Drugs Used in the Treatment of Angina Pectoris
Drugs used in angina pectoris

Vasodilators
- Nitrates
  - Short duration (sublingual nitroglycerin)
  - Intermediate (oral nitroglycerin)
  - Long duration (transdermal nitroglycerin)

Cardiac depressants
- Calcium blockers (verapamil)
- Beta blockers (propranolol)
- Metabolism modifiers; rate inhibitors

Other drugs

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Overview of drugs used in the treatment of angina

- **Symptom control**
  - Short-acting nitrate, eg GTN plus
    - Beta-blocker or calcium-channel blocker (if one not tolerated -> switch to other)
  - If symptoms not controlled
    - Add dihydropyridine calcium-channel blocker to beta-blocker
    - If not tolerated/contraindicated consider:
      - long-acting nitrates
      - nicorandil
      - ivabradine
      - ranolazine

- **Primary prevention of cardiovascular events**
  - Lifestyle modification advice
  - Aspirin 75mg once daily
  - Lipid-lowering therapy as per guidelines
  - Consider ACE inhibitor/angiotensin II-receptor antagonist in presence of diabetes/hypertension/LVSD

If symptoms not controlled:
- Refer to cardiology for consideration of angiography ± revascularisation
- Consider adding third agent
Drugs used in angina pectoris

- **Nitrates and nitrites**: decrease vasoconstriction and coronary spasm; increase myocardial perfusion by relaxing coronary arteries.

- **Ca++ channel antagonists**: cause relaxation of the arterial smooth muscle but have little effect on veins.

- **β-blockers**: improve the survival rate in ischemic heart disease because they are effective in increasing endurance during physical exercise.

- **Other drugs** (second and third line therapies).

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Overview of drugs used in the treatment of angina

<table>
<thead>
<tr>
<th>DRUG CLASS</th>
<th>COMMON ADVERSE EFFECTS</th>
<th>DRUG INTERACTIONS</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-blockers</td>
<td>Bradycardia, worsening peripheral vascular disease, fatigue, sleep disturbance, depression, blunt hypoglycemia awareness, inhibit β₂-mediated bronchodilation in asthmatics</td>
<td>β₂ agonists (blunted effect); non-dihydropyridine calcium-channel blockers (additive effects)</td>
<td>β₁-selective agents preferred (atenolol, metoprolol). Avoid agents with ISA for angina therapy (pindolol).</td>
</tr>
<tr>
<td>atenolol</td>
<td></td>
<td>CYP 3A4 substrates (will increase drug concentrations)</td>
<td></td>
</tr>
<tr>
<td>metoprolol</td>
<td></td>
<td></td>
<td>Avoid short-acting agents as they can worsen angina (may use extended-release formulations)</td>
</tr>
<tr>
<td>propranolol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dihydropyridine calcium-channel blockers</td>
<td>Peripheral edema, headache, flushing, rebound tachycardia (immediate release formulations), hypotension</td>
<td>CYP 3A4 substrates (will increase drug concentrations); increase digoxin levels; β-blockers and other drugs affecting AV node conduction (additive effects)</td>
<td>Avoid in patients with heart failure. Adjust dose of both agents in patients with hepatic dysfunction.</td>
</tr>
<tr>
<td>amlodipine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>felodipine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nifedipine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-dihydropyridine calcium-channel blockers</td>
<td>Bradycardia, constipation, heart failure exacerbations, gingival hyperplasia (verapamil), edema (diltiazem)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>diltiazem</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>verapamil</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organic nitrates</td>
<td>Headache, hypotension, flushing, tachycardia</td>
<td>Contraindicated with PDE5 inhibitors (sildenafil and others)</td>
<td>Ensure nitrate-free interval to prevent tolerance</td>
</tr>
<tr>
<td>isosorbide dinitrate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>isosorbide mononitrate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nitroglycerin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium-channel Inhibitor</td>
<td>Constipation, headache, edema, dizziness, QT interval prolongation</td>
<td>Avoid use with CYP 3A4 inducers (phenytoin, carbamazepine, St. John’s wort) and strong inhibitors (clarithromycin, azole antifungals) and agents that prolong QT interval (citalopram, quetiapine, others)</td>
<td>No effect on hemodynamic parameters</td>
</tr>
<tr>
<td>ranolazine</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CYP = cytochrome P450; ISA = intrinsic sympathomimetic activity; PDE5 = phosphodiesterase type 5
The discovery of Nitrates
# Uses of NO derivatives

<table>
<thead>
<tr>
<th>Substance</th>
<th>Utilization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aniline dyes</td>
<td>Laundry inks, markers</td>
</tr>
<tr>
<td>Benzocaine, lidocaine</td>
<td>Local anesthetics</td>
</tr>
<tr>
<td>Chlorates</td>
<td>Matches</td>
</tr>
<tr>
<td>Isobutyl nitrite</td>
<td>Room deodorizers</td>
</tr>
<tr>
<td>Naphtalene</td>
<td>Moth balls</td>
</tr>
<tr>
<td>Nitrate/nitrite</td>
<td>Drinking water, fruits, vegetables, cured meats</td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>Inhalant used to treat pulmonary hypertension in newborns</td>
</tr>
<tr>
<td>Nitrobenzene</td>
<td>Metal cleaners</td>
</tr>
<tr>
<td>Nitroethane</td>
<td>Nail care products</td>
</tr>
<tr>
<td>Nitrogen oxides</td>
<td>Auto emissions, wood smoke, gas-burning appliances</td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>Angina drug, explosives</td>
</tr>
<tr>
<td>Resorcinol</td>
<td>Antipruritic, over-the-counter medications</td>
</tr>
<tr>
<td>Sodium nitrite</td>
<td>Pickling salts, boiler conditioners, cleaning solutions</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>Antibiotics</td>
</tr>
</tbody>
</table>
Effects of NO in the body

- Increases mucus secretion
- Reduces adherence & secretion
- Reduced oxidative stress
- Reduces superoxide radicals
- Accelerates wound healing
- Increases formation of new vessels
- Vasodilates
- Reduces cytokine release
- Reduces degranulation & mediator release
- Stimulation
- Inhibition

**Nitric Oxide**

**Mast Cells**

**Epithelium**

**Neutrophils**

**Macrophages**

**Angiogenesis**

**Vasculature**

**Fibroblasts**
Synthesis of NO

**Step A:**
- Arginine
- NADPH + H⁺ + O₂ → NOS → N-Hydroxyarginine

**Step B:**
- 2N-Hydroxyarginine
- NADPH + H⁺ + O₂ → NOS → 2Citrulline + 2NO
Nitric oxide synthase isoforms

<table>
<thead>
<tr>
<th>Property</th>
<th>Isoform I</th>
<th>Isoform II</th>
<th>Isoform III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td>bNOS, cNOS, nNOS</td>
<td>iNOS, mNOS</td>
<td>eNOS</td>
</tr>
<tr>
<td>Tissue</td>
<td>Neuronal, epithelial, skeletal,</td>
<td>Macrophages, smooth muscle cells</td>
<td>Endothelial, smooth muscle cells</td>
</tr>
<tr>
<td></td>
<td>cardiac muscle cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expression</td>
<td>Constitutive</td>
<td>Transcriptional induction</td>
<td>Constitutive</td>
</tr>
<tr>
<td>Calcium requirement</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Chromosome</td>
<td>12</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>Approximate mass of protein</td>
<td>150–160 kDa</td>
<td>125–135 kDa</td>
<td>133 kDa</td>
</tr>
</tbody>
</table>

bNOS = brain NOS, cNOS = constitutive or Ca\(^{+}\) regulated NOS, nNOS = neuronal NOS, iNOS = inducible NOS, mNOS = macrophage NOS, eNOS = endothelial NOS.
Synthesis of NO and mechanism of vasodilation

Dr. Robert Furchgott (Nobel prize in 1998)
Mechanism of action of Nitrates

Nitrates produce dilatation of veins, arteries, and coronary arteries by relaxing vascular smooth muscle.

Myosin light chain phosphatase
Pharmacological feature of Nitrates

- Nitrates are available in different formulations and both **short and long-acting organic nitrates** have been shown to be effective in treating angina.

- Nitrates are **as effective as β-blockers and Ca++ channel antagonists.** Sublingual nitroglycerin tablets and oral nitroglycerin spray are rapidly absorbed and when taken prophylactically can improve exercise tolerance and reduce the incidence of myocardial ischemia.

- Nitrates **increase the blood perfusion** by relaxing the coronaries. The powerful dilation of the veins decreases the venous return to the heart and therefore the work and the oxygen demand of the heart.

- One of the major side-effects of nitrate use is **headache.** Administered at high doses, nitrates can induce flushing, tachycardia and postural hypotension.

- When nitrates are administered concomitantly with **sildefanil, tadalafil or vardenafil** a potential dangerous postural hypotension can appear. For this reason, concomitant therapy of nitrates and sildenafil requires a six-hour-interval between the administration of the two drugs.
Route of administration and doses of nitro derivatives

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-acting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin, sublingual</td>
<td>0.15–1.2 mg</td>
<td>10–30 minutes</td>
</tr>
<tr>
<td>Isosorbide dinitrate, sublingual</td>
<td>2.5–5 mg</td>
<td>10–60 minutes</td>
</tr>
<tr>
<td>Amyl nitrite, inhalant</td>
<td>0.18–0.3 mL</td>
<td>3–5 minutes</td>
</tr>
<tr>
<td><strong>Long-acting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin, oral sustained-action</td>
<td>6.5–13 mg per 6–8 hours</td>
<td>6–8 hours</td>
</tr>
<tr>
<td>Nitroglycerin, 2% ointment, transdermal</td>
<td>1–1.5 inches per 4 hours</td>
<td>3–6 hours</td>
</tr>
<tr>
<td>Nitroglycerin, slow-release, buccal</td>
<td>1–2 mg per 4 hours</td>
<td>3–6 hours</td>
</tr>
<tr>
<td>Nitroglycerin, slow-release patch, transdermal</td>
<td>10–25 mg per 24 hours (one patch per day)</td>
<td>8–10 hours</td>
</tr>
<tr>
<td>Isosorbide dinitrate, sublingual</td>
<td>2.5–10 mg per 2 hours</td>
<td>1.5–2 hours</td>
</tr>
<tr>
<td>Isosorbide dinitrate, oral</td>
<td>10–60 mg per 4–6 hours</td>
<td>4–6 hours</td>
</tr>
<tr>
<td>Isosorbide dinitrate, chewable oral</td>
<td>5–10 mg per 2–4 hours</td>
<td>2–3 hours</td>
</tr>
<tr>
<td>Isosorbide mononitrate, oral</td>
<td>20 mg per 12 hours</td>
<td>6–10 hours</td>
</tr>
<tr>
<td>Pentaerythritol tetranitrate (PETN)</td>
<td>50 mg per 12 hours</td>
<td>10–12 hours</td>
</tr>
</tbody>
</table>

All these agents are effective, but they differ in their onset of action and rate of elimination.
Importance of vasodilation action of nitrates on collateral vessels

Nitrates

- INCREASED blood flow to normal myocardium
- INCREASED blood flow to ischemic myocardium
- INCREASED blood flow to normal area

Dipyridamole

- DECREASED blood flow to ischemic area
Nitroglycerin

- The half-life of nitroglycerin is very short (1-4 min) and the systemic clearance usually exceeds the cardiac output. Therefore, common routes of administration for nitroglycerin are sublingual or via transdermal patch.

- FDA approved nitroglycerin use for the acute relief from an angina attack or acute prophylaxis of angina pectoris secondary to coronary artery disease.

- Nitroglycerin has adverse effects resulting from the vasodilatory effects of the medication. These include: headaches, dizziness, weakness, palpitations, vertigo, nausea, vomiting, diaphoresis, syncope. Many of these adverse effects are secondary to the hypotensive effects of nitroglycerin. Tolerance.

Sildenafil Citrate and Blood-Pressure-Lowering Drugs: Results of Drug Interaction Studies with an Organic Nitrate and a Calcium Antagonist

David J. Webb, MD, Stephen Freestone, MD, Michael J. Allen, MD, and Gary J. Muirhead, BSc

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EXPRESS PUBLICATION

Time Course of the Interaction Between Tadalafil and Nitrates

Robert A. Kloner, MD, PhD,* Adolph M. Hutter, MD,† Jeffrey T. Emmick, MD, PhD,‡ Malcolm I. Mitchell, MBBS, MFPM,§ Jonathan Denne, PHD,‡ Graham Jackson, MD||
Isosorbide dinitrate is bioavailable to the systemic circulation after oral administration.

Isosorbide dinitrate is used for angina, in addition to other medications for congestive heart failure, and for esophageal spasms.

Isosorbide dinitrate can cause severe headaches, necessitating analgesic (very rarely up to morphine) administration for relief of pain, as well as severe hypotension, and, in certain cases, bradycardia. This makes some physicians nervous and should prompt caution when starting nitrate administration. Tolerance.
Tolerance as a side effect of nitrates

- Long-term therapy with nitrates is frequently associated with **tolerance**.

- Tolerance is a progressive reduction of hemodynamic and antiaggregatory effects.

- Tolerance imposes a major limitation to the efficacy of nitrate therapy for stable angina pectoris, congestive heart failure, and acute myocardial infarction.

- The mechanism responsible for tolerance remains controversial. Multiple theories have been proposed, but the major categories are:
  1. **Impaired nitrate bioconversion** resulting in diminished NO release;
  2. **Increased NO clearance** mediated by the incremental generation of superoxide (O₂⁻).

The supporting evidence for these mechanisms has been derived almost entirely from animal studies; definitive evidence from studies in human subjects is lacking.

- Interval dosing with eccentric doses providing a nitrate-free interval of 10-12 hours should be observed to **reduce or prevent tolerance**. Other (less consistent) ways to reduce the incidence of tolerance are the co-therapy with ACE inhibitors, carvedilol, hydralazine, vitamin C.
Their effects in the treatment of angina have been attributed to the following actions:

1) **blockade of β1 receptors in the SA node** decreases the heart rate, resulting in decreased myocardial oxygen demand and increased oxygen delivery to the heart.

2) **blockade of β1 receptors in the ventricular myocardium** decreases myocardial contractility, helping to preserve energy or to decrease the demand.
β–blockers used in the treatment of angina

<table>
<thead>
<tr>
<th>Drug</th>
<th>Receptor Selectivity</th>
<th>Onset of Action</th>
<th>Usual Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>β₁</td>
<td>2–4 h</td>
<td>50–200 mg/d</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>β₁</td>
<td>2–4 h</td>
<td>10 mg/d</td>
</tr>
<tr>
<td>Esmolol (IV)</td>
<td>β₁</td>
<td>9 min</td>
<td>50–300 μg/kg/min</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>β₁</td>
<td>1–2 h</td>
<td>50–200 mg twice daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(extended release once daily preparation available)</td>
</tr>
<tr>
<td>Propranolol</td>
<td>None</td>
<td>1–2 h</td>
<td>80–120 mg twice daily</td>
</tr>
<tr>
<td>Nadolol</td>
<td>None</td>
<td>3–4 h</td>
<td>40–80 mg/d</td>
</tr>
<tr>
<td>Timolol</td>
<td>None</td>
<td>1–2 h</td>
<td>10 mg twice daily</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>Nonselective β and selective α₁</td>
<td>1.0–1.5 h</td>
<td>3.125–25 mg twice daily</td>
</tr>
<tr>
<td>Labetalol</td>
<td>Nonselective β and selective α₁</td>
<td>2–4 h</td>
<td>200–600 mg twice daily</td>
</tr>
</tbody>
</table>
Side effects and drug-drug interactions of β–blockers used in the treatment of angina

- β-blockers may induce diarrhea, stomach cramps, nausea, vomiting, rash, blurred vision, disorientation, insomnia, hair loss, weakness, muscle cramps, fatigue.

- β-blockers, especially the non-cardioselective blockers, **should not be used in patients with pathologies** such as asthma, diabetes and severe bradycardia (block of the effect of adrenaline).

- β-blockers **should not be withdrawn suddenly** because sudden withdrawal may worsen angina and cause heart attacks, serious abnormal heart rhythms, or sudden death.

- β-blockers **can interact with certain other cardiac drugs**, including Ca^{++} channel antagonists and some drugs used to treat arrhythmias.
Ca++ channel antagonists used in the treatment of angina

- All the Ca++ channel antagonists have been used for the treatment of angina (especially longer-acting forms of diltiazem and verapamil).

- In general, while Ca++ channel antagonists are useful for relieving angina, they are considered to be **inferior to β-blockers**. Current recommendations for using Ca++ channel blockers for the treatment of angina are:

  1) Ca++ channel blockers should be tried in **patients who cannot tolerate β-blockers**.

  2) Ca++ channel blockers should be **added to β-blockers** in patients who have insufficient relief of symptoms with β-blockers.
Role of Ca\(^{++}\) in the cardiac muscle contraction

1. Ca\(^{2+}\) entry from outside the cell triggers the release of a much larger quantity of Ca\(^{2+}\) from the sarcoplasmic reticulum.

2. Increased Ca\(^{2+}\) concentration initiates the contractile process.

3. Ca\(^{2+}\) is removed by reuptake into the sarcoplasmic reticulum and by extrusion from the cell by a Ca\(^{2+}\)/Na\(^{+}\) exchange.

4. Sodium balance is restored by Na\(^{+}\)/K\(^{+}\) ATPase.

Ca floods in from outside the cell

Voltage-sensitive slow Ca\(^{2+}\) channel

Na\(^{+}\)/Ca\(^{2+}\) exchange

Na\(^{+}\)/K\(^{+}\) ATPase

CCB

MEMBRANE OF CARDIAC MUSCLE

Ca\(^{2+}\) stores (sarcoplasmic reticulum)

Free Ca\(^{2+}\)

Myofibrils
Mechanism of Ca\textsuperscript{++} channel antagonists in the treatment of angina

- Similar to nitrates, Ca\textsuperscript{++} channel antagonists can \textit{dilate the coronary vessels}, improving the blood supply to the ischemic area.

- Ca\textsuperscript{++} channel antagonists \textit{slow the conduction} of the cardiac action potential in tissues dependent on Ca\textsuperscript{++} currents, such as the AV node.

- Similar to β-blockers, Ca\textsuperscript{++} channel antagonists \textit{reduce the amount of oxygen required by the heart muscle}. Reducing cardiac oxygen demand helps to prevent cardiac ischemia, even when blood flow through the coronary arteries is partially blocked by an atherosclerotic plaque.

- In people who have stable angina, Ca\textsuperscript{++} channel antagonists usually \textit{increase the amount of physical exercise} they can perform before they experience angina.

- Ca\textsuperscript{++} channel antagonists can be especially useful in people with \textit{Prinzmetal’s angina} since they can directly reduce spasm of the coronary arteries.

- Ca\textsuperscript{++} channel antagonists are thought to possess \textit{antiplatelet effects}, which may be beneficial in angina. The antiplatelet effect of verapamil is evident both at rest and after exercise-induced platelet activation in vivo.
Ca\textsuperscript{++} channel blockers used in the treatment of angina

**A** Dilation of coronary vessels

- Nifedipine
- Verapamil
- Diltiazem

Weak action | Strong action

**B** AV Conduction

- Nifedipine
- Verapamil
- Diltiazem

Decreased | Increased

Little effect

**C** Frequency of adverse effects

- Nifedipine: 18%
- Verapamil: 9%
- Diltiazem: 2%

Infrequent | Frequent
Side effects of Ca^{++} channel antagonists

- Constipation
- Vertigo
- Headache
- Fatigue
- Hypotension
Other drugs used for the treatment of angina: Nicorandil

- At low plasma concentrations, nicorandil, similar to nitrates, dilates the coronary arteries. At high plasma concentrations, nicorandil reduces coronary vascular resistance, which is associated with increased ATP-sensitive K⁺ channel opening (unknown mechanisms).

- Nicorandil is usually administered when nitrates, such as nitroglycerine, are not effective.
Other drugs used for the treatment of angina: Ivabradine

Ivabradine selectively inhibits the inward-depolarizing Na\(^+\)-K\(^+\) current in the SA node, decreasing the rate of diastolic depolarization and, consequently, the heart rate. Thus, ivabradine is used in select patients with **systolic heart failure** and **chronic stable angina** without clinically significant adverse effects.
Other drugs used for the treatment of angina:
HMG-CoA reductase inhibitors (statins)

- Lipid-lowering drugs as statins **reduce the incidence and severity of ischemia** during physical exercise and the incidence of fatal cardiac events.

- The **pleiotropic effects** of statins may be primarily responsible for their anti-ischemic and anti-anginal properties.

- These pleiotropic effects include **improvement of endothelial function**, **enhancement of the ischemic vasodilatory response**, **modulation of inflammation**, and **protection from ischemia-reperfusion injury**.
Treatment of angina with comorbidities

<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>RECENT MYOCARDIAL INFARCTION</td>
<td>Long-acting nitrate</td>
</tr>
<tr>
<td>ASTHMA, COPD</td>
<td>Long-acting nitrate</td>
</tr>
<tr>
<td>HYPERTENSION</td>
<td>Long-acting nitrate</td>
</tr>
<tr>
<td>DIABETES</td>
<td>Long-acting nitrate</td>
</tr>
<tr>
<td>CHRONIC RENAL DISEASE</td>
<td>Long-acting nitrate</td>
</tr>
</tbody>
</table>

**KEY:**
- Drug class
- Commonly used drugs
- Less effective drugs