**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:
   - $\uparrow$ $O_2$ demand - fixed supply

B. Variant (Prinzmetal's) angina:
   - $\downarrow$ $O_2$ supply - unchanged demand
   - ie. at rest, coronary spasm (PGs?)

C. Unstable angina:
   - $\downarrow$ $O_2$ 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

Toni Braxton: Microvascular angina (Syndrome X)

Due to atherosclerosis in very small coronary arteries (5%)
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 $O_2$ extraction with demand
- heart extracts near maximal amount of $O_2$ at rest
- therefore can only increase $O_2$ delivery by increasing coronary blood flow

Angina – Coronary Occlusion

When a clogged artery keeps the heart from getting enough blood and oxygen, angina can occur.
Angina – Surgical Treatment
(Coronary bypass, angioplasty, stents)

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) ↓TPR → ↓BP → ↓Afterload, ↓O₂ demand
   (Nitrates, calcium channel blockers and beta-blockers)

b. Relaxation of capacitance vessels (veins and venules)
   ↓Venous return, ↓heart size, ↓Preload, ↓O₂ demand
   (Nitrates)

c. Blockade or attenuation of sympathetic influence on the heart
   ↓Contactility, ↓HR, ↓O₂ demand
   (Beta-blockers)

d. Coronary vessel dilation
   - Important mechanism for relieving vasospastic angina
   - ↑O₂ supply
   (Nitrates)

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Nitroglycerin
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Nitrogen oxide (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 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

Tolerance: frequency / dose dependence (absence periods)

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

Toxicity: headache, flushing, hypotension, possible circulatory collapse

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
   • Tablet placed in buccal cavity
   • Adheres to mouth's mucosal surface, NG released for 3-6 hrs
3. Oral (translingual) spray
   • Oral tablet - 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 NG 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>
<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>15-30 min</td>
</tr>
<tr>
<td></td>
<td>Spray</td>
<td>0.4 mg as needed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ointment</td>
<td>2 x 6 x 6 m 15 x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Transdermal</td>
<td>0.200 mg/h every 12 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral sustained</td>
<td>2.5-13 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Buccal</td>
<td>1-3 mg, 3 times daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intranasal</td>
<td>5200 mg/m²/min</td>
<td>Tolerance in 7-9 h</td>
</tr>
<tr>
<td>isosorbide diniclate</td>
<td>Sublingual</td>
<td>2.5-15 mg</td>
<td>Up to 60 min</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>5-8 mg 2-3 times daily</td>
<td>Up to 8 h</td>
</tr>
<tr>
<td></td>
<td>Spray</td>
<td>1-25 mg       daily</td>
<td>3-24 h</td>
</tr>
<tr>
<td></td>
<td>Chewable</td>
<td>5 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral slow release</td>
<td>40 mg 1-2 times daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Transdermal</td>
<td>1-25-50 mg</td>
<td>Tolerance in 7-9 h</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>20 mg twice daily</td>
<td>12-24 h</td>
</tr>
<tr>
<td>isosorbide mimoninate</td>
<td>Sublingual</td>
<td>10-20 mg once daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>20-60 mg</td>
<td></td>
</tr>
<tr>
<td>isosorbide mononitrate</td>
<td>Sublingual</td>
<td>10 mg as needed</td>
<td>Not known</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>10-20 mg</td>
<td></td>
</tr>
<tr>
<td>isosorbide tetracitrate</td>
<td>Sublingual</td>
<td>5-10 mg as needed</td>
<td>Not known</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>10-10 mg, 3 times daily</td>
<td>Not known</td>
</tr>
</tbody>
</table>


Viagra (Sildenafil)

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

That's odd. This bottle of Viagra was full two days ago.
Beta-Adrenoceptor Antagonists

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

Multiple mechanisms of action:
1. block cardiac beta1-receptors: ↓HR → ↓CO → ↓BP
2. ↓myocardial O₂ consumption by ↓HR and ↓force contraction, ↓CO
3. ↓BP → ↓after-load, ↓pre-load

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**Beta-Adrenoceptor Blocking Agents** (-olol)  
(A-M β1-selective)

Properties of several beta-receptor blocking drugs

<table>
<thead>
<tr>
<th>Drug</th>
<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>
<td>50%</td>
</tr>
<tr>
<td>Atenolol</td>
<td>β₁</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>6-9 hours</td>
<td>40%</td>
</tr>
<tr>
<td>Betaxiol</td>
<td>β₁</td>
<td>No</td>
<td>Slight</td>
<td>Low</td>
<td>14-22 hours</td>
<td>50%</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>β₁</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>9-12 hours</td>
<td>80%</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>None</td>
<td>Yes</td>
<td>No</td>
<td>Low</td>
<td>6 hours</td>
<td>85%</td>
</tr>
<tr>
<td>Celiprolol</td>
<td>β₁</td>
<td>Yes¹</td>
<td>No</td>
<td>Low</td>
<td>4-5 hours</td>
<td>70%</td>
</tr>
<tr>
<td>Esmolol</td>
<td>β₁</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>10 minutes</td>
<td>...</td>
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<tr>
<td>Labetalol²</td>
<td>None</td>
<td>Yes¹</td>
<td>Yes</td>
<td>Moderate</td>
<td>5 hours</td>
<td>30%</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>β₁</td>
<td>No</td>
<td>Yes</td>
<td>Moderate</td>
<td>3-4 hours</td>
<td>50%</td>
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<tr>
<td>Nadolol</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>14-24 hours</td>
<td>33%</td>
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<tr>
<td>Pindolol</td>
<td>None</td>
<td>Yes</td>
<td>No</td>
<td>High</td>
<td>5 hours</td>
<td>&gt;90%</td>
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<tr>
<td>Pranolol</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
<td>3-4 hours</td>
<td>50%</td>
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<tr>
<td>Propranolol</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
<td>High</td>
<td>3-6 hours</td>
<td>30%</td>
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<tr>
<td>Sotalol</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>12 hours</td>
<td>50%</td>
</tr>
<tr>
<td>Timolol</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Moderate</td>
<td>4-5 hours</td>
<td>50%</td>
</tr>
</tbody>
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¹Partial agonist effects at β₁ receptors.  
²Labetalol also causes α₁-selective blockade.  
Bioavailability is dose-dependent.
Clinical use – Beta-blockers

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<thead>
<tr>
<th>Class/Drug</th>
<th>HT</th>
<th>Angina</th>
<th>Arrh</th>
<th>MI</th>
<th>HF</th>
<th>Comments</th>
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<tr>
<td><strong>Non-selective β₁/β₂</strong></td>
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<tr>
<td>Carteolol</td>
<td>X</td>
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<td>ISA; long acting; also for glaucoma</td>
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<tr>
<td>Carvedilol</td>
<td>X</td>
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<td></td>
<td></td>
<td>X</td>
<td>α-blocking activity</td>
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<tr>
<td>Labetalol</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>ISA; α-blocking activity</td>
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<tr>
<td>Nadolol</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<td>long acting</td>
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<td>Penbutolol</td>
<td>X</td>
<td>X</td>
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<td>ISA</td>
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<tr>
<td>Pindolol</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>ISA; MSA</td>
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<tr>
<td>Propranolol</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>MSA; prototypical beta-blocker</td>
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<tr>
<td>Sotalol</td>
<td></td>
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<td></td>
<td></td>
<td>X</td>
<td>K-channel blocker</td>
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<tr>
<td>Timolol</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>primarily used for glaucoma</td>
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<tr>
<td><strong>β₁-selective</strong></td>
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<td>X</td>
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<td></td>
<td>ISA</td>
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<td></td>
<td>MSA</td>
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<td>X</td>
<td></td>
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<tr>
<td>Esmolol</td>
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<td></td>
<td></td>
<td></td>
<td>X</td>
<td>short acting; operative arrhythmia</td>
</tr>
<tr>
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<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>MSA</td>
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</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 5. Beta Blockers for Chronic Stable Angina

<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>2.5-7.5 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
- T½: 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 (↑ 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>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dose</th>
<th>Duration of Action</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dihydropyridines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Immediate release: 30-90 mg daily orally</td>
<td>Short</td>
<td>Hypotension, dizziness, flushing, nausea, constipation, edema</td>
</tr>
<tr>
<td></td>
<td>Slow release: 30-180 mg 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>Isradipine</td>
<td>2.5-10 mg bid</td>
<td>Medium</td>
<td>Headache, tongue</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>20-40 mg tid</td>
<td>Short</td>
<td>Headache, dizziness, flushing, edema</td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>20-40 mg qd</td>
<td>Short</td>
<td>Similar to nifedipine</td>
</tr>
<tr>
<td></td>
<td>20-40 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>Arrhythmias, dizziness, rashes, flushing, bradycardia, edema</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Immediate release: 30-80 mg, 4 times daily</td>
<td>Short</td>
<td>Hypotension, dizziness, flushing, bradycardia, edema</td>
</tr>
<tr>
<td></td>
<td>Slow release: 120-300 mg qd</td>
<td>Long</td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>Immediate release: 80-160 mg bid</td>
<td>Short</td>
<td>Hypotension, myocardial depression, heart failure, edema, bradycardia</td>
</tr>
<tr>
<td></td>
<td>Slow release: 120-480 mg qd</td>
<td>Long</td>
<td></td>
</tr>
</tbody>
</table>

Other Agents

1. Dipyridamole (Persantin)
   – inhibitor of thromboxane synthase (↓TXA2)
   – decrease platelet aggregation

2. Aspirin (low dose)
   – also an inhibitor of platelet aggregation

3. Ranolazine (Ranexa)
   – reserve agent for chronic, resistant angina
   – inhibits cardiac late Na current, ↓Ca
   – ↓cardiac contractivity, [metabolic action]
   – ↑QT interval, no change in HR, BP
   – CI with other agents that ↑QT (ie. quinidine)

Antianginals on Primary Determinants of Myocardial O₂ 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
B. Variant: nitrates, calcium blockers
C. Unstable: nitrates, calcium blockers, beta blockers, aspirin, anticoagulants, thrombolytics

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 anticipated physical or emotional stress may 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, β-blockers, aspirin, anticoagulants, thrombolytics

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 thromboxane A₂
  - 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
  - aspirin (325 mg), given on alternate days to asymptomatic persons, associated with a decreased incidence of MI
Angina Drug Treatment

<table>
<thead>
<tr>
<th>CONCOMITANT DISEASE</th>
<th>DRUGS COMMONLY USED IN TREATING ANGINA</th>
</tr>
</thead>
<tbody>
<tr>
<td>NONE</td>
<td>Long-acting nitrate</td>
</tr>
<tr>
<td></td>
<td>β-Blockers</td>
</tr>
<tr>
<td></td>
<td>Ca(^{2+}) channel blockers</td>
</tr>
<tr>
<td>RECENT MYOCARDIAL INFARCTION</td>
<td>Long-acting nitrate</td>
</tr>
<tr>
<td></td>
<td>β-Blockers</td>
</tr>
<tr>
<td></td>
<td>Ca(^{2+}) channel blockers</td>
</tr>
<tr>
<td>ASTHMA, COPD</td>
<td>Long-acting nitrate</td>
</tr>
<tr>
<td></td>
<td>β-Blockers</td>
</tr>
<tr>
<td></td>
<td>Ca(^{2+}) channel blockers</td>
</tr>
<tr>
<td>HYPERTENSION</td>
<td>Long-acting nitrate</td>
</tr>
<tr>
<td></td>
<td>β-Blockers</td>
</tr>
<tr>
<td></td>
<td>Ca(^{2+}) channel blockers</td>
</tr>
<tr>
<td>DIABETES</td>
<td>Long-acting nitrate</td>
</tr>
<tr>
<td></td>
<td>β-Blockers</td>
</tr>
<tr>
<td></td>
<td>Ca(^{2+}) channel blockers</td>
</tr>
<tr>
<td>CHRONIC RENAL DISEASE</td>
<td>Long-acting nitrate</td>
</tr>
<tr>
<td></td>
<td>β-Blockers</td>
</tr>
<tr>
<td></td>
<td>Ca(^{2+}) channel blockers</td>
</tr>
</tbody>
</table>

KEY: Commonly used drugs | Less effective drugs

Determinants of Myocardial Oxygen Supply and Demand

Myocardial oxygen supply

- Diastolic perfusion pressure
- Coronary vascular resistance
  - external compression
  - intrinsic regulation
    - local metabolites
    - endothelial factors
    - neural innervation
- O\(_2\)-carrying capacity

Myocardial oxygen demand

- Wall tension (P, r/2h)
- Heart rate
- Contractility

Figure 6.1. Major determinants of myocardial oxygen supply and demand. P, ventricular systolic pressure; r, ventricular radius; h, ventricular wall thickness.