Drugs Used in the Treatment of Angina Pectoris
Angina Pectoris

Angina pectoris is a primary symptom of myocardial ischemia, characterized by severe chest pain, often radiating to the left shoulder, left arm, jaw, neck, epigastrium or back, that occurs when coronary blood flow is inadequate to supply the oxygen required by the heart.

Causes:

1) Obstructions in diameter of 60% or greater are likely to be associated with angina, whereas lesions of less than 50% usually do not cause ischemia. Severe angina is usually associated with obstructions in diameter of 80-100%.

2) Imbalance between the increased demand and the insufficient supply of oxygen, due to physical exercise, spasm of the vascular smooth muscle or atherosclerotic lesions, may be associated with angina.

These two transient episodes (15 sec-15 min) of myocardial ischemia do not cause cellular death, as in myocardial infarction.
Risk factors for angina

- Smoking
- Alcohol
- Drug abuse
- Hypertension
- High cholesterol
- Age
- Obesity
- Gender
- Family History
Clinical classifications of angina

Angina can be classified into:

1) **Stable angina pectoris.** Also called typical angina pectoris, is the most common form of angina. Stable angina is characterized by burning, heavy or squeezing feeling in the chest, which appears during physical activity or stressful situations. Stable angina is caused by the reduction of coronary perfusion due to a fixed obstruction produced by coronary atherosclerosis. The pharmacological treatment is based on the use of nitroglycerin.

2) **Unstable angina pectoris.** Episodes of unstable angina pectoris tend to be changing in the character, i.e. increasing severity, frequency, duration as well as precipitating factors. Unstable angina is caused by the reduction of coronary perfusion due to the broken of the obstruction. When an episode of unstable angina occurs at rest, nitroglycerin is able to relieve the symptoms. Unstable angina requires a more aggressive pharmacotherapy based on the administration of anticoagulants or blood thinners.

3) **Prinzmetal’s or variant or vasospastic angina.** Prinzmetal’s angina is an uncommon angina that occurs at rest and is due to coronary artery spasm. Attacks are not related to physical activity, pressure or frequency. It responds promptly to nitroglycerin and calcium channel blockers.
Clinical classifications of angina

- **Normal Blood flow**
  - Normal Coronary Vessel
- **Unstable Angina**
  - Ruptured Plaque
  - Myocardial Infarction
- **Stable Angina**
  - Coronary Vessel Plaque
- **Blocked Coronary Vessel**

Diagram showing the progression from normal to unstable angina, including normal blood flow, normal coronary vessel, stable angina with a plaque, ruptured plaque, and blocked coronary vessel leading to myocardial infarction.
Drugs used in angina pectoris

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

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

Other drugs

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Drugs used in angina pectoris

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

- β-blockers: improve the survival rate in ischemic heart disease because they are effective in increasing endurance during exercise in case of stable angina.

- Calcium antagonists: cause relaxation of the arterial smooth muscle but have little effect on most venous districts.

- Other drugs.
In 1846, Dr. Ascanio Sobrero during an experiment with mannitol, produced nitromannite, a highly explosive substance. During successive experiments he obtained other nitrating organic compounds, as pyroglycerin and then nitroglycerin. He experienced the therapeutic effects of nitroglycerin on himself, but was scared by its enormous explosive power. Alfred Nobel, who was enriched with the discovery of dynamite (obtained by absorbing nitroglycerine from a porous material, which allowed the explosive to be handled without danger), aware of the great discovery made by Sobrero, assigned him an annuity.
# 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><strong>Inhalant used to treat pulmonary hypertension in newborns</strong></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><strong>Angina drug, explosives</strong></td>
</tr>
<tr>
<td>Resorcinol</td>
<td><strong>Antipruritic, over-the-counter medications</strong></td>
</tr>
<tr>
<td>Sodium nitrite</td>
<td>Pickling salts, boiler conditioners, cleaning solutions</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td><strong>Antibiotics</strong></td>
</tr>
</tbody>
</table>
Effects of NO in the body

- Increases mucus secretion
- Reduces adherence & secretion
- Reduces superoxide radicals
- Increases formation of new vessels
- Oxidative stress
- Accelerates wound healing
- Stimulation
- Inhibition

- Mast Cells: Reduces degranulation & mediator release
- Epithelium: Increases mucus secretion
- Neutrophils: Reduces adherence & secretion
- Macrophages: Reduces cytokine release
- Angiogenesis
- Vasculature: Vasodilates
- Fibroblasts: Accelerates wound healing
## 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, cardiac muscle cells</td>
<td>Macrophages, smooth muscle cells</td>
<td>Endothelial, smooth muscle cells</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
Mechanism of action of Nitrates

Nitrates produce dilatation of veins, arteries, and coronary arteries by relaxing vascular smooth muscle. In order to produce these effects, nitrates enter into the vascular smooth muscle cells where they are metabolized to 1,2-glyceryl dinitrate and nitrite, via mitochondrial aldehyde dehydrogenase-2 (ALDH2 or mtALDH), and then NO and S-nitrosothiols. Sulfhydryl groups on ALDH2 are required for activity, which can explain the known sulfhydryl requirement for vascular smooth muscle relaxation by nitrates.
Pharmacological feature of Nitrates

- Nitrates are able to quickly reduce the oxygen demand and in this manner they relieve the symptoms of angina.

- 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.

- Nitrates can induce headache. Administered at high doses, nitrates can induce flushing, tachycardia and postural hypotension. When nitrates are administered concomitantly with sildefanil, a potential dangerous postural hypotension can appears. 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 nitroderivatives

<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.
For prompt relief of an ongoing attack of angina precipitated by physical exercise or emotional stress, sublingual or spray nitroglycerin is the drug of choice.
Importance of vasodilation action of nitrates on collateral vessels

Nitrates:
- INCREASED INCREASED
- Normal arteriolar tone
- Blood flow to normal myocardium

Dipyridamole:
- DECREASED
- Fully dilated arterioles
- Blood flow to normal area
- Blood flow to ischemic area
Nitroglycerin

- Usually, newer drugs quickly replace older remedies, but this has not been the case with nitroglycerin, now in continuous medical use for more than a century.

- Nitroglycerin binds moderately to plasma proteins (60%). As a consequence of rapid metabolism in the liver and in other tissues, 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 the sublingual or via transdermal patch, thereby avoiding this route of elimination. Nitroglycerin metabolites are excreted through the kidneys.

- FDA approved nitroglycerin use for the acute relief of an attack or acute prophylaxis of angina pectoris secondary to coronary artery disease. Off-label, non-FDA approved uses include treatment for hypertensive urgency/emergency, coronary artery spasm, angina secondary to cocaine use, congestive heart failure, and chronic anal fissures.

- Nitroglycerin has many adverse effects, most resulting from the vasodilatory effects of the medication. These include: dizziness, weakness, palpitations, vertigo, headaches, nausea, vomiting, diaphoresis, syncope. Many of these adverse effects are secondary to the hypotensive effects of nitroglycerin. Tollerance.
Isosorbide dinitrate is the dinitrate salt form of isosorbide.

Isosorbide dinitrate is significantly bioavailable to the systemic circulation after oral administration; the oral bioavailability is about 20% relative to an intravenous dose and about 45% relative to a sublingual dose, with the balance metabolized to isosorbide mononitrates. These pharmacologically active metabolites have longer biologic half-lives than isosorbide dinitrate and are thus believed to contribute to the sustained duration of action of this drug.

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. Tollerance.
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 the major limitation of efficacy on nitrate therapy for stable angina pectoris, congestive heart failure, and acute myocardial infarction.
- The mechanism(s) responsible for tolerance remain 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. Others (less consistent) ways to reduce the incidence of tolerance are: co-therapy with ACE inhibitors, carvedilol, hydralazine, vit C.
**β-blockers**

- 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 the energy or 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>$\beta_1$</td>
<td>2–4 h</td>
<td>50–200 mg/d</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>$\beta_1$</td>
<td>2–4 h</td>
<td>10 mg/d</td>
</tr>
<tr>
<td>Esmolol (IV)</td>
<td>$\beta_1$</td>
<td>9 min</td>
<td>50–300 μg/kg/min</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>$\beta_1$</td>
<td>1–2 h</td>
<td>50–200 mg twice daily (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 $\beta$ and selective $\alpha_1$</td>
<td>1.0–1.5 h</td>
<td>3.125–25 mg twice daily</td>
</tr>
<tr>
<td>Labetalol</td>
<td>Nonselective $\beta$ and selective $\alpha_1$</td>
<td>2–4 h</td>
<td>200–600 mg twice daily</td>
</tr>
</tbody>
</table>
Side effects of β–blockers used in the treatment of angina

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

- β-blockers should not be used in patients with asthma, diabetes and severe bradycardia.

- β-blockers should not be withdrawn suddenly because sudden withdrawal may worsen angina (chest pain) and cause heart attacks, serious abnormal heart rhythms, or sudden death.
Ca++ channel antagonists used in the treatment of angina

All the Ca++ channel antagonists have been used for treating angina. However, the most commonly used for this purpose are the longer-acting forms of diltiazem and verapamil, amlodipine, or felodipine.

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

- All the effects of Ca\textsuperscript{++} channel antagonists (blood vessel dilation, reduction in heart muscle contraction, and slower heart rate) 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 increase the amount of exercise they can perform before they experience angina.

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

- Ca\textsuperscript{++} channel antagonists can improve the blood supply to the ischemia.

- Antiplatelet therapy reduces the risk of myocardial infarction, and Ca\textsuperscript{++} channel antagonists are thought to possess antiplatelet effects which may be beneficial. The antiplatelet effect of verapamil was evident both at rest and after exercise-induced platelet activation in vivo.

- Ca\textsuperscript{++} channel antagonists protect ischemic cardiac myocytes.
Ca^{++} channel blockers used in the treatment of angina

A. Dilation of coronary vessels
- Nifedipine
- Verapamil
- Diltiazem

Weak action: Nifedipine
Strong action: Verapamil, Diltiazem

B. AV Conduction
- Nifedipine: Little effect
- Verapamil: Decreased
- Diltiazem: Increased

C. Frequency of adverse effects
- Nifedipine: 18%
- Verapamil: 9%
- Diltiazem: 2%

Infrequent: Nifedipine, Verapamil
Frequent: Diltiazem
Side effects of Ca^{++} channel antagonists

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

- Nicorandil has the dual properties of a nitrate and ATP-sensitive $K^+$ channel agonist. The nitrate action of nicorandil dilates the large coronary arteries at low plasma concentrations. At high plasma concentrations nicorandil reduces coronary vascular resistance, which is associated with increased ATP-sensitive $K^+$ channel opening.

- The effect of nicorandil as a vasodilator is mainly attributed to its nitrate property. Yet, nicorandil is effective in cases where nitrates, such as nitroglycerine, are not effective. Nicorandil activates ATP-sensitive $K^+$ channel channels in the mitochondria of the myocardium, which appears to relay the cardioprotective effects, although the mechanism is still unclear.

![Nicorandil dual action diagram]

Nicorandil dual action

- Nitrate-like action
  - Dilates epicardial Coronary arteries
  - Venodilatation
    - Decreased Preload
      - $\uparrow$ coronary blood flow
      - $\downarrow$ Myocardial $O_2$ requirement
  - Venodilatation

- $K^+$ channel opener ATP
  - Dilates peripheral arterioles
    - Decreased afterload
      - $\downarrow$ Myocardial $O_2$ requirement
      - $\uparrow$ coronary blood flow
  - Dilates coronary Resistance vessels
Other drugs used for the treatment of angina: Ivabradine

- Ivabradine selectively inhibits the inward-depolarizing mixed Na⁺-K⁺ current in the sinoatrial nodal tissue, resulting in a decrease in the rate of diastolic depolarization and, consequently, the heart rate. Thus, it has been evaluated and 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: statins

- 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
Overview of drugs used in the treatment of angina

Angina symptoms

Symptom control
- 1st line
  - 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
### 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 metoprolol 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)</td>
<td>Avoid short-acting agents as they can worsen angina (may use extended-release formulations)</td>
</tr>
<tr>
<td>amlodipine felodipine 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>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>diltiazem 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 isosorbide mononitrate 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