Pharmacotherapy of Angina Pectoris

Edward JN Ishac, Ph.D.

Smith Building, Room 742
eishac@vcu.edu
828-2127

Department of Pharmacology and Toxicology
Medical College of Virginia
Campus of Virginia Commonwealth University
Richmond, Virginia, USA

Angina Pectoris

- Chronic disease, intermittent attacks of chest pain, radiate through chest, shoulder & arm
- 3 million in USA (~ 1% pop.)

A. Typical (Stable, Effort) angina:
   - ↑ O₂ demand - fixed supply

B. Variant (Prinzmetal's) angina:
   - ↓ O₂ supply - unchanged demand
   - ie. at rest, coronary spasm (PGs?)

C. Unstable angina (ACS):
   - ↓ O₂ supply, plaque, platelets, clot

D. Microvascular angina (Syndrome X):
   - atherosclerosis in small coronary a.
Angina - Pathophysiology

A. Normal

B. Stable angina

C. Unstable angina

D. Variant angina

Unstable angina

Determinants of Oxygen Demand

Need to improve ratio
Coronary blood flow / cardiac work
or
Cardiac O₂ Supply / Cardiac O₂ Requirement
Determinants of Oxygen Demand

Need to improve ratio
Cardiac O₂ Supply / Cardiac O₂ Requirement

1. The primary determinants of myocardial O₂ supply:
   a. Coronary blood flow (major determinant)
   b. O₂ content of the blood
   c. O₂ extraction by the myocardium

2. The primary determinants of myocardial O₂ consumption:
   a. Ventricular systolic pressure (afterload)
   b. Heart size (preload)
   c. Heart rate
   d. Myocardial contractility

Coronary Circulation vs Other Circulation

- most tissues can increase O₂ extraction with demand
- heart extracts near maximal amount of O₂ at rest
- therefore can only increase O₂ delivery by increasing coronary blood flow
Lifestyle - Angina Risk Factors

- Obesity
- Physical inactivity
- Smoking
- Hypertension
- High cholesterol
- Age
- Gender
- Family history

Can regulate

Inherent

Improving supply/demand ratio

a. Relaxation of resistance vessels (small arteries and arterioles) \( \downarrow \text{TPR} \rightarrow \downarrow \text{BP} \rightarrow \downarrow \text{Afterload} \), \( \downarrow \text{O}_2 \) demand
   (Nitrates, calcium channel blockers and beta-blockers)

b. Relaxation of capacitance vessels (veins and venules)
   \( \downarrow \) Venous return, \( \downarrow \) heart size, \( \downarrow \) Preload, \( \downarrow \text{O}_2 \) demand
   (Nitrates)

c. Blockade or attenuation of sympathetic influence on the heart
   \( \downarrow \) Contactility, \( \downarrow \) HR, \( \downarrow \text{O}_2 \) demand
   (Beta-blockers)

d. Coronary vessel dilation
   - Important mechanism for relieving vasospastic angina
   - \( \uparrow \text{O}_2 \) supply
   (Nitrates)
Nitrates - MOA

- Direct smooth m. relaxation
- High specificity vascular sm
- Vasodilation: veins > arteries
- ↓Preload > ↓Afterload

a. Formation of NO in endothelial cells involving sulfhydryl (SH) groups
b. Interaction between NO and thiols in smooth mus. to form nitrosothiols
c. Nitrosothiol activates guanylate cyclase and increased formation of cGMP

Tolerance: oxidation of SH groups and formation of disulfide bonds
  - develops fast and recovers fast ie. “Monday syndrome or Head”

Nitroglycerin

Nitroprusside

Nitrate

Sodium Nitroprusside

Note: Nitroglycerin tablets and sprays for angina contain tiny amounts of nitroglycerin diluted by inert matter and are completely non-explosive.
Nitrates and Nitrites

- Formation of Nitric oxide (NO) → activation of guanylate cyclase
- ↑Ca** uptake SR, dephosphorylation of myosin-LC

Tolerance: frequency / dose dependence (absence periods)

Absorption and disposition: well absorbed, first-pass metabolism with oral administration (10-20%)

Adverse actions: headache, flushing, hypotension, tachycardia, possible circulatory collapse CI: PDE5 inhibitors (ie. Viagra)

a. Nitroglycerin
   - Sublingual (duration 30min), buccal (4hr)
   - Oral spray (30min), oral tablets (6hr)
   - Topical: ointment (4hr), transdermal patches (8hr)
   - Intravenous: instant action
b. Isosorbide dinitrate (ISDN): sublingual (2hr), oral (4hr)
c. Isosorbide mononitrate: oral (8hr), metabolite of ISDN
d. Amyl nitrite, butyl nitrite: volatile, "recreational use/abuse"

Viagra
(Sildenafil)

- phosphodiesterase type 5 inhibitor
- ↑NO release
- leads to ↑cGMP
- initially developed for angina
- CI with nitrates, alpha-blockers
Nitroglycerin - Routes of administration

1. Sublingual tablet
   - Avoids first-pass effect
   - Onset: 30 sec, Duration: 30 min

2. Buccal tablet
   - Tablet placed in buccal cavity
   - Adheres to mouth’s mucosal surface, NG released for 3-6 hrs

3. Oral
   - Translingual spray – Duration 30 min
   - Oral tablet – Duration 6 hrs, subject to first-pass effect

4. Topical
   a) ointment (paste)
      - Duration: 3-4 hrs, used in acute care setting
      - Inconvenient, messy, largely replaced by patch
   b) Transdermal system (patch)
      - Delivers nitroglycerin over 24 hr period
      - Avoid continuous use to prevent tolerance (remove at night)

Nitrates and Nitrites

Other compounds have been developed with the intent of having a longer duration of action for prophylaxis

b. Isosorbide dinitrate [ISDN] – converted to ISMN

c. Isosorbide mononitrate [ISMN]
   - Active metabolite of ISDN
   - Not subject to first-pass metabolism
   - Greater bioavailability (100%)
   - Clinical efficacy not greater than ISDN

Both forms have: 30 min onset, 6 hr duration
Nitroglycerin and Nitrates

Table 4. Nitroglycerin and Nitrates for Chronic Stable Angina

<table>
<thead>
<tr>
<th>Compound</th>
<th>Route</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroglycerin</td>
<td>Sublingual</td>
<td>0.3-0.6 mg up to 1.5 mg</td>
<td>15-45 min</td>
</tr>
<tr>
<td></td>
<td>Spray</td>
<td>0.4 mg as needed</td>
<td>Similar to sublingual tablets</td>
</tr>
<tr>
<td></td>
<td>Ointment</td>
<td>2% 6 x 6 in 15 x</td>
<td>Effect up to 7 h</td>
</tr>
<tr>
<td></td>
<td>Transdermal</td>
<td>0.2 mg 8 mg 12 h</td>
<td>12 h during intermittent therapy</td>
</tr>
<tr>
<td></td>
<td>Oral sustained release</td>
<td>2.5-13 mg</td>
<td>4-8 h</td>
</tr>
<tr>
<td></td>
<td>Buccal</td>
<td>Maximal 1-3 mg 3 times daily</td>
<td>3-5 h</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Intravenous</td>
<td>Maximal 5-20 mg/ml daily</td>
<td>Tolerance in 1-8 h</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Inhalation</td>
<td>Up to 60 mg</td>
<td>Up to 24 h</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Oral</td>
<td>5-80 mg 2-3 times daily</td>
<td>Up to 8 h</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Spray</td>
<td>1-25 mg 4 h</td>
<td>2-3 h</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Chewable</td>
<td>5 mg</td>
<td>2-2.5 h</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Oral slow release</td>
<td>4-6 mg 2-3 times daily</td>
<td>Up to 8 h</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Transdermal</td>
<td>125-500 mg 4 h</td>
<td>Tolerance in 7-8 h</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Intravenous</td>
<td>100 mg 1 ml</td>
<td>Not effective</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Oral</td>
<td>20 mg twice daily</td>
<td>12-24 h</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Sublingual</td>
<td>Maximal 10 mg as needed</td>
<td>Not known</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Oral</td>
<td>5-10 mg 3 times daily</td>
<td>Not known</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Oral</td>
<td>10-30 mg 3 times daily</td>
<td>Not known</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Oral</td>
<td>40 mg 2-4 times daily</td>
<td>Not known</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Oral</td>
<td>125-500 mg 4 h</td>
<td>Tolerance in 7-8 h</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Oral</td>
<td>100 mg 1 ml</td>
<td>Not effective</td>
</tr>
</tbody>
</table>

Beta-Adrenoceptor Antagonists

Frontline, high clinical value
- ↓response elderly, Afro-Americans, smokers

Multiple mechanisms of action:
  i. block cardiac beta1-receptors: ↓HR → ↓CO → ↓BP
  ii. ↓myocardial O2 consumption by ↓HR and ↓force contraction, ↓CO
  iii. ↓BP → ↓after-load, ↓pre-load
### Beta-Adrenoceptor Blocking Agents (-olol)

#### (A-M β1-selective)

Properties of several beta-receptor blocking drugs

<table>
<thead>
<tr>
<th>Selectivity</th>
<th>Partial Agonist Activity</th>
<th>Local Anesthetic Action</th>
<th>Lipid Solubility</th>
<th>Elimination Half-Life</th>
<th>Approximate Bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>β1</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
<td>3–4 hours</td>
</tr>
<tr>
<td>Atenolol</td>
<td>β1</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>6–9 hours</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>β1</td>
<td>No</td>
<td>Slight</td>
<td>Low</td>
<td>14–22 hours</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>β1</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>9–12 hours</td>
</tr>
<tr>
<td>Catechol</td>
<td>None</td>
<td>Yes</td>
<td>No</td>
<td>Low</td>
<td>6 hours</td>
</tr>
<tr>
<td>Celiprolol</td>
<td>β1</td>
<td>Yes</td>
<td>No</td>
<td>Low</td>
<td>4–5 hours</td>
</tr>
<tr>
<td>Esmolol</td>
<td>β1</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>10 minutes</td>
</tr>
<tr>
<td>Labetalol²</td>
<td>None</td>
<td>Yes¹</td>
<td>Yes</td>
<td>Moderate</td>
<td>5 hours</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>β1</td>
<td>No</td>
<td>Yes</td>
<td>Moderate</td>
<td>3–4 hours</td>
</tr>
<tr>
<td>Nadolol</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>14–24 hours</td>
</tr>
<tr>
<td>Penbutolol</td>
<td>None</td>
<td>Yes</td>
<td>No</td>
<td>High</td>
<td>5 hours</td>
</tr>
<tr>
<td>Pindolol</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
<td>3–4 hours</td>
</tr>
<tr>
<td>Propranolol</td>
<td>None</td>
<td>No</td>
<td>Yes</td>
<td>High</td>
<td>3½–6 hours</td>
</tr>
<tr>
<td>Sorbogol</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>12 hours</td>
</tr>
<tr>
<td>Timolol</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Moderate</td>
<td>4–5 hours</td>
</tr>
</tbody>
</table>

*Partial agonist effects at β1 receptors. ²Labetalol also causes α1-selective blockade. ³Bioavailability is dose-dependent.

#### Clinical use – Beta-blockers

<table>
<thead>
<tr>
<th>Class/Drug</th>
<th>HT</th>
<th>Angina</th>
<th>Arrh</th>
<th>MI</th>
<th>HF</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-selective β1/β2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carteolol</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ISA; long acting; also for glaucoma</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>α-blocking activity</td>
</tr>
<tr>
<td>Labetalol</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>ISA; α-blocking activity</td>
</tr>
<tr>
<td>Nadolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>long acting</td>
</tr>
<tr>
<td>Penbutolol</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>ISA</td>
</tr>
<tr>
<td>Pindolol</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>ISA; MSA</td>
</tr>
<tr>
<td>Propranolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>MSA; prototypical beta-blocker</td>
</tr>
<tr>
<td>Sotalol</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>also K-channel blocker</td>
</tr>
<tr>
<td>Timolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>primarily used for glaucoma</td>
</tr>
<tr>
<td><strong>β1-selective</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acebutolol</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>ISA</td>
</tr>
<tr>
<td>Atenolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betaxolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>MSA</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esmolol</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>short acting; operative arrhythmia</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>MSA</td>
</tr>
</tbody>
</table>
β-Blockers: Untoward Effects, Cautions

• Supersensitivity: Abrupt withdrawal → Rebound HT, less with β-blockers with partial agonist (ie. pindolol).

• Cardiac: ↓reserve, fatigue, dizziness

• Asthma: Blockade of pulmonary β2-receptors leads to increase in airway resistance. β1-selective better

• Diabetes: Compensatory hyperglycemic effect of EPI in insulin-induced hypoglycemia is removed by block of β2-ARs in liver. β1-selective agents preferred

• Raynaud D: Decreased peripheral circulation

• CNS: nightmares, mental depression, insomnia

• Elderly: ↓Effectiveness, ↑adverse effects (ie. depression)

Angina – Beta Blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Selectivity</th>
<th>Partial Agonist Activity</th>
<th>Usual Dose for Angina</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>None</td>
<td>No</td>
<td>20-80 mg twice daily</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>β1</td>
<td>No</td>
<td>50-200 mg twice daily</td>
</tr>
<tr>
<td>Atenolol</td>
<td>β1</td>
<td>No</td>
<td>50-200 mg/day</td>
</tr>
<tr>
<td>Nadolol</td>
<td>None</td>
<td>No</td>
<td>40-80 mg/day</td>
</tr>
<tr>
<td>Timolol</td>
<td>None</td>
<td>No</td>
<td>10 mg twice daily</td>
</tr>
<tr>
<td>Acebutolol</td>
<td>β1</td>
<td>Yes</td>
<td>200-600 mg twice daily</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>β1</td>
<td>No</td>
<td>10-20 mg/day</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>β1</td>
<td>No</td>
<td>10 mg/day</td>
</tr>
<tr>
<td>Esmolol (intravenous)</td>
<td>β1</td>
<td>No</td>
<td>50-300 µg/kg/min</td>
</tr>
<tr>
<td>Labetalol*</td>
<td>None</td>
<td>Yes</td>
<td>200-600 mg twice daily</td>
</tr>
<tr>
<td>Pindolol</td>
<td>None</td>
<td>Yes</td>
<td>25-75 mg 3 times daily</td>
</tr>
</tbody>
</table>

*Labetalol is a combined alpha and beta blocker.

Calcium Channel Blockers

- frontline class, oral and generally well absorbed
- bind to L-type calcium channels in cardiac and vascular smooth muscle
- inhibition of calcium influx into cardiac and arterial smooth muscle cells
- minimal effect on venous capacitance vessels.
- dilate arterioles $\rightarrow \downarrow$ TPR $\rightarrow \downarrow$ BP (less verapamil, more nifedipine), $\downarrow$ afterload
- negative inotropic action on heart (more verapamil, less nifedipine), $\rightarrow \downarrow$ oxygen demand
- $T\frac{1}{2}$: most 2-5 hrs, bepridil 42 hrs, amlodipine 30-50- hrs

Calcium Channel Blockers

Non-dihydropyridines (non-DHPs):
Verapamil, Diltiazem, Bepridil

Dihydropyridines (DHPs): [-dipine]
Nifedipine, Amlodipine, Nicardipine, Felodipine

Nifedipine:
- mainly arteriole vasodilation, little cardiac effect
- reflex tachycardia, flushing, peripheral edema

Verapamil:
- significant cardiac depression, constipation
- caution in digitalized patients ($\uparrow$ digoxin levels)

Diltiazem:
- similar to Verapamil / Nifedipine (less)
- actions on cardiac and vascular beds
Intracellular Action of Calcium

Calcium channels:
Type: L, T, N
T & N: neurons, glands
L: dominant in cardiac and smooth muscle

L-Type channel contains several receptors:
Dihydropyridines (ie. nifedipine) and verapamil/diltiazem bind to different receptors in L channel to decrease calcium influx

CCBs: Cardiovascular & renal actions:

<table>
<thead>
<tr>
<th></th>
<th>Diltiazem</th>
<th>Verapamil</th>
<th>Nifedipine (DHPs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>↓</td>
<td>↓</td>
<td>↑ (reflex)</td>
</tr>
<tr>
<td>Myocardial contractility</td>
<td>↓</td>
<td>↓↓</td>
<td>↓ or ↑ (reflex)</td>
</tr>
<tr>
<td>Nodal conduction</td>
<td>↓</td>
<td>↓↓</td>
<td>↑ (reflex)</td>
</tr>
<tr>
<td>Peripheral vasodilation</td>
<td>↑</td>
<td>↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Renal blood flow</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>
Calcium-Blockers: Adverse effects

- constipation (more likely with non-DHPs)
- non-DHPs: cardiac depression, bradycardia, AV block
- non-DHPs are contraindicated with beta-blockers
- mostly DHPs: hypotension, reflex tachycardia, flushing, headache, edema
- hypotension (more likely with DHPs)
- gingival hyperplasia (nifedipine, 10%)
- CHF non-DHPs contraindicated, DHPs not recommended
- CYP3A4 inhibitors: grapefruit, verapamil, diltiazem
- CYP3A4 substrates: amlodipine, verapamil

Calcium blockers - Gingival Hyperplasia

- Calcium blockers – especially nifedipine (10%)
- Phenytoin (Dilantin) – for seizures (40%)
- Cyclosporine – immunosuppressant (30%)
### Angina – Calcium Antagonists

**Table 6. Calcium Antagonists for Chronic Stable Angina**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dose</th>
<th>Duration of Action</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dihydroergotines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Immediate release</td>
<td>Short</td>
<td>Hypertension, dizziness, flushing, nausea, constipation, edema</td>
</tr>
<tr>
<td>Slow release</td>
<td>30-90 mg daily orally</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amlodipine</td>
<td>5-10 mg qd</td>
<td>Long</td>
<td>Headache, edema</td>
</tr>
<tr>
<td>Felodipine</td>
<td>5-10 mg qd</td>
<td>Long</td>
<td>Headache, edema</td>
</tr>
<tr>
<td>Lercanidipine</td>
<td>2.5-10 mg bid</td>
<td>Medium</td>
<td>Headache, fatigue</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>20-40 mg qd</td>
<td>Short</td>
<td>Headache, dizziness, flushing, edema</td>
</tr>
<tr>
<td>Niidipine</td>
<td>20-40 mg qd</td>
<td>Short</td>
<td>Similar to nifedipine</td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>20 mg qd or bid</td>
<td>Medium</td>
<td>Similar to nifedipine</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bepridil</td>
<td>200-400 mg qd</td>
<td>Long</td>
<td>Arrhythmia, dizziness, nausea</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Immediate release</td>
<td>Short</td>
<td>Hypertension, dizziness, flushing, bradycardia, edema</td>
</tr>
<tr>
<td>Slow release</td>
<td>200-400 mg qd</td>
<td>Long</td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>Immediate release</td>
<td>Short</td>
<td>Hypertension, hypotension, depression, edema, bradycardia</td>
</tr>
<tr>
<td>Slow release</td>
<td>60-120 mg qd</td>
<td>Long</td>
<td></td>
</tr>
</tbody>
</table>


### Other Agents (Adjuncts)

1. **Dipyridamole** (Persantin)
   - inhibitor of thromboxane synthase (\(\downarrow\)TXA\(_2\))
   - inhibitor of PDE (\(\uparrow\)cAMP)
   - decrease platelet aggregation

2. **Aspirin** (low dose)
   - also inhibitor of platelet aggregation (\(\downarrow\)TXA2)

3. **Ranolazine** (Ranexa)
   - reserve agent for chronic, resistant angina
   - inhibits cardiac late Na current, \(\downarrow\)Ca
   - \(\downarrow\)cardiac contractivity, [metabolic action]
   - \(\uparrow\)QT interval, no change in HR, BP
   - CI with other agents that \(\uparrow\)QT (ie. quinidine)
Antianginals on Primary Determinants of Myocardial $O_2$ Consumption

<table>
<thead>
<tr>
<th></th>
<th>Calcium Blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nitrates</td>
</tr>
<tr>
<td>VSP (Afterload)</td>
<td>↓</td>
</tr>
<tr>
<td>Heart Size (Preload)</td>
<td>↓↓</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>↑(R)</td>
</tr>
<tr>
<td>Contractile Force</td>
<td>0↑(R)</td>
</tr>
</tbody>
</table>

Drug Choices in Angina

A. Effort: nitrates, calcium-blockers, beta-blockers, aspirin
B. Variant: nitrates, calcium-blockers
C. Unstable (ACS): nitrates, calcium-blockers, beta-blockers, antiplatelets, anticoagulants

Aims in the use of antianginal drugs:

a. Treatment of acute attack - nitroglycerin very effective (i.v., sublingual, oral spray)
b. Short term prophylaxis - taking nitroglycerin prior to physical or emotional stress to prevent attack
c. Long term prophylaxis - objective is to reduce frequency of angina attacks. Many options are now available ie. long-acting nitrates, $Ca^{++}$-blockers, $\beta$-blockers, aspirin, anticoagulants
Angina Drug Treatment

CONCOMITANT DISEASE

- NONE
- RECENT MYOCARDIAL INFARCTION
- ASTHMA, COPD
- HYPERTENSION
- DIABETES
- CHRONIC RENAL DISEASE

DRUGS COMMONLY USED IN TREATING ANGINA

- Long-acting nitrates
- β-Blockers
- Ca<sup>2+</sup> channel blockers

Agent for Peripheral Vascular Disease & Thrombosis

Edward JN Ishac, Ph.D.

Smith Building, Room 742
eishac@vcu.edu
828-2127

Department of Pharmacology and Toxicology
Medical College of Virginia
Campus of Virginia Commonwealth University
Richmond, Virginia, USA
Background and Significance

• Peripheral arterial disease (PAD) is a progressive atherosclerotic disease

• Affects approximately 9 million Americans

• Symptoms of PAD are related to insufficient arterial blood flow, which results in debilitating, activity-induced, ischemic pain (claudication)

• Associated with major limitations in mobility and physical functioning, and decreased quality of life.
Deep Vein Thrombosis (DVT)

Myocardial Infarction (MI)

Artery

Q waves after an Inferior MI

Heart Attack
Classified according to mechanism of action

Older agents: results have been generally unsatisfactory

1. Beta-adrenergic stimulants: not useful, adverse effects

2. Alpha-blocking agents: not useful, adverse effects

3. Calcium entry blockers: some usefulness
   a. Nifedipine, Diltiazem - used for Raynaud’s disease
   b. Nimodipine - used for subarachnoid hemorrhage
      • structurally related to nifedipine
      • highly lipid soluble, crosses BBB well
      • used to inhibit cerebral vasospasm after hemorrhage from a ruptured intracranial aneurysm;
      ↓ permanent neurological damage from ischemia

Raynaud’s Syndrome

• Excessive sympathetic tone in nerves supplying hands and feet. Minor cold, or even thought of cold, causes pronounced vasoconstriction that can be severe enough to cause necrosis of tissues

• Discoloration of the fingers and/or toes when the patient is exposed to changes in temperature (cold or hot) or emotional events

• Abnormal spasm of blood vessels causes diminished blood supply

• Initially, the digit(s) turn white because of diminished blood supply.

• Then turn blue because of prolonged lack of oxygen

• Finally turn red, the blood vessels reopen, causing a local “flushing”

• Three-phase color sequence (white to blue to red) is typical

• Treatment: Ca++ blockers if severe

• Nifedipine, Diltiazem
Phosphodiesterase inhibitors - cAMP

a. Pentoxifylline (↑cAMP, PDE-4)
   - may improve capillary flow by increasing erythrocytic flexibility
   - not a vasodilator
   - used for intermittent claudication
     (characterized by difficulty in walking; drug efficacy → increase walking distance)

b. Cilostazol (↑cAMP, PDE-3)
   - inhibits platelet aggregation
   - vasodilator, increase erythrocytic flexibility
   - used for intermittent claudication

Vascular smooth muscle - Calcium / cAMP

Abbreviations: SR, sarcoplasmic reticulum; Gq, Gs-protein; MLC, myosin light chain; MLCK, myosin light chain kinase; Pi, myosin phosphorylation
Phosphodiesterase Isoforms

<table>
<thead>
<tr>
<th>Specificity</th>
<th>Inhibitors</th>
<th>Clinical use</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDE-1</td>
<td>cAMP/cGMP</td>
<td>Vinpocetine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑memory, vasodilator</td>
</tr>
<tr>
<td>PDE-2</td>
<td>cAMP/cGMP</td>
<td></td>
</tr>
<tr>
<td>PDE-3</td>
<td>cAMP</td>
<td>Cilostazol, Milrinone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PAD, ↑Cardiac output</td>
</tr>
<tr>
<td>PDE-4</td>
<td>cAMP</td>
<td>Pentoxifylline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PAD</td>
</tr>
<tr>
<td>PDE-5</td>
<td>cGMP</td>
<td>Sildenafil, Vardenafil</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ED, Pulmonary HT</td>
</tr>
<tr>
<td>PDE-6</td>
<td>cGMP</td>
<td></td>
</tr>
<tr>
<td>PDE-7</td>
<td>cAMP</td>
<td></td>
</tr>
<tr>
<td>PDE-8</td>
<td>cAMP</td>
<td></td>
</tr>
<tr>
<td>PDE-9</td>
<td>cGMP</td>
<td></td>
</tr>
<tr>
<td>PDE-10</td>
<td>cAMP/cGMP</td>
<td></td>
</tr>
<tr>
<td>PDE-11</td>
<td>cAMP/cGMP</td>
<td></td>
</tr>
</tbody>
</table>

Caffeine, Theophylline: non-selective phosphodiesterase inhibitors

Phosphodiesterase-5 inhibitors - cGMP

↑cGMP by inhibition of isoform PDE-5
Potentiate action of nitrates
CI: Severe hypotension with nitrates or alpha blockers

c. Sildenafil (Viagra): ED, Pulmonary HT
   - selective vasodilation for treating erectile dysfunction
   - visual disturbances, but cause/effect unknown

d. Vardenafil (Levitra): ED
   - ↑QT interval: avoid quinidine, procainamide, amiodarone

e. Tadalafil (Cialis): ED
   - duration much longer (up to 36 hrs)
   - adverse effects include back pain and muscle aches
VIII. Agents that Prevent or Remove Thrombus

A. Activators of antithrombin (also called antithrombin III)
   • Expose active sites on AT-III, OK in pregnancy
   • Increase rate of thrombin inactivation by antithrombin

1. Unfractionated Heparin (12,000-30,000MW)
   • highly-sulfated glycosaminoglycan, high -ve charge
   • main adverse effect is hemorrhage, given iv or sc
   • variable response, need to monitor aPTT
   • can cause heparin-induced thrombocytopenia (HIT) which is treated with Lepirudin (Refludin)

2. Enoxaparin, Dalteparin, Ardeparin, Tinzaparin
   • Low molecular weight heparins (6K-15K), given sc
   • More bioavailable, Longer acting (5 hrs vs 1.5 hr)
   • Less hemorrhage, no monitoring required

3. Fondaparinux
   • pentasaccharide, inhibits only Xa
Heparin action

Response is variable, Need monitoring

aPTT | activated partial thromboplastin time test

aPTT measures anti-factor IIa activity

Actions of Heparin & related anticoagulants

1 : 1 (Xa/AT)

AT = antithrombin,
Xa = activated factor X.

Rudins: direct thrombin inh.
Bivalirudin,
Lepirudin,
Desirudin;
Argatroban
Unfractionated Heparin - Thrombocytopenia

Treatment Lepirudin

Inhibition of Thrombin

B. Direct Inhibition of Thrombin: rudins: Hirudin, Bivalirudin, Lepirudin, Desirudin; univalent: Argatroban, 1. - used for anticoagulation during angioplasty
C. Inhibition of Clotting Factor Synthesis

Warfarin (oral agent) - interfere with vitamin K action to inhibit synthesis of prothrombin (II)
- Best kinetics, intermediate duration
- First order elimination

Warfarin inhibits the ability of Vitamin K to carboxylate the Vit. K dependent clotting factors, reducing their coagulant activity.

Coagulation cascade – Vitamin K

- **Intrinsic system** (surface contact)
- **Extrinsic system** (tissue damage)

Heparin

Vitamin K dependant factors

Vitamin K dependent factors:
Warfarin vs Heparins

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Heparin (unfrac.)</th>
<th>LMW Heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size (mw)</td>
<td>308</td>
<td>12,000-30,000</td>
<td>6,000-15,000</td>
</tr>
<tr>
<td>Routes</td>
<td>oral or i.v.</td>
<td>i.v., s.c.</td>
<td>s.c.</td>
</tr>
<tr>
<td>Half-life</td>
<td>2.5 d</td>
<td>1.5 hrs</td>
<td>5 hrs</td>
</tr>
<tr>
<td>Onset</td>
<td>Delayed, 12 hr</td>
<td>Immediate</td>
<td>Immediate</td>
</tr>
<tr>
<td>Duration</td>
<td>2-5 d</td>
<td>4 hrs</td>
<td>16 hrs</td>
</tr>
<tr>
<td>MOA</td>
<td>Inh. Vit K action ↓ II, VII, IX, X</td>
<td>Activate ATIII → Inhibit Xa, IIa</td>
<td>Activate ATIII → Inhibit Xa &gt; IIa</td>
</tr>
<tr>
<td>Concerns</td>
<td>Many drugs, resins, (s-) 2C9, (r-) 3A4, Thrombocytopenia (HIT) Monitor aPTT</td>
<td>No monitoring, bleeding all drugs</td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>No (teratogenic)</td>
<td>OK</td>
<td>OK</td>
</tr>
<tr>
<td>Toxicity Rx</td>
<td>Vit. K or plasma</td>
<td>Protamine sulfate</td>
<td>Protamine sulfate</td>
</tr>
<tr>
<td>Uses</td>
<td>DVT, PE, AF, MI, stroke, (TIA), PCI</td>
<td>DVT, PE, AF, MI, angina</td>
<td>DVT, PE, AF, MI, angina</td>
</tr>
</tbody>
</table>

D. Anti-platelet Drugs – TXA₂

Drugs inhibiting platelet aggregation and adhesiveness can prevent thrombus formation and are most useful for arterial thrombosis

a. Aspirin: inhibits cyclooxygenase-1 → ↓TXA₂
b. Dipyridamole: inhibits thromboxane synthase → ↓TXA₂, also inhibits PDE → ↑cAMP
c. Aggrenox - fixed dose combo of aspirin & dipyridamole
D. Anti-platelet Drugs – ADP Blockers

d. Clopidogrel
• inhibit the ADP pathway for platelet activation by blocking ADP to its receptors (irreversible, P2Y, glycoproteins on platelet membrane)
• uses include
  - prevention of TIA or ischemic stroke
  - acute coronary syndrome, acute MI
  - PCI (percutaneous coronary intervention)
• adverse effects - fewer than ticlopidine (no neutropenia)
  - GI effects - nausea, diarrhea (20%), hemorrhage (5%)
e. Ticlopidine
  - introduced before clopidogrel, more adverse effects
  - associated with neutropenia and thrombocytopenia
  - regular blood tests are recommended
f. Prasugrel
  - also ADP receptor inhibitor (approved July 2009)

Platelet IIb, IIIa receptor blockers

Abciximab, Eptifibatide, Tirofiban
• IIb and IIIa are platelet membrane proteins
• function as receptors for fibrinogen and von Willebrand factors which link platelets to walls of injured vessels
• Adhesion leads to aggregation and thrombus formation
• used in patients undergoing high-risk angioplasty or atherectomy and for acute coronary syndrome
• iv, oral drugs in development
• Adverse effect: ↑bleeding risk
Factors involved in Platelet Activation

Action of aspirin and dipyridamole

PLATELET

Arachidonic acid

<table>
<thead>
<tr>
<th>Aspirin</th>
<th>Cyclooxygenase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thromboxane A2</td>
</tr>
<tr>
<td>Decreases accumulation</td>
<td></td>
</tr>
<tr>
<td>Platelet Aggregation</td>
<td></td>
</tr>
</tbody>
</table>

VESSSEL WALL

Arachidonic acid

<table>
<thead>
<tr>
<th>Cyclooxygenase</th>
<th>Prostacyclin (PGI2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclic AMP</td>
<td>Inhibition of Platelet Aggregation</td>
</tr>
<tr>
<td>PDE</td>
<td>S-AMP</td>
</tr>
</tbody>
</table>

Aspirin → irreversible acetylation platelet COX-1 enzyme (low dose < 300mg/dl)
Platelet lacks nucleus, cannot generate new enzyme during its ten day lifetime
Other NSAIDs have similar but shorter and reversible effect
Aspirin to Prevent MI and Death

- Aspirin 75 to 325 mg daily should be used routinely to all patients with acute and chronic ischemic heart disease in the absence of contraindications
  - aspirin exerts an antithrombotic effect by inhibiting cyclooxygenase and synthesis of platelet TXA₂
  - in patients with stable angina, aspirin reduces the risk of adverse cardiovascular events by 33%
  - in patients with unstable angina, aspirin decreases the short and long-term risk of fatal and nonfatal MI by 36%
  - aspirin (325 mg), given on alternate days to asymptomatic persons, associated with a decreased incidence of MI

Efficacy of aspirin in preventing MI

Unstable angina patient  +++
Post MI patient        ++
“Healthy” person        +

Optimum dose of aspirin - still unclear

“Low” doses (81 - 325 mg/day) appear more effective than higher doses
Thrombosis

Blood Clot

Tissue Plasminogen Activator (tPA)

Plasminogen

Plasmin

Plasmin dissolves the blood clot

Tissue Plasminogen Activator (tPA)

Induces the secretion of tPA

Coagulation Pathways

Extrinsic Pathway

Damage to tissue outside the vessel

Tissue Thromboplastin

Intrinsic Pathway

Damage to the blood vessel

Cascade of clotting factors

Activated Factor X

Prothrombin

Thrombin

Fibrinogen

Fibrin

Factor XII

Blood Clot
Thrombolytic Agents - “clot busters”

Streptokinase, Alteplase (Tissue plasminogen activator [TPA]), Retaplace, Anistreplase, Tenectplace

Activate plasminogen leading to:
- activation of plasmin, degradation of fibrin and clot
- Accelerate dissolution of thrombi

- Critical factor in use: elapsed time between thrombotic event and administration, greatest if used within 2-3 hrs

Thrombolytics differ with respect to:
- allergenicity, clot specificity
- half-life (or duration required for infusion)
- cost

Properties of Thrombolytics “Clot busters”

<table>
<thead>
<tr>
<th></th>
<th>Streptokinase</th>
<th>Alteplase</th>
<th>Retaplace</th>
<th>Anistreplase</th>
<th>Tenectplace</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allergenic</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Clot selectivity</strong></td>
<td>Not selective</td>
<td>High</td>
<td>High</td>
<td>Intermediate</td>
<td>High</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>Very short</td>
<td>Short</td>
<td>Longer</td>
<td>Long</td>
<td>Long</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

Clot selectivity: selective for clot-bound plasminogen
Critical factor: elapsed time between thrombotic event and use
Benefit greatest if used within 2-3 hours
Surface vs Fluid Plasminogen

Fluid Phase

Plasminogen Activation → Plasmin Degradation → Fibrinogen Factor V Factor VIII

Nonfibrin-Specific or Less Fibrin-Specific Plasminogen Activators

Fibrin-Specific Plasminogen Activators

PAI-1 α2-Antiplasmin

Plasmin Degradation Products

Fibrin Strands Network

PVD, Antiplatelets, Anticoagulants, Fibrinolytics

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAD</td>
<td>Pentoxifylline, cilostazol</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Warfarin, heparin, LMWH, (aspirin)</td>
</tr>
<tr>
<td>DVT: Treatment</td>
<td>Warfarin, heparin, LMWH</td>
</tr>
<tr>
<td>DVT: Surgical</td>
<td>LMWH, (heparin)</td>
</tr>
<tr>
<td>MI: Prevention</td>
<td>Aspirin, clopidogrel, prasugrel, (ticlopidine)</td>
</tr>
<tr>
<td>MI: Treatment</td>
<td>Alteplase, heparin, aspirin, abciximab</td>
</tr>
<tr>
<td>Heart valve</td>
<td>Aspirin, warfarin, (dipyridamole)</td>
</tr>
<tr>
<td>Stroke</td>
<td>Aspirin, clopidogrel, warfarin, (ticlopidine)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>Aspirin, LWMH, heparin, abciximab</td>
</tr>
<tr>
<td>Pulmonary E.</td>
<td>Warfarin, heparin, LMWH, (alteplase)</td>
</tr>
<tr>
<td>PCI</td>
<td>Heparin, aspirin, clopidogrel, abciximab, (ticlopidine)</td>
</tr>
<tr>
<td>TIA</td>
<td>Aspirin, (warfarin)</td>
</tr>
<tr>
<td>Raynaud’s D.</td>
<td>Calcium blockers</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>Sildenafil, Vardenafil, Tadalafil</td>
</tr>
</tbody>
</table>