>diltiazem</th>
<th>verapamil</th>
</tr>
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<tr>
<td>cardiac Ca²⁺ channels</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>vascular Ca²⁺ channels</td>
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Pharmacotherapy

CCBs - subclasses

Non-dihydropyridines: verapamil (phenylalkylamine)

- cardiac conduction effect > vasodilating effect
- negative chronotrope/inotrope

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Avoid in cardiac depression

Angina pectoris

Less headache, edema...
Pharmacotherapy

CCBs - subclasses

Non-dihydropyridines: diltiazem (benzothiazepine)

• intermediate properties

• coronary vasodilator (mild arterial vasodilator);
  negative chronotrope (not negative inotrope)

• useful in variant angina (relieves coronary artery spasm)

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Pharmacotherapy

![Graph showing cumulative procedure rate percent over months for Placebo and Amiodipine]
Pharmacotherapy

ACEIs in stable angina?

• some ACEIs have been shown to ↓ M&M

• mechanism of benefit unclear
  - anti-inflammatory effect in plaque?
  - reduction of LV hypertrophy

• consider adding in non-responders

• no clinical evidence regarding ARBs
Pharmacotherapy

Anti-platelet Tx in stable angina?

• for prevention of thrombus formation
• aspirin generally accepted for 1°/ 2° prevention
• also indicated in unstable angina
• addition of clopidogrel
Pharmacotherapy

Stable angina

- 1\textsuperscript{st}-line: \(\beta\)-blocker (prevent progression to MI)
- combine as needed with nitrate/CCB
  - nitrates advantageous in LV dysfunction
  - CCBs advantageous in HTN
- triple therapy as needed
- consider ACEI
Pharmacotherapy

Unstable angina (non-acute Tx)

- 1st-line: β-blocker (prevent progression to MI)
- nitrate
- CCB - for refractory cases
- aspirin +/- clopidogrel
- statin
- ACEI (ARB)
- aldosterone antagonist in some
Pharmacotherapy

Prinzmetal angina

- 1\textsuperscript{st}-line: CCBs (antispastic effect)
- if uncontrolled - combine a nitrate
- β-blockers not indicated (may induce vasospasms)
Myocardial infarction

Pathophysiology

• deterioration of unstable angina
• atherosclerotic thrombus formation
• complete occlusion of coronary artery
• massive cellular necrosis/death
• rarely caused by vasospasms w/o atherosclerosis
Myocardial infarction

Presentation

- chest pain, may radiate to arms/neck/jaw etc.
- shortness of breath
- diaphoresis
- nausea
- ~20% “silent MI”
Myocardial infarction

Diagnosis

- symptoms
- ECG
- cardiac enzymes
Myocardial infarction

Pharmacotherapy

- thrombolytics
- antiplatelet/anticoagulant Tx
- β-blockers
- CCBs
- nitrates
- anti-arrhythmics
- analgesics
- stool softeners
angina pectoris

DRUGS FOR EXAM

- isosorbide mononitrate