Drug Class Review

Antianginal Agents
24:12.08 Nitrates and Nitrites
24:04.92 Cardiac Drugs, Miscellaneous

Amyl Nitrite
Isosorbide Dinitrate (IsoDitrate ER®, others)
Isosorbide Mononitrate (Imdur®)
Nitroglycerin (Minitran®, Nitrostat®, others)
Ranolazine (Ranexa®)

Final Report
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Executive Summary

Introduction: A number of therapies are available for the treatment of angina, including: beta-blockers, calcium channel blockers, nitrates and a number of miscellaneous vasodilation agents. Four nitrates are currently available for use in the United States: amyl nitrite, isosorbide dinitrate, isosorbide mononitrate and nitroglycerin. Ranolazine is a newer agent with a unique mechanism of action which may also be used in the treatment and prevention of chronic angina. Sublingual nitroglycerin is used to treat an angina attack and the long-acting nitrates (transdermal and extended release nitroglycerin, isosorbide mononitrate, isosorbide dinitrate) are used for prophylaxis of angina.

Ischemic heart disease is one of the most frequently reported cardiovascular diseases in the US and angina pectoris is the most common symptom of ischemic heart disease. ACCF/AHA Guidelines for patients with Stable Ischemic Heart Disease recommend beta-blockers with or without short-acting sublingual nitroglycerin as first-line treatment. The long-acting nitrates and ranolazine may be considered second-line or add-on options in patients who are not able to tolerate beta-blockers or who require additional therapy to control angina. The nitrates and ranolazine may also be used in the treatment of unstable angina and angina associated with heart failure or myocardial infarction.

Clinical Efficacy: No comparative clinical evidence is available for the antianginal therapies. When compared to placebo, the agents demonstrate efficacy in reducing the severity and frequency of angina episodes. Clinical evidence comparing the agents to other therapies (such as beta-blockers and calcium channel blockers) suggests the agents have similar rates of safety and efficacy.

Adverse Drug Reactions: The most common adverse events reported with nitrate therapy are headache and flushing. Nitrate tolerance may develop with continuous nitrate therapy and can be avoided or overcome with daily nitrate-free intervals ranging from 12-14 hours, depending on dosage form. Ranolazine is not associated with the development of tolerance. The most common adverse events reported with ranolazine therapy are dizziness, headache and gastrointestinal upset. Ranolazine is also associated with dose-related increases in the QT interval and should not be used in patients who are at an increased risk of developing QT prolongation.

Summary: In general, the antianginal agents appear to have similar rates of efficacy and are generally well tolerated. Development of tolerance and dosing recommendations vary between the agents. Pharmacokinetic factors, in addition to guideline recommendations, should be used when selecting an agent and mode of therapy with the antianginal therapies.
Introduction

A number of therapies are available for the treatment of angina, including: beta-blockers, calcium channel blockers, nitrates and a number of miscellaneous vasodilation agents. This report will include a review of the nitrates currently available for use in the United States: amyl nitrite, isosorbide dinitrate, isosorbide mononitrate, nitroglycerin and ranolazine. The agents included in this review are available in oral, inhalation and injectable formulations and are used variably, depending on severity of disease and concurrent pharmacotherapies. Table 1 provides a summary of all therapies used in the treatment of angina and Table 2 provides a summary of the agents included in this drug class review.

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Indicated Products</th>
<th>Route of Administration</th>
<th>Labeled Uses</th>
<th>Generic Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers</td>
<td>Atenolol, Metoprolol, Nadolol, Propranolol</td>
<td>Intravenous, Oral</td>
<td>All agents: Treatment of hypertension, alone or in combination with other agents; management of angina pectoris.</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Atenolol, Metoprolol, Propranolol: Secondary prevention postmyocardial infarction.</td>
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<td></td>
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<td></td>
<td>Propranolol: Management of pheochromocytoma; essential tremor; supraventricular arrhythmias, ventricular tachycardias; migraine headache prophylaxis; hypertrophic subaortic stenosis; proliferating infantile hemangioma.</td>
<td></td>
</tr>
<tr>
<td>Calcium Channel</td>
<td>Amlodipine, Diltiazem, Nifedipine, Nifedipine, Verapamil</td>
<td>Intravenous, Oral</td>
<td>All agents: Treatment of hypertension; angina pectoris</td>
<td>Yes</td>
</tr>
<tr>
<td>Blockers</td>
<td></td>
<td></td>
<td>Verapamil: Treatment of supraventricular tachyarrhythmia (PSVT, atrial fibrillation/flutter [rate control])</td>
<td></td>
</tr>
<tr>
<td>Nitrates</td>
<td>Amyl Nitrite, Isosorbide Dinitrate, Isosorbide Mononitrate, Nitroglycerin</td>
<td>Inhalation, Intravenous Oral, Rectal, Topical</td>
<td>Treatment of angina pectoris</td>
<td>Yes</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Ranolazine</td>
<td>Oral</td>
<td>Treatment of chronic angina</td>
<td>No</td>
</tr>
<tr>
<td>Vasodilator</td>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>

Table 1. Antianginal Therapies\textsuperscript{1,2}
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Available Formulations</th>
<th>Uses</th>
<th>Dose Range, Adult</th>
<th>Dose Range, Pediatric</th>
<th>Clinical Notes</th>
<th>Generic Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyl Nitrite</td>
<td>Liquid, for inhalation: USP: 85%-103% (0.3 mL)</td>
<td>Labeled: Coronary vasodilator in angina pectoris Off-label: Cyanide toxicity; Production of changes in the intensity of heart murmurs; Provocation of latent left ventricular outflow tract (LVOT) gradient during echocardiography in patients with hypertrophic cardiomyopathy (HCM)</td>
<td>Angina: 2-6 nasal inhalations from 1 crushed ampule; may repeat in 3-5 minutes Cyanide toxicity (off-label use): 0.3 mL ampule crushed into a gauze pad and placed in front of the patient’s mouth to inhale over 15-30 seconds; repeat every minute until sodium nitrite can be administered</td>
<td>Not currently labeled for use in pediatric patients Cyanide toxicity (off-label use): Refer to adult dosing</td>
<td>Given the widespread use of newer nitrate compounds, the use of amyl nitrite for patients experiencing angina pectoris has fallen out of favor</td>
<td>Yes</td>
</tr>
<tr>
<td>Isosorbide Dinitrate (Dilatrate-SR; IsoDilrate ER; Isordil Tritadose)</td>
<td>Oral Capsule, ER (Dilatrate-SR®): 40 mg Oral Tablet (generic): 5 mg, 10 mg, 20 mg, 30 mg Oral Tablet, ER (generic): 40 mg Oral Tablet, sublingual (generic): 2.5 mg [DSC]</td>
<td>Labeled: Prevention of angina pectoris Off-label: Heart failure with reduced ejection fraction; Esophageal spastic disorders</td>
<td>Immediate release: Initial: 5-20 mg 2-3 times daily; Maintenance: 10-40 mg 2-3 times daily or 5-80 mg 2-3 times daily Sustained release: 40-160 mg/day with nitrate free interval of &gt;18 hours is recommended or 40 mg 1-2 times daily; Maximum dose: 160 mg/day Sublingual: 5-10 mg every 2-4 hours for prophylaxis of acute angina; may supplement with 5-10 mg prior to activities which may provoke an anginal episode</td>
<td>Not currently labeled for use in pediatric patients</td>
<td>Due to slower onset of action, not the drug of choice for acute anginal episode</td>
<td>Product dependent</td>
</tr>
<tr>
<td>Isosorbide Mononitrate (Imdur)</td>
<td>Oral Tablet (generic): 10 mg, 20 mg Oral Tablet, ER (generic): 30mg, 60 mg, 120 mg</td>
<td>Prevention of angina pectoris</td>
<td>Immediate release: 5-20 mg twice daily with the 2 doses given 7 hours apart (eg, 8 AM and 3 PM) to decrease tolerance development Extended release: 30-60 mg given once daily in the morning; titrate upward as needed, giving at least 3 days between increases; maximum daily single dose: 240 mg</td>
<td>Not currently labeled for use in pediatric patients</td>
<td>Tolerance to nitrate effects develops with chronic exposure; dose escalation does not overcome this effect, tolerance can only be overcome by short periods of nitrate absence from the body</td>
<td>Yes</td>
</tr>
<tr>
<td>Nitroglycerin (Minitrans; Nitro-Bid; Nitro-Dur; Nitro-Time; Nitrolingual; NitroMist; Nitronal; Nitrostat; Rectiv)</td>
<td>Intravenous Solution (Nitronal®): 1 mg/mL (25 mL, 50 mL); (generic): 25 mg (250 mL); 50 mg (250 mL, 500 mL); 100 mg (250 mL); 200 mg (500 mL); 5 mg/mL (10 mL)</td>
<td>Oral capsule, ER (generic): 2.5 mg, 6.5 mg, 9 mg</td>
<td>Oral tablet, sublingual (Nitrostat®): 0.3 mg, 0.4 mg, 0.6 mg</td>
<td>Rectal ointment (Rectiv): 0.4% (30 g)</td>
<td>Transdermal ointment (Nitro-Bid®): 2% (1 g, 30 g, 60 g)</td>
<td>Transdermal Patch, 24 Hour (generic): 0.1 mg/hr; 0.2 mg/hr; 0.4 mg/hr; 0.6 mg/hr; (Nitro-Dur®): 0.3 mg/hr; 0.8 mg/hr</td>
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<td>Labeled: Oral: Treatment or prevention of angina pectoris (IV): Treatment or prevention of angina pectoris; acute decompensated heart failure; periperal hypotension; induction of intraoperative hypotension Intra-anal Sublingual: 0.4% solution: Topical: 2% ointment: ½-2&quot; 1-2 times daily; include a nitrate free-interval ~10-12 hours/day Transdermal: 0.4 mg/hr; 0.8 mg/hr; 1.2 mg/hr</td>
<td>Angina/coronary artery disease: Oral: 2.5-6.5 mg 3-4 times/day (maximum dose: 26 mg 4 times/day) IV: 5 mcg/minute, increase by 5 mcg/minute every 3-5 minutes to 20 mcg/minute (maximum dose: 400 mcg/minute) Sublingual: 0.3-0.6 mg every 5 minutes for maximum of 3 doses in 15 minutes; may also use prophylactically 5-10 minutes prior to activities which may provoke an attack Topical patch: 0.2-0.8 mg/hour; patch-off period of 12-14 hours/day and patch-off period of 10-12 hours/day Translingual: 1-2 sprays onto or under tongue approximately every 5 minutes for maximum of 3 doses in 15 minutes, may also be used prophylactically 5-10 minutes prior to activities which may provoke an angina attack</td>
<td>Not currently labeled for use in pediatric patients Extravasation (off-label use; optimal dosing has not been established): Topical ointment, 4 mm/kg applied to the affected area; after 8 hours, if no improvement, the dose may be reapplied</td>
<td>Hemodynamic and antianginal tolerance often develop within 24-48 hours of continuous nitrate administration. Nitrate-free interval (10-12 hours/day) is recommended to avoid tolerance development; gradually decrease dose in patients receiving NTG for prolonged period to avoid withdrawal reaction.</td>
<td>Product dependent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranolazine (Ranexa®)</td>
<td>Oral Tablet ER, 12 Hour: 500 mg, 1000 mg</td>
<td>Treatment of chronic angina</td>
<td>500 mg twice daily; may increase to 1000 mg twice daily as needed; maximum: 1000 mg twice daily</td>
<td>Not currently labeled for use in pediatric patients</td>
<td>Ranolazine dose should not exceed 500 mg twice daily when given concurrently with diltiazem, erythromycin, fluconazole, verapamil and other moderate CYP3A inhibitors. Ranolazine dose should be titrated to clinical response when used concurrently with P-glycoprotein inhibitors (e.g., cyclosporine)</td>
<td>No</td>
</tr>
</tbody>
</table>

Key: ER = extended release, DSC = discontinued, IV = intravenous
**Disease Overview**

Cardiovascular diseases are the most common causes of death in the United States and are rapidly growing problems throughout the world.\(^3\)-\(^{12}\) Diseases included in this category are hypertension, congestive heart failure, ischemic heart disease, stroke and peripheral arterial disease. A sedentary lifestyle, unhealthy diet, tobacco use and alcohol abuse are some of the risk factors for developing a cardiovascular disease. According to the American Heart Association, each day over 2000 Americans will die of a cardiovascular disease (averaging one death every 39 seconds) and each year nearly 800,000 Americans will experience a stroke (averaging one cerebrovascular accident every 40 seconds). Therapeutic approaches to prevent cardiovascular disease include lifestyle modification (weight reduction, physical activity, smoking cessation), blood pressure control, fluid management, lipid-lowering treatment, and use of antiplatelet and antithrombotic agents.\(^3\)-\(^9\)

Ischemic heart disease is a condition defined as a reduced blood supply to the heart.\(^13\)-\(^{15}\) Cardiac ischemia is caused by atherosclerosis, or hardening of the arteries, and can result in angina, heart attack and death. In developed countries, ischemic heart disease is one of the most frequently reported cardiovascular diseases and causes of death. Angina pectoris is the most common symptom of ischemic heart disease and is characterized as chest pain which results from an imbalance in the coronary vessels where the oxygen demand in the heart is greater than the oxygen supplied to the heart. The pain may be mild or intense and feel like a crushing, burning, or squeezing discomfort that can spread to the neck or arms. Typically, the pain lasts for 5-10 minutes and is relieved with sublingual nitroglycerin. Angina pectoris is divided into three types: secondary angina, or effort angina, wherein inadequate blood flow during exercise or times of stress results in chest pain; primary angina, or variant angina, wherein the ischemia causes spasm of the coronary vessels and chest pain without increases in cardiac demand; and unstable angina wherein a sudden worsening of the patients chronic angina occurs.\(^13\)-\(^{15}\) All types of angina demonstrate the same characteristic chest pains and are relieved with the administration of nitroglycerin.

As mentioned, nitroglycerin is commonly used to treat chest pain associated with ischemic heart disease. Nitroglycerin is an organic nitrate and considered the standard treatment for immediate relief of angina. Overall, three drug classes are typically used in the treatment and prevention of angina: organic nitrates, calcium channel blockers and beta-blockers.\(^14\),\(^{15}\) Each of these therapeutic drug classes reduce myocardial oxygen requirements by decreasing heart rate, blood pressure and/or contractility. Sublingual nitroglycerin is used to treat an angina attack. Calcium channel blockers, beta-blockers and long-acting nitrates (transdermal and extended release nitroglycerin, isosorbide mononitrate, isosorbide dinitrate) are used for prophylaxis of angina. Ranolazine is a newer agent with a unique mechanism of action which may also be used in the treatment and prevention of chronic angina. According to the 2012 Guidelines for Patients with Stable Ischemic Heart Disease\(^{16}\), beta-blockers with or without short-acting sublingual nitroglycerin is recommended as first-line treatment.\(^{16}\) The long-acting nitrates, calcium channel blockers and ranolazine are considered second-line or add-on options in patients...
who are not able to tolerate beta-blockers or who require additional therapy to control angina. The nitrates and ranolazine may also be used in the treatment of unstable angina and angina associated with heart failure or myocardial infarction. Table 3 provides a summary of the current clinical guideline recommendations for treatment of angina.

**Table 3. Summary of Current Clinical Practice Guidelines**

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Treatment Recommendations</th>
</tr>
</thead>
</table>
| ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2012 | Recommendations:  
First-line: β-blockers + short-acting sublingual nitrates prn  
Second-line: long-acting nitrates, calcium channel blockers, ranolazine  
Add-on: β-blockers + long-acting nitrates, calcium channel blockers, ranolazine |
| Institute for Clinical Systems Improvement (ICSI): Stable Coronary Artery Disease, 2013 | Recommendations:  
Daily aspirin (81-162 mg)  
Patients with mild, stable CAD and angina:  
First-line: β-blockers + short-acting sublingual nitrates prn  
Second-line: long-acting nitrates  
Third-line: calcium channel blockers  
Last line: ranolazine  
Add-on: β-blockers + long-acting nitrates  
Second-line add-on: β-blockers + calcium channel blockers |
| ACCF/AHA Guideline for the Management of Heart Failure, 2013 | African Americans with NYHA class III–IV HFrEF:  
Combination of hydralazine and isosorbide dinitrate with ACE inhibitors and beta blockers |
| ACCF/AHA guideline for the management of ST-elevation myocardial infarction, 2013 | Intravenous nitroglycerin may be useful to treat patients with STEMI and hypertension or heart failure  
There is no role for the routine use of oral nitrates in the convalescent phase of STEMI |
| Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction, 2012 | Patients with UA/NSTEMI:  
First-line: beta-blocker and ace inhibitor  
Second-line or add-on: calcium channel blocker, angiotensin receptor blocker  
Patients with UA/NSTEMI and ongoing ischemic discomfort:  
sublingual NTG (0.4 mg) every 5 min for a total of 3 doses  
intravenous NTG is indicated in the first 48 h for treatment of persistent ischemia, heart failure or hypertension |
| AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes, 2014 | Patients with NSTE-ACS:  
First-line: aspirin, beta-blocker (sustained-release metoprolol succinate, carvedilol or bisoprolol), ace inhibitor, high-intensity statin, anticoagulation  
Second-line: calcium channel blocker (verapamil or diltiazem), clopidogrel or ticagrelor  
Patients with NSTE-ACS continuing ischemic pain:  
intravenous nitroglycerin (0.3-0.4 mg) every 5 minutes for up to 3 doses  
intravenous nitroglycerin for patients with persistent ischemia, heart failure or hypertension |

Key: prn- as needed; CAD- coronary artery disease; HFrEF - heart failure with reduced ejection fraction; STEMI - ST segment elevation myocardial infarction; NTG - nitroglycerin; UA/NSTEMI - Unstable Angina/Non-ST- Segment Elevation myocardial infarction; NSTE-ACS - non–ST-elevation acute coronary syndromes
Pharmacology

Organic nitrates are simple nitric and nitrous acid esters of polyalcohols. Nitroglycerin is considered the prototype but all of the agents have a similar mechanism of action. Nitroglycerin forms a free radical, nitric oxide, which activates guanylate cyclase in smooth muscle and causes myosin (MYLK) dephosphorylation, resulting in:

- Relaxation of smooth muscle
- Vasodilation of the peripheral veins (primarily) and arteries
- Dilation of coronary arteries
- Reduction of cardiac oxygen demand by decreasing preload (left ventricular end-diastolic pressure)
- Modest reduction of afterload
- Improvement of collateral flow to ischemic regions

Tolerance may develop with continuous nitrate therapy. The development of nitrate tolerance is not fully understood but may result from activation of a neurohormonal mechanism, expansion of plasma volume, production of super oxide, from abnormalities in biotransformations of nitrates or nitric oxide signaling mechanisms. Nitrate tolerance may be avoided or overcome by daily nitrate-free intervals ranging from 12-14 hours for most long-acting nitrates, depending on the dosage form. The addition of hydralazine to the nitrate product may help to improve efficacy and reduce the development of tolerance.

Amyl Nitrate: With the widespread use and proven efficacy for nitroglycerin and isosorbide, the use of amyl nitrite for angina pectoris is not generally recommended. Amyl nitrate may be used in the treatment of cyanide poisoning and works by binding to the cyanide ion to form cyanomethemoglobin which results in release of the cytochrome oxidase and allows aerobic metabolism to continue.

Isosorbide: The isosorbide agents are indicated in the prevention of angina pectoris and are not generally the agent of choice for acute angina episodes due to the slower onset of action (30-60 minutes). Isosorbide is available in a dinitrate or mononitrate formulation, which is simply the active metabolite of isosorbide dinitrate. Both formulations are given once daily (with the extended release agents) or 2-3 times daily (with the immediate release formulations). Tolerance can be avoided by short periods of nitrate-free intervals (10-12 hours/day).

Nitroglycerin: The conventional sublingual tablet form of nitroglycerin offers relief within 1-5 minutes and should not be chewed, crushed, or swallowed as the onset of action is quicker when absorbed through the lining of the mouth. The sublingual tablets are stored in tightly closed glass containers as the tablets can lose potency through volatilization and adsorption to plastic surfaces. Nitroglycerin is also available as an translingual spray and IV formulation for immediate relief as well as an extended release tablet and transdermal patch for prevention of angina. To avoid the development of tolerance, the transdermal patch requires a daily 10 hour nitrate-free period and the extended release product should be dosed with an 18 hour nitrate-free period daily. When used in the treatment of rectal fissures, topical nitroglycerin cream works by decreasing sphincter tone and intra-anal pressure.
Ranolazine: The newest agent in the class, ranolazine, produces antianginal and anti-ischemic effects without changing hemodynamic parameters, such as heart rate or blood pressure. Ranolazine’s mechanism of action is not fully understood but it is thought to work by inhibiting late phase sodium influx in ischemic cardiac tissue during cardiac repolarization. This results in reduced intracellular sodium concentrations, ventricular tension and myocardial oxygen consumption. At high doses, ranolazine may inhibit the rectifier potassium current, prolong ventricular action and, subsequently, prolong the QT interval; caution should be taken when using ranolazine in patients at risk for developing QT prolongation.2,22

Table 4. Pharmacokinetic Properties of the Antianginal Agents2,22

<table>
<thead>
<tr>
<th>Agent</th>
<th>Bioavailability</th>
<th>Time to Peak</th>
<th>Half-life</th>
<th>Metabolism</th>
<th>Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyl Nitrite</td>
<td>41-45%</td>
<td>Onset: Within 30 seconds</td>
<td>1.4-1.5 minutes</td>
<td>Metabolized rapidly, likely by hydrolytic denitrification</td>
<td>~33% excreted in the urine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Duration: 3-15 minutes</td>
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<tr>
<td>Isosorbide Dinitrate</td>
<td>Oral immediate release formulations: Highly variable (10% to 90%); increases with chronic therapy Vd: 2 to 4 L/kg</td>
<td>Onset of action: Sublingual tablet: ~2-5 minutes Oral tablet and capsule: ~1 hour Duration: Sublingual tablet: 1-2 hours Oral tablet and capsule: Up to 8 hours</td>
<td>Parent drug: ~1 hour Metabolites 5-mononitrate: 5 hours 2-mononitrate: 2 hours</td>
<td>Extensively hepatic to conjugated metabolites, including isosorbide 5-mononitrate (active) and 2-mononitrate (active)</td>
<td>Urine and feces</td>
</tr>
<tr>
<td>Isosorbide Mononitrate</td>
<td>~100% Vd: ~0.6 L/kg</td>
<td>Onset of action: 30-60 minutes Duration: Immediate release: ≥26 hours Extended release: ≥12-24 hours</td>
<td>~5-6 hours</td>
<td>Protein binding: &lt;5% Metabolism: Hepatic</td>
<td>Predominantly urine (2% as unchanged drug); feces (1% of dose)</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>~40% Vd: ~3 L/kg</td>
<td>Onset of action Sublingual tablet and translingual spray: 1-3 minutes Extended release: ~60 minutes Topical: 15-30 minutes Transdermal: ~30 minutes IV: Immediate Peak effect Sublingual tablet: 5 minutes Translingual spray: 4-10 minutes Extended release: 2.5-4 hours Topical: ~60 minutes Transdermal: 120 minutes</td>
<td>~1-4 minutes</td>
<td>Protein binding: 60% Metabolism: Extensive first-pass effect; metabolized hepatically to glycerol di- and mononitrate metabolites via liver reductase enzyme; further metabolism to glycerol and organic nitrate; nonhepatic metabolism via red blood cells and vascular walls</td>
<td>Urine (as inactive metabolites)</td>
</tr>
<tr>
<td>IV: Immediate Duration</td>
<td>Sublingual tablet and translingual spray: &gt;25 minutes</td>
<td>Extended release: 4-8 hours</td>
<td>Topical: 7 hours</td>
<td>Transdermal: 10-12 hours</td>
<td>IV: 3-5 minutes</td>
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<tr>
<td>Ranolazine 76% Time to peak: 2-5 hours</td>
<td>7 hours Metabolites (activity undefined): 6-22 hours</td>
<td>Protein binding: ~62%</td>
<td>Metabolism: Extensive; Hepatic via CYP3A (major) and 2D6 (minor); intestines</td>
<td>Primarily urine (75% mostly as metabolites; &lt;5% as unchanged drug); feces (25% mostly as metabolites; &lt;5% as unchanged drug)</td>
<td></td>
</tr>
</tbody>
</table>

Key: IV-intravenous, HTN- hypertension, CYP- cytochrome P450
Methods

A literature search was conducted to identify articles evaluating the antianginal agents, searching the MEDLINE database (1950 – 2014), the Cochrane Library, and reference lists of review articles. For the clinical efficacy section, only clinical trials published in English, evaluating the comparative efficacy of the antianginal agents are included. Trials evaluating the agents as monotherapy or combination therapy where adjunctive medications remained constant throughout the trial are included. Noncomparative trials and trials comparing monotherapy with combination regimens are excluded. The following reports were excluded (note: some were excluded for more than 1 reason):24-31

- Individual clinical trials which evaluated endpoints other than reduction of symptoms, such as pharmacokinetics, pharmacodynamics, pharmacoconomics or other outcomes unrelated to reduction of symptoms.32-42
- Individual trials comparing the agents in dose-finding43-51 and placebo-controlled studies51-55 or in healthy volunteers.39,56
- Individual clinical trials evaluating agents or formulations not currently available in the US or clinical trials without access to the full article.57-63

Clinical Efficacy

The efficacy of the antianginal agents has not been directly compared in any comparative clinical trials or meta-analyses. The agents have been studied in the prevention or treatment of angina in a number of placebo-controlled trials. Trials comparing the safety and efficacy of the agents with other therapies, including beta-blockers and calcium channel blockers, are also available. In a recent review of nitrates for acute heart failure syndromes (2013)64, no significant differences in efficacy were reported between nitrate vasodilator therapy and alternative interventions (furosemide and morphine, furosemide alone, hydralazine, beta-blockers, intravenous nesiritide and placebo). According to the systemic review, nitrate therapy may be associated with a lower incidence of adverse effects but no differences in symptom relief or hemodynamic variables were demonstrated. Ranolazine has been directly compared to calcium channel blocking therapy (amlodipine), beta-blocker therapy (atenolol) and placebo and demonstrated statistically significant improvements in exercise stress test parameters, reduced angina frequency and nitroglycerin use compared with placebo.65,66 In general, the antianginal agents demonstrate efficacy in reducing the severity and frequency of angina episodes.
Adverse Drug Reactions

The antianginal agents are generally well-tolerated. The most common adverse events reported with nitrate therapy include headache and flushing. Hypotension may also occur and should be used with caution in elderly patients. Tolerance may develop with chronic antianginal therapy and nitrate-free intervals are recommended and vary depending on agent and dosage form. Nitrate therapy is contraindicated in patients with hypertrophic cardiomyopathy or suspected right ventricular infarction and nitrates should not be given to patients with hypotension, aortic stenosis, volume depletion or moderate-severe bradycardia/tachycardia. Nitrate are also contraindicated in patients with 5'phosphodiesterase inhibitor use within the previous 24-48 hours due to risk of severe hypotension. Table 5 provides a summary of important drug interactions associated with these agents.

The most common adverse events reported with ranolazine therapy are dizziness, constipation, headache and nausea. Ranolazine is not associated with the development of tolerance, as seen with standard nitrate therapy. Ranolazine does produce a dose-dependent increase in the QT interval and is contraindicated in patients with preexisting QT interval prolongation or hepatic disease and in patients taking other drugs that prolong the QT interval. Table 6 provides a list of the most frequent adverse events reported with each of the agents, according to package labeling.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Interaction Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organic nitrates &amp; Ranolazine</strong></td>
<td>Clinical studies with each of the phosphodiesterase 5 (PDES) inhibitors have found evidence that these agents potentiate the hypotensive effects of nitrates. Concurrent use of phosphodiesterase 5 (PDES) inhibitors with an organic nitrate is contraindicated; this includes both regular and intermittent nitrate use. No safe interval between use of any PDES inhibitor and a nitrate has been identified. Based on the elimination half-lives of the PDES inhibitors, nitrate doses should not be given within at least 24 hours of sildenafil or vardenafil, and nitrates should not be given within at least 48 hours of tadalafil. Avanafil US prescribing information states that in a life-threatening situation where a nitrate is desired in a patient who has taken avanafil, a nitrate may be administered at least 12 hours after the last avanafil dose was ingested, but only with close medical supervision and monitoring.</td>
</tr>
<tr>
<td><strong>Bromocriptine; Cabergoline; Dihydroergotamine; Ergoloid Mesylates; Ergonovine; Ergotamine; Methylergonovine</strong></td>
<td>Ergot alkaloids are known precipitants of angina and would be expected to oppose the antianginal effects of nitroglycerin. Additionally, nitroglycerin increases the bioavailability of dihydroergotamine and could thereby increase the risk of adverse effects (e.g., ergotism). It is unknown whether the bioavailability of ergot derivatives other than dihydroergotamine would be similarly affected.</td>
</tr>
<tr>
<td><strong>Conivaptan, Fusidic Acid, Idelalisib, others</strong></td>
<td>Are strong CYP3A inhibitor and likely inhibited the metabolism of these agents, and it is expected that conivaptan would have similar effects on other CYP3A4 substrates. As a result, the conivaptan prescribing information recommends avoiding concurrent use with drugs metabolized primarily via CYP3A. Also, initiation of treatment with any drug metabolized primarily via CYP3A should be delayed for at least 7 days following discontinuation of conivaptan.</td>
</tr>
<tr>
<td><strong>Ranolazine only</strong></td>
<td>Moderate Risk QTc-Prolonging Agents may enhance the QTc-prolonging effect of Highest Risk QTc-Prolonging Agents. The concomitant use of highest risk QTc-prolonging agents with any other QTc-prolonging agent should be avoided. Many such combinations are listed contraindications for these drugs. Concomitant use is expected to substantially increase the risk for serious toxicities, including the development of torsades de pointes (TdP) or other significant ventricular tachyarrhythmias. Patients with other risk factors present (e.g., older age, female sex, bradycardia, hypokalemia, hypomagnesemia, heart disease, and higher drug concentrations), would be at an even higher risk for these potentially life-threatening toxicities.</td>
</tr>
</tbody>
</table>
### Table 6. Adverse Events Reported with Antianginal Therapies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Cardiovascular</th>
<th>Central Nervous System</th>
<th>Dermatologic</th>
<th>Gastrointestinal</th>
<th>Neuromuscular &amp; Skeletal</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyl Nitrite</td>
<td>Cerebral ischemia, facial flushing, hypotension, orthostatic hypotension, pallor, shock, syncope, tachycardia, vasodilatation</td>
<td>Dizziness, headache, intracranial pressure increased, restlessness</td>
<td>Dermatitis, irritation</td>
<td>Fecal incontinence, nausea, vomiting</td>
<td>Weakness</td>
<td>Urinary incontinence, Hemolytic anemia, methemoglobinemia, intraocular pressure increased, irritation, Diaphoresis</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Bradycardia, flushing, hypotension, orthostatic hypotension, peripheral edema, syncope, tachycardia, cardiovascular collapse, crescendo angina, palpitation, rebound hypertension</td>
<td>Headache (common), dizziness, lightheadedness, blurred vision, restlessness, vertigo</td>
<td>Pallor, rash</td>
<td>Nausea (≤3%), abdominal pain (≤2%), diarrhea (≤2%), anorexia, dyspepsia, taste disturbance, thirst, vomiting, xerostomia</td>
<td>Back pain, muscle cramps, neck pain</td>
<td>Upper respiratory infection (≤4%), cough increased (≥2%), Allergic reaction (≥2%), Amblyopia, asthma, diaphoresis, dyspnea, methemoglobinemia (common), prostatic disorder, sinusitis</td>
</tr>
<tr>
<td>Ranolazine</td>
<td>Bradycardia (≤4%), hypotension (≤4%), orthostatic hypotension (≤4%), palpitation (≤4%), peripheral edema (≤4%), prolonged QT interval on ECG (&gt;500 msec; ≤1%), torsade de pointes [case report (Morrow, 2007)]</td>
<td>Headache (≤6%), dizziness (1% to 6%), confusion (≤4%), vertigo (≤4%), syncope (≤4%), ataxia, hallucination, paresthesia</td>
<td>Hyperhidrosis (≤4%), pruritus</td>
<td>Constipation (5%), abdominal pain (≤4%), anorexia (≤4%), dyspepsia (≤4%), nausea (≤4%; dose related), vomiting (≤4%), xerostomia (≤4%)</td>
<td>Weakness</td>
<td>Hematuria (≤4%), blurred vision (≤4%), tinnitus (≤4%), dyspnea (≤4%), angioedema, decreased glycosylated hemoglobin, dysuria, esoinophilia, increased blood urea nitrogen, increased serum creatinine, leukopenia, pancytopenia, renal failure, thrombocytopenia</td>
</tr>
</tbody>
</table>
Summary

Ischemic heart disease is one of the most frequently reported cardiovascular diseases in the US and angina pectoris is the most common symptom of ischemic heart disease. A number of therapies are available for the treatment of angina, including: beta-blockers, calcium channel blockers, nitrates and a number of miscellaneous vasodilation agents. Sublingual nitroglycerin is used to treat an angina attack and long-acting nitrates (transdermal and extended release nitroglycerin, isosorbide mononitrate, isosorbide dinitrate) are used for prophylaxis of angina. Ranolazine is a newer agent with a unique mechanism of action which may also be used in the treatment and prevention of chronic angina. ACCF/AHA Guidelines for patients with Stable Ischemic Heart Disease recommend beta-blockers with or without as needed short-acting sublingual nitroglycerin as first-line treatment. The long-acting nitrates, calcium channel blockers and ranolazine may be considered second-line or add-on options in patients who are not able to tolerate beta-blockers or who require additional therapy to control angina. The nitrates and ranolazine may also be used in the treatment of unstable angina and angina associated with heart failure or myocardial infarction.

The nitrate agents work by relaxing smooth muscle, reducing cardiac oxygen demand and improving collateral flow to ischemic regions. Ranolazine works by inhibiting late phase sodium influx in ischemic cardiac tissue and reducing myocardial oxygen consumption. Nitrate tolerance may develop with continuous nitrate therapy and can be avoided or overcome with daily nitrate-free intervals ranging from 12-14 hours, depending on dosage form. Ranolazine is not associated with the development of tolerance. No comparative clinical evidence is available for the antianginal therapies. Clinical evidence comparing the agents to other therapies (like beta-blockers and calcium channel blockers) suggests the agents have similar rates of safety and efficacy. The most common adverse events reported with nitrate therapy are headache and flushing and the most common adverse events reported with ranolazine therapy are dizziness, headache and gastrointestinal upset. Ranolazine is also associated with dose-related QT prolongation. In general, the antianginal agents appear to have similar rates of efficacy and are generally well tolerated but development of tolerance and dosing recommendations vary between the agents. Pharmacokinetic factors, in addition to guideline recommendations, should be used when selecting an agent and mode of therapy with the antianginal therapies.
References


