Drug Treatment of Ischemic Heart Disease
Categories of Ischemic Heart Disease

Fixed "Stable", Effort Angina

Variant Angina “Primary Angina”

Unstable Angina

Myocardial Infarction
Ischemic heart disease

- Coronary thrombosis
  - Myocardial infarction

- Transient coronary ischemia
  - Angina pectoris
    - Atherosclerosis and exertion
      - Typical angina
    - Acute vasospasm
      - Variant angina
        - Plaque rupture and platelet aggregation
          - Stable angina
          - Unstable angina
<table>
<thead>
<tr>
<th>Secondary Angina</th>
<th>Primary Angina</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical</td>
<td>Variant (Prinzmetal’s)</td>
</tr>
<tr>
<td>Angina of Effort</td>
<td>Angina at Rest</td>
</tr>
<tr>
<td>Typical</td>
<td>Atypical</td>
</tr>
<tr>
<td>Small vessels</td>
<td>Large vessels</td>
</tr>
<tr>
<td>Single or multiple</td>
<td>Single</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>Vasospasm</td>
</tr>
<tr>
<td>ST depression</td>
<td>ST elevation</td>
</tr>
</tbody>
</table>
**Stunning?:**

- **Myocardial stunning** is the reversible reduction of function of heart contraction after reperfusion not accounted for by tissue damage or reduced blood flow.
Control of smooth muscle contraction

- Contraction is triggered by influx of calcium through L-type transmembrane calcium channels.
- The calcium combines with calmodulin to form a complex that converts the enzyme myosin light-chain kinase to its active form (MLCK*).

- MLCK phosphorylates the myosin light chains, thereby initiating the interaction of myosin with actin.

- Beta2 agonists (and other substances that increase cAMP) may cause relaxation in smooth muscle by accelerating the inactivation of MLCK and by facilitating the expulsion of calcium from the cell.
Control of vascular smooth muscle contraction

Ca\(^{2+}\) channel blockers

Ca\(^{2+}\)

Ca\(^{2+}\) - Calmodulin complex

MLCK\(^*\)

Myosin-LC kinase (MLCK)

ATP

β\(_2\) agonists

ATP

cAMP

MILK(PO\(_4\))\(_2\)

cGMP

Myosin-LC

Relaxation

Myosin-LC-PO\(_4\)

Contraction

Actin

Vascular smooth muscle cell

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Mechanism of IHD

Due to an imbalance of the ratio:

$O_2$ Supply (Coronary Blood Flow)

$O_2$ Demand (Work of the Heart)
## Major Determinants of Myocardial Oxygen Supply and Demand

<table>
<thead>
<tr>
<th>Oxygen supply</th>
<th>Oxygen demand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen extraction (%)</td>
<td>Wall tension</td>
</tr>
<tr>
<td>Coronary blood flow</td>
<td>Ventricular volume</td>
</tr>
<tr>
<td>Aortic diastolic pressure</td>
<td>Radius or heart size</td>
</tr>
<tr>
<td>Coronary arteriolar resistance</td>
<td>Ventricular pressure</td>
</tr>
<tr>
<td>Metabolic autoregulation</td>
<td>Systolic pressure</td>
</tr>
<tr>
<td>Endocardial-epicardial flow</td>
<td>(afterload)</td>
</tr>
<tr>
<td>Coronary collateral blood flow</td>
<td>Diastolic pressure</td>
</tr>
<tr>
<td>Large coronary artery diameter</td>
<td>(preload)</td>
</tr>
<tr>
<td></td>
<td>Heart rate</td>
</tr>
<tr>
<td></td>
<td>Contractility</td>
</tr>
</tbody>
</table>
Pharmacological modification of the major determinants of myocardial O2 supply

Agents decreasing O2 demand
- β Adrenergic antagonists
- Some Ca<sup>2+</sup> entry blockers
- Organic nitrates
- Ca<sup>2+</sup> entry blockers

Heart rate
Contractility
Preload
Afterload

O2 Demand

Agents increasing O2 Supply
- Coronary blood flow
- Regional myocardial blood flow
- Vasodilators (esp. Ca<sup>2+</sup> entry blockers)
- Also statins, anti-thrombotics

Balance

Ischemia

Source: Brunton LL, Chabner BA, Knollmann BC: Goodman & Gilman’s The Pharmacological Basis of Therapeutics, 12th Edition: www.accessmedicine.com
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19.1 Simplified diagram of atherosclerosis, angina and myocardial infarction, and drugs used in treatment.
Drug effects on vascular smooth muscle contraction.

► Calcium influx is inhibited by CCBs, leading to muscle relaxation.

► Organic nitrates release nitric oxide, which activates guanylyl cyclase and increases formation of cyclic guanosine monophosphate.
  ◆ cGMP causes smooth muscle relaxation by activating kinases that increase myosin phosphatase activity and decrease myosin phosphate levels.

► \( \alpha \) 1-Adrenoceptor agonists activate phospholipase C (PLC), which increases formation of inositol triphosphate (IP\(_3\)) from phosphatidylinositol bisphosphate (PIP\(_2\)), leading to increased release of calcium from the sarcoplasmic reticulum.

► \( \beta \) 2-Adrenoceptor agonists increase formation of cyclic adenosine monophosphate (cAMP), which activates kinases that inhibit myosin light-chain kinase.
Organic Nitrates

Nitroglycerine (GTN):

- Prototype, used for more than 140 years.
- Nonspecific smooth muscle relaxant.
- Action not antagonized by any known antagonist.
Nitrates, nitrites, and other substances that increase the concentration of nitric oxide (NO) in vascular muscle.
Nitroglycerine (GTN)

► Usually administered sublingually.
► Can be administered by various routes.
► Fast onset of action (1-3 minutes, Peaks at 10 minutes).
► Short duration (15-30 minutes).
► Reductase enzyme in liver will breakdown the drug.
Nitroglycerine (GTN)

- Causes general vasodilation:
  - Arteriolar dilation: short lived (5-10 min)
    - Decreases systemic blood pressure (afterload) and causes reflex tachycardia and increased contractility, might increase MVO2.
  - Venous dilation: more intense, even with low doses, lasts for 30 minutes.
    - Decreases venous return (preload) and decreases MVO2.
Figure 19-2
A schematic drawing indicating the major actions of the nitrates on the ischemic heart and peripheral circulation. \( \downarrow = \text{decrease}; \uparrow = \text{increase}; \rightarrow = \text{unchanged}; \downarrow\uparrow = \text{variable effect.} \)
<table>
<thead>
<tr>
<th>Effect</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potential beneficial effects</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased ventricular volume</td>
<td>Decreased myocardial oxygen requirement</td>
</tr>
<tr>
<td>Decreased arterial pressure</td>
<td></td>
</tr>
<tr>
<td>Decreased ejection time</td>
<td></td>
</tr>
<tr>
<td>Vasodilation of epicardial coronary arteries</td>
<td>Relief of coronary artery spasm</td>
</tr>
<tr>
<td>Increased collateral flow</td>
<td>Improved perfusion to ischemic myocardium</td>
</tr>
<tr>
<td>Decreased left ventricular diastolic pressure</td>
<td>Improved subendocardial perfusion</td>
</tr>
<tr>
<td><strong>Potential deleterious effects</strong></td>
<td></td>
</tr>
<tr>
<td>Reflex tachycardia</td>
<td>Increased myocardial oxygen requirement</td>
</tr>
<tr>
<td>Reflex increase in contractility</td>
<td>Increased myocardial oxygen requirement</td>
</tr>
<tr>
<td>Decreased diastolic perfusion time due to tachycardia</td>
<td>Decreased coronary perfusion</td>
</tr>
</tbody>
</table>
Nitroglycerine (GTN)

**Side Effects:**

- Headache.
- Hypotension and tachycardia.
- Increased intraocular and intracranial pressures.
- Methemoglobinemia.
- Tolerance: only for the arteriolar effects.
- Withdrawal: in workers in ammunition industry.
# Nitrate and Nitrite Drugs Used in the Treatment of Angina.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-acting:</strong></td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin, <em>sublingual</em></td>
<td>10–30 minutes</td>
</tr>
<tr>
<td>Isosorbide dinitrate, <em>sublingual</em></td>
<td>10–60 minutes</td>
</tr>
<tr>
<td>Amyl nitrite, <em>inhalant</em></td>
<td>3–5 minutes</td>
</tr>
<tr>
<td><strong>Long-acting:</strong></td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin, <em>oral sustained-action</em></td>
<td>6–8 hours</td>
</tr>
<tr>
<td>Nitroglycerin, 2% <em>ointment</em>, transdermal</td>
<td>3–6 hours</td>
</tr>
<tr>
<td>Nitroglycerin, <em>slow-release</em>, buccal</td>
<td>3–6 hours</td>
</tr>
<tr>
<td>Nitroglycerin, <em>slow-release patch</em>,</td>
<td>8–10 hours</td>
</tr>
<tr>
<td>transdermal</td>
<td></td>
</tr>
<tr>
<td>Isosorbide dinitrate, <em>sublingual</em></td>
<td>1.5–2 hours</td>
</tr>
<tr>
<td>Isosorbide dinitrate, <em>oral</em></td>
<td>4–6 hours</td>
</tr>
<tr>
<td>Isosorbide dinitrate, <em>chewable oral</em></td>
<td>2–3 hours</td>
</tr>
</tbody>
</table>
Beta Adrenergic Blockers

- Prevent actions of catecholamines, so more effective during exertion.
- Do not dilate coronary arteries.
- Do not increase collateral blood flow.
- Cause subjective and objective improvement: decreased number of anginal episodes, nitroglycerine consumption, enhanced exercise tolerance, and improved ECG.
Figure 19-3
A schematic drawing indicating the major actions of the β-blockers on the ischemic heart and peripheral circulation. For key, see Fig. 19-2.
Calcium Channel Blockers

Particularly beneficial in vasospasm.
Can affect platelets aggregation.
May be dangerous in heart failure and in patients susceptible to hypotension.
## Properties of Several Recognized Voltage-Activated Calcium Channels

<table>
<thead>
<tr>
<th>Type</th>
<th>Channel Name</th>
<th>Where Found</th>
<th>Properties of the Calcium Current</th>
<th>Blocked By</th>
</tr>
</thead>
<tbody>
<tr>
<td>L</td>
<td>Ca(\gamma)1.1–Ca(\gamma)1.3</td>
<td>Cardiac, skeletal, smooth muscle, neurons (Ca(\gamma)1.4 is found in retina), endocrine cells, bone</td>
<td>Long, large, high threshold</td>
<td>Verapamil, DHPs, Cd(^{2+}), -aga-IIIA</td>
</tr>
<tr>
<td>T</td>
<td>Ca(\gamma)3.1–Ca(\gamma)3.3</td>
<td>Heart, neurons</td>
<td>Short, small, low threshold</td>
<td>sFTX, flunarizine, Ni(^{2+}), mibefradil(^1)</td>
</tr>
<tr>
<td>N</td>
<td>Ca(\gamma)2.2</td>
<td>Neurons, sperm(^2)</td>
<td>Short, high threshold</td>
<td>Ziconotide,(^3) gabapentin,(^4) -CTX-GVIA, -aga-IIIA, Cd(^{2+})</td>
</tr>
<tr>
<td>P/Q</td>
<td>Ca(\gamma)2.1</td>
<td>Neurons</td>
<td>Long, high threshold</td>
<td>-CTX-MVIIC, -aga-IVA</td>
</tr>
<tr>
<td>R</td>
<td>Ca(\gamma)2.3</td>
<td>Neurons, sperm(^2)</td>
<td>Pacemaking</td>
<td>SNX-482, -aga-IIIA</td>
</tr>
</tbody>
</table>
Cell Plasma Membrane

Phospholipid Bilayer

Calcium Ions

Antidiuretic

Receptor Binding Site

L-type Calcium Channel
Figure 19-4
A schematic drawing indicating the major actions of the calcium antagonists on the ischemic heart and coronary circulation. For key, see Fig. 19-2.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral Bioavailability (%)</th>
<th>Half-Life (hours)</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dihydropyridines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amlodipine</td>
<td>65–90</td>
<td>30–50</td>
<td>Angina, hypertension</td>
</tr>
<tr>
<td>Felodipine</td>
<td>15–20</td>
<td>11–16</td>
<td>Hypertension, Raynaud's phenomenon</td>
</tr>
<tr>
<td>Isradipine</td>
<td>15–25</td>
<td>8</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>35</td>
<td>2–4</td>
<td>Angina, hypertension</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>45–70</td>
<td>4</td>
<td>Angina, hypertension, Raynaud's phenomenon</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>13</td>
<td>1–2</td>
<td>Subarachnoid hemorrhage</td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>&lt; 10</td>
<td>6–12</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Nitrendipine</td>
<td>10–30</td>
<td>5–12</td>
<td>Investigational</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td>40–65</td>
<td>3–4</td>
<td>Angina, hypertension, Raynaud's phenomenon</td>
</tr>
<tr>
<td>Verapamil</td>
<td>20–35</td>
<td>6</td>
<td>Angina, hypertension, arrhythmias, migraine</td>
</tr>
</tbody>
</table>
Calcium Channel Blockers

- **Side Effects:**
- Hypotension.
- Headache, dizziness.
- Flushing.
- Peripheral edema.
## Effects of Nitrates Alone and with Beta Blockers or Calcium Channel Blockers in Angina Pectoris

<table>
<thead>
<tr>
<th></th>
<th>Nitrates Alone</th>
<th>Beta Blockers or Calcium Channel Blockers</th>
<th>Combined Nitrates with Beta Blockers or Calcium Channel Blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart rate</strong></td>
<td>Reflex increase</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td><strong>Arterial pressure</strong></td>
<td>Decrease</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td><strong>End-diastolic volume</strong></td>
<td>Decrease</td>
<td>Increase</td>
<td>Non or decrease</td>
</tr>
<tr>
<td><strong>Contractility</strong></td>
<td>Reflex increase</td>
<td>Decrease</td>
<td>Non</td>
</tr>
<tr>
<td><strong>Ejection time</strong></td>
<td>Decrease</td>
<td>Increase</td>
<td>Non</td>
</tr>
</tbody>
</table>
Dipyridamole

- Inhibits the uptake of adenosine and inhibits adenosine deaminase enzyme.
- Thought to be a good coronary dilator.
- Increases the blood flow to the normal area i.e. “Coronary Steal Phenomenon”.
- Still used as an antiplatelet drug (in TIA's), but not better than aspirin.
Others

- ACEI.
- Anticoagulants and/or Thrombolytic Therapy.
- Cholesterol Lowering Agents.
- Angioplasty
- Surgery.
Stent addresses the existing lesion but not future lesions.

Bypass grafting addresses the existing lesion and also future culprit lesions.

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Newer Antianginal Drugs

- Metabolic modulators: Ranolazine.
- Direct bradycardic agents: Ivabradine.
- Potassium channel activators: Nicorandil.
- Rho-kinase inhibitors: Fasudil.
- Sulfonylureas: Glibenclamide.
- Thiazolidinediones.
- Vaso-opeptidase inhibitors.
- Nitric oxide donors: L-arginine.
- Capsaicin.
- Amiloride.
Newer Antianginal Drugs

► Ranolazine is a newer antianginal drug that appears to act by reducing a late sodium current (I_{Na}) that facilitates calcium entry via the sodium-calcium exchanger.

► The resulting reduction in intracellular calcium concentration reduces cardiac contraction.
Newer Antianginal Drugs

- trimetazidine: metabolic modulators are known as pFOX inhibitors because they partially inhibit the fatty acid oxidation pathway in myocardium.

- Because metabolism shifts to oxidation of fatty acids in ischemic myocardium, the oxygen requirement per unit of ATP produced increases.
Newer Antianginal Drugs

► Ivabradine: relatively selective I f sodium channel the hyperpolarization-activated sodium channel in the sinoatrial reported.

► Ivabradine appears to reduce anginal attacks with an efficacy similar to that of calcium channel blockers and β blockers.

► The lack of effect on gastrointestinal and bronchial smooth muscle is an advantage of ivabradine, and Food and Drug Administration approval is expected.
Newer Antianginal Drugs

The Rho kinases comprise a family of enzymes that inhibit vascular relaxation and diverse functions of several other cell types. Excessive activity of these enzymes has been implicated in coronary spasm, pulmonary hypertension, apoptosis, and other conditions. Drugs targeting the enzyme have therefore been sought for possible clinical applications.

Fasudil is an inhibitor of smooth muscle Rho kinase and reduces coronary vasospasm in experimental animals. In clinical trials in patients with CAD, ivabradine it has improved performance in stress tests.
Newer Antianginal Drugs

► allopurinol, represents another type of metabolic modifier. Allopurinol inhibits xanthine oxidase, an enzyme that contributes to oxidative stress and endothelial dysfunction.

► A recent study suggests that high-dose allopurinol prolongs exercise time in patients with atherosclerotic angina.
Risk Factors Associated with ED

- Diabetes
- Hypertension
- Cigarette Smoking
- Homocysteine
- LDL
- Inflammation

Endothelial Dysfunction
Production of Nitric Oxide (NO) in Arteries

- **ENDOTHELIAL CELLS**
- **INTIMA** - innermost layer of blood vessel lined with endothelial cells that release nitric oxide
- **ARTERIAL LUMEN**
- **RED BLOOD CELLS**
- **MEDIA** - middle layer of blood vessel containing smooth muscle cells
- **ADVENTITIA** - outer layer of blood vessel
- **NITRIC OXIDE**
Consequences of ED

- Dilation
- Growth Inhibition
- Anti-thrombosis
- Anti-inflammation

- Constriction
- Growth Promotion
- Prothrombosis
- Proinflammation
Background: arginase and NOS

- Diabetes
- Aging
- Hypertension
- Atherosclerosis

Arginase

L-arginine

NOS

NO

Citrulline

Ornithine

Urea
NO produces cGMP in CSM

- **cGMP**
  - PKG
    - channels
    - pumps
    - transporters
    - enzymes

\[ Ca^{2+} \]
Dynamic Balance Between PDE & Cyclase

L-arginine $\rightarrow$ Nitric oxide synthase $\rightarrow$ Citrulline

Nitric oxide (NO) $\rightarrow$ Outside cell

Smooth muscle cell

Guanylate cyclase $\rightarrow$ GTP $\rightarrow$ cGMP $\rightarrow$ 5’GMP $\rightarrow$ Phosphodiesterase

Cavernosal smooth muscle relaxation $\rightarrow$ Erection
Basic Pharmacological Strategy

- Elevate Cyclic Nucleotides
  - PDE inhibitors
    - cGMP
    - cAMP
  - cyclase stimulators

- Block Adrenergic Tone
  - Alpha blockers
SILDENAFIL

• Type V PDE inhibitor
  – inhibits “cGMP-specific” PDE
  – increases [cGMP] in cavernosal smooth muscle
Sildenafil DOES NOT Induce Erection

• Requires intact NO-releasing mechanisms
  – NANC nerves
  – endothelial cells

• Can MAINTAIN, but not MANUFACTURE
  – requires intact libido

• Limited use in some patients
  – vascular or neurological disease
    • diabetes
  – trauma
    • radical prostatectomy
    • spinal cord injury
Advantages

• Effective oral medication
  – no penile injections or inserts
• Good patient compliance
• Convenient
• Relatively few side effects
NITRATES
nitroglycerine
nitroprusside

NO

VSM

cGMP

vasorelaxation
lower TPR
hypotensive effect
NITRATES
- nitroglycerine
- nitroprusside

NO

VSM

cGMP

sildenafil

vasorelaxation
- lower TPR
- hypotensive effect
Primary Side Effect

Sildenafil is contraindicated in patients taking nitrates because of the potential of SEVERE HYPOTENSION.
Potential Side Effects of Sildenafil

• Severe hypotension in combination with nitrate therapy
• Headache, flushing, nasal congestion
• Visual disturbance: blue - green discrimination
• (M.I.)