Pharmacotherapy of Angina Pectoris

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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
   - i.e. at rest, coronary spasm (PGs?)
C. Unstable angina (ACS):
   - ↓ O₂ supply, plaque, platelets, clot
D. Microvascular angina (Syndrome X):
   - atherosclerosis in small coronary a.

Determinants of Oxygen Demand

Need to improve ratio
Coronary blood flow / cardiac work
or
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**

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

Can regulate

Inherent

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**Improving supply/demand ratio**

a. Relaxation of resistance vessels (small arteries and arterioles) ↓ TPR → ↓ BP → ↓ Afterload, ↓ O\(_2\) demand  
(Nitrates, calcium channel blockers and beta-blockers)

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

c. Blockade or attenuation of sympathetic influence on the heart  
↓ Contractility, ↓ HR, ↓ O\(_2\) demand  
(Beta-blockers)

d. Coronary vessel dilation  
- Important mechanism for relieving vasospastic angina  
- ↑ O\(_2\) supply  
(Nitrates)

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**Nitroglycerin**

- Formation of Nitric oxide (NO) → activation of guanylate cyclase
- ↑ Ca\(^{2+}\) uptake SR, dephosphorylation of myosin-LC

**Nitroglycerin MOA**

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

**Nitrates - MOA**

- Direct smooth muscle relaxation
- High specificity vascular smooth
- Vasodilation: veins > arteries
- ↓ Preload > ↓ Afterload

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**Nitroglycerin**

- Formation of NO in endothelial cells involving sulfhydryl (SH) groups
- Interaction between NO and thios in smooth mus. To form nitrosothiols
- 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”

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**Nitroglycerin**

- Sublingual (duration 30min), buccal (4hr)
- Oral spray (30min), oral tablets (6hr)
- Topical: ointment (4hr), transdermal patches (8hr)
- Intravenous: instant action

**Isosorbide dinitrate (ISDN):**

- Sublingual (2hr), oral (4hr)

**Isosorbide mononitrate:**

- Oral (8hr), metabolite of ISDN

**Amyl nitrite, butyl nitrite:** volatile, “recreational use/abuse”

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

**Sodium Nitroprusside**

Note:

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**Nitroglycerin**

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

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**Sildenafil**

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

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**Viagra**

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

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**Nitrates and Nitrites**

- Formation of Nitric oxide (NO) → activation of guanylate cyclase
- ↑ Ca\(^{2+}\) 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”
Nitroglycerin - Routes of administration

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

2. Buccal 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)

Nitroglycerin and Nitrates

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

Beta-Adrenoceptor Antagonists

- High clinical value
- block cardiac beta1-receptors
  i. ↓ HR → ↓ CO → ↓ BP
  ii. ↓ myocardial O$_2$ consumption by ↓ HR and ↓ force contraction, ↓ CO
  iii. ↓ BP → ↓ after-load, ↓ pre-load

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

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   • Active metabolite of ISDN
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   • Greater bioavailability (100%) 
   • Clinical efficacy not greater than ISDN

Both forms have: 30 min onset, 6 hr duration

Nitroglycerin and Nitrates

<table>
<thead>
<tr>
<th>Compound</th>
<th>Route</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroglycerin</td>
<td>Sublingual tablet</td>
<td>0.3-0.6 mg up to 3.5 mg</td>
<td>3-7 min</td>
</tr>
<tr>
<td></td>
<td>Buccal tablet</td>
<td>2% 5 x 15 15 cm 7.5-40 mg</td>
<td>15-60 min</td>
</tr>
<tr>
<td></td>
<td>Transdermal</td>
<td>0.1-0.8 mg/24 h up to 12 h</td>
<td>6-12 h</td>
</tr>
<tr>
<td></td>
<td>Oral caplet</td>
<td>3.5-9 mg</td>
<td>4 h</td>
</tr>
<tr>
<td></td>
<td>Oral spray</td>
<td>1-3 mg/5 ml</td>
<td>5-10 min</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>Sublingual</td>
<td>3-6 mg</td>
<td>20-45 min</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>10-50 mg</td>
<td>2-4 h</td>
</tr>
<tr>
<td></td>
<td>Transdermal</td>
<td>40-400 mg/24 h</td>
<td>1-4 h</td>
</tr>
<tr>
<td></td>
<td>Oral caplet</td>
<td>100 mg</td>
<td>6 h</td>
</tr>
</tbody>
</table>

Beta-Adrenoceptor Blocking Agents (-olol)

<table>
<thead>
<tr>
<th>Class/Drug</th>
<th>HT</th>
<th>Angina</th>
<th>Arrh</th>
<th>Beta-Blocker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Esmolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Timolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Atenolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Acebutolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Labetalol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Propranolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pindolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Non-selective Beta-blocker</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical use – Beta-blockers

- Short acting, short duration
- Long acting, extended duration
- Selective (beta-1, beta-2)

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<tr>
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<td>Bisoprolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Timolol</td>
<td>X</td>
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<tr>
<td>Atenolol</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<td>Acebutolol</td>
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<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Labetalol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Propranolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pindolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

- Non-selective Beta-blocker

- Selective (beta-1, beta-2)

- MSA: monosodium azide
- ISA: insulin-stimulating activity
- MIB: myocardial ischaemia
- GPA: glucagonase activity
- APS: adenosine phosphate synthase
- COX: cyclooxygenase
- PGH: prostaglandin H
- PGI: prostaglandin I
- PGI$\alpha$: prostaglandin I$_\alpha$
- PGI$\beta$: prostaglandin I$_\beta$
- PGI$\gamma$: prostaglandin I$_\gamma$
- PGI$\delta$: prostaglandin I$_\delta$
- PGI$\epsilon$: prostaglandin I$_\epsilon$
- PGI$\zeta$: prostaglandin I$_\zeta$
- PGI$\eta$: prostaglandin I$_\eta$
- PGI$\theta$: prostaglandin I$_\theta$
- PGI$\iota$: prostaglandin I$_\iota$
- PGI$\kappa$: prostaglandin I$_\kappa$
- PGI$\lambda$: prostaglandin I$_\lambda$
- PGI$\mu$: prostaglandin I$_\mu$
- PGI$\nu$: prostaglandin I$_\nu$
- PGI$\xi$: prostaglandin I$_\xi$
- PGI$\omicron$: prostaglandin I$_\omicron$
- PGI$\pi$: prostaglandin I$_\pi$
- PGI$\rho$: prostaglandin I$_\rho$
- PGI$\sigma$: prostaglandin I$_\sigma$
- PGI$\tau$: prostaglandin I$_\tau$
- PGI$\upsilon$: prostaglandin I$_\upsilon$
- PGI$\phi$: prostaglandin I$_\phi$
- PGI$\chi$: prostaglandin I$_\chi$
- PGI$\psi$: prostaglandin I$_\psi$
- PGI$\omega$: prostaglandin I$_\omega$
- PGI$\alpha'$: prostaglandin I$_\alpha'$
- PGI$\beta'$: prostaglandin I$_\beta'$
- PGI$\gamma'$: prostaglandin I$_\gamma'$
- PGI$\delta'$: prostaglandin I$_\delta'$
- PGI$\epsilon'$: prostaglandin I$_\epsilon'$
- PGI$\zeta'$: prostaglandin I$_\zeta'$
- PGI$\eta'$: prostaglandin I$_\eta'$
- PGI$\theta'$: prostaglandin I$_\theta'$
- PGI$\iota'$: prostaglandin I$_\iota'$
- PGI$\kappa'$: prostaglandin I$_\kappa'$
- PGI$\lambda'$: prostaglandin I$_\lambda'$
- PGI$\mu'$: prostaglandin I$_\mu'$
- PGI$\nu'$: prostaglandin I$_\nu'$
- PGI$\xi'$: prostaglandin I$_\xi'$
- PGI$\omicron'$: prostaglandin I$_\omicron'$
- PGI$\pi'$: prostaglandin I$_\pi'$
- PGI$\rho'$: prostaglandin I$_\rho'$
- PGI$\sigma'$: prostaglandin I$_\sigma'$
- PGI$\tau'$: prostaglandin I$_\tau'$
- PGI$\upsilon'$: prostaglandin I$_\upsilon'$
- PGI$\phi'$: prostaglandin I$_\phi'$
- PGI$\chi'$: prostaglandin I$_\chi'$
- PGI$\psi'$: prostaglandin I$_\psi'$
- PGI$\omega'$: prostaglandin I$_\omega'$
- PGI$\alpha''$: prostaglandin I$_\alpha''$
- PGI$\beta''$: prostaglandin I$_\beta''$
- PGI$\gamma''$: prostaglandin I$_\gamma''$
- PGI$\delta''$: prostaglandin I$_\delta''$
- PGI$\epsilon''$: prostaglandin I$_\epsilon''$
- PGI$\zeta''$: prostaglandin I$_\zeta''$
- PGI$\eta''$: prostaglandin I$_\eta''$
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- PGI$\iota''$: prostaglandin I$_\iota''$
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- PGI$\phi''$: prostaglandin I$_\phi''$
- PGI$\chi''$: prostaglandin I$_\chi''$
- PGI$\psi''$: prostaglandin I$_\psi''$
- PGI$\omega''$: prostaglandin I$_\omega''$
β-Blockers: Untoward Effects, Cautions

- Supersensitivity: Abrupt withdrawal → Rebound HT, less with β-blockers with partial agonist (e.g., 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 (e.g., depression)

Calcium Channel Blockers

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

Dihydropyridines (DHPs): [D-pine]
- 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 (↑ digoxin levels)
Diltiazem:
- similar to Verapamil / Nifedipine (less)
- actions on cardiac and vascular beds

Angina – Beta Blockers

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 → ↓ TPR → ↓ BP (less verapamil, more nifedipine), ↓ afterload
- negative inotropic action on heart (more verapamil, less nifedipine), → ↓ oxygen demand
- T½: most 2-5 hrs, bepridil 42 hrs, amlodipine 30-50- hrs

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

Table 5. Beta Blockers for Chronic Stable Angina

<table>
<thead>
<tr>
<th>Drug</th>
<th>Selectivity</th>
<th>Partial Agonist</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>Atenolol</td>
<td>β1</td>
<td>Yes</td>
<td>200-600 mg twice daily</td>
</tr>
<tr>
<td>Bepranolol</td>
<td>β1</td>
<td>No</td>
<td>10-20 mg/day</td>
</tr>
<tr>
<td>Beoprolol</td>
<td>None</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>Labetalolβ</td>
<td>None</td>
<td>Yes</td>
<td>200-400 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>

β1 selective blockers

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</td>
<td>↓</td>
<td>↓</td>
<td>↓ or ↑ (reflex)</td>
</tr>
<tr>
<td>contractility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodal conduction</td>
<td>↓</td>
<td>↓</td>
<td>↑ (reflex)</td>
</tr>
<tr>
<td>Peripheral</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>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: amloidine, verapamil

**Calcium blockers - Gingival Hyperplasia**
- Calcium blockers – especially nifedipine (10%)
- Phenytoin (Dilantin) – for seizures (40%)
- Cyclosporine – immunosuppressant (30%)

**Antianginals on Primary Determinants of Myocardial O₂ Consumption**

<table>
<thead>
<tr>
<th></th>
<th>Nitrates</th>
<th>Beta-Blockers</th>
<th>Verapamil/Diltiazem</th>
<th>DHPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSP (Afterload)</td>
<td>↓</td>
<td>0↓→↓</td>
<td>↓↓↓</td>
<td>↓</td>
</tr>
<tr>
<td>Heart Size (Preload)</td>
<td>↓↓→↓</td>
<td>0↓→↓</td>
<td>↓↓↓</td>
<td>↓</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>↑ (R)</td>
<td>↓↓↑</td>
<td>0↑</td>
<td>↑ (R)</td>
</tr>
<tr>
<td>Contractile Force</td>
<td>0↑ (R)</td>
<td>↓↓↓</td>
<td>↓↓↓</td>
<td>0</td>
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</tbody>
</table>

**Drug Choices in Angina**

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

Aims in the use of antianginal drugs:
- Treatment of acute attack - nitroglycerin very effective (i.v., sublingual, oral spray)
- Short term prophylaxis - taking nitroglycerin prior to physical or emotional stress to prevent attack
- Long term prophylaxis - objective is to reduce frequency of angina attacks. Many options are now available i.e. long-acting nitrates, Ca**+-blockers, beta-blockers, aspirin, anticoagulants
Angina Drug Treatment

<table>
<thead>
<tr>
<th>CONCOMITANT DISEASE</th>
<th>DRUGS COMMONLY USED IN TREATING ANGINA</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOE</td>
<td>Long-acting nitrates, β-Blockers, CA^2+ channel blockers</td>
</tr>
<tr>
<td>RECENT MYOCARDIAL INFARCTION</td>
<td>Long-acting nitrates, β-Blockers, CA^2+ channel blockers</td>
</tr>
<tr>
<td>ASTHMA, COPD</td>
<td>Long-acting nitrates, β-Blockers, CA^2+ channel blockers</td>
</tr>
<tr>
<td>HYPERTENSION</td>
<td>Long-acting nitrates, β-Blockers, CA^2+ channel blockers</td>
</tr>
<tr>
<td>DIABETES</td>
<td>Long-acting nitrates, β-Blockers, CA^2+ channel blockers</td>
</tr>
<tr>
<td>CHRONIC RENAL DISEASE</td>
<td>Long-acting nitrates, β-Blockers, CA^2+ channel blockers</td>
</tr>
</tbody>
</table>

KEY: Drug class

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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.
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 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>1memory, 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, condition 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 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

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/eff ect 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
Guanylate cyclase/cGMP – PDE 5 Inhibition

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 (Refudin)

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

Unfractionated Heparin - Thrombocytopenia

VIII. Agents that Prevent or Remove Thrombus
A. Activators of antithrombin (also called antithrombin III)
- Expose active sites on AT-III, OK in pregnancy
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Heparin action

B. Direct Inhibition of Thrombin:
rudins: Hirudin, Bivalirudin, Lepirudin, Desirudin; univalent: Argatroban
- Used for anticoagulation during angioplasty
Inhibition of Clotting Factors

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

Vitamin K

Antagonism of Vitamin K

Warfarin

Inhibition of Clotting Factors

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

D. Anti-platelet Drugs – TXA₂
Drugs inhibiting platelet aggregation and adhesiveness can prevent thrombus formation and are most useful for arterial thrombosis
- Aspirin: inhibits cyclooxygenase-1 → ↓ TXA₂
- Dipyridamole: inhibits thromboxane synthase → ↓ TXA₂, also inhibits PDE → ↑ cAMP
- 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

Abciximab
HIV/IIia antagonists
Black Fibrinogen, von Willebrand factors

Aspirin

Other NSAIDs have similar but shorter and reversible effect

Action of aspirin and dipyridamole

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

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

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

Thrombosis

Tissue Plasminogen Activator (tPA)

Extrinsic Pathway

Intrinsic Pathway

Damage to tissue outside the vessel
Activated Factor X
Damage to the blood vessel
Tissue Thromboplastin
Factor XIII
Prothrombin
Thrombin
Fibrinogen
Fibrin

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>Allergenic</th>
<th>Clot selectivity</th>
<th>Half-life</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptokinase</td>
<td>Yes</td>
<td>Very short</td>
<td>Low</td>
</tr>
<tr>
<td>Alteplase</td>
<td>No</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Retaplace</td>
<td>No</td>
<td>Medium</td>
<td>Medium</td>
</tr>
<tr>
<td>Anistreplase</td>
<td>Yes</td>
<td>Long</td>
<td>Long</td>
</tr>
<tr>
<td>Tenectplace</td>
<td>No</td>
<td>Long</td>
<td>Long</td>
</tr>
</tbody>
</table>

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

Surface vs Fluid Plasminogen

Fluid Phase

Plasminogen Activator

Plasmin

Fibrinogen

Factor V Factor VIII

Nonfibrin-Specific or Less Fibrin-Specific Plasminogen Activators

Fibrin-Specific Plasminogen Activators

PAI-1

α2-Antiplasmin

Fibrin strands network

Fibrin degradation products