Angina pectoris is the term for chest pain or discomfort due to coronary heart disease. It is a symptom of a condition called myocardial ischemia. In this lesson, we will discuss a number of factors related to treatment of angina pectoris. Background descriptions and classification of the disease are discussed in Part 1. We will also provide a detailed synopsis of organic nitrate therapy. In Part 2, we will provide explanations and information regarding the other 3 classes of angina medications, along with summaries of therapeutic treatment rationale.

### Learning Objectives

**Pharmacist**
1. List determinants of myocardial oxygen demand and myocardial oxygen supply
2. Describe the pharmacology of antianginal medications
3. Prepare a pharmacotherapeutic plan to prevent stable angina and variant angina from occurring
4. Identify common adverse effects of antianginal drugs
5. Counsel patients when dispensing SL nitroglycerin drugs
6. Describe angina treatment using beta-receptor blockers, calcium channel blockers and ranolazine
7. Discuss pharmacotherapeutic approaches to angina therapy
8. List the rationale for using non-pharmacological treatments, SL nitroglycerin, and dual platelet therapy for angina
9. Describe an approach for treating unstable angina

**Pharmacy Technician**
1. List determinants of myocardial oxygen demand and myocardial oxygen supply
2. Describe the pharmacology of antianginal medications
3. Identify common adverse effects of antianginal drugs
4. Describe angina treatment using beta-receptor blockers, calcium channel blockers and ranolazine
5. Discuss pharmacotherapeutic approaches to angina therapy
6. List the rationale for using non-pharmacological treatments, SL nitroglycerin, and dual platelet therapy for angina
7. Describe an approach for treating unstable angina

**Nurse**
1. List determinants of myocardial oxygen demand and myocardial oxygen supply
2. Describe the pharmacology of antianginal medications
3. Prepare a pharmacotherapeutic plan to prevent stable angina and variant angina from occurring
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5. Counsel patients when dispensing SL nitroglycerin drugs
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Target Audience
Pharmacists, Pharmacy Technicians, Nurses

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Part 1 - Angina Pectoris: Review and Update

BACKGROUND & DEFINITIONS

Ischemic Heart Disease (IHD) is a form of heart disease that results from the narrowing of one or more of the major coronary arteries supplying the heart. This results from an imbalance between myocardial oxygen supply or oxygen demand.

Angina pectoris is the most common symptom of IHD. It is a clinical sign resulting from transient myocardial ischemia (lack of blood supply to the heart muscle). The typical episode lasts 3-5 minutes and is brought on usually by physical exertion or emotional stress. Other signs and symptoms may include: shortness of breath, weakness, abdominal fullness, sweating, peripheral vasoconstriction, and palpitation.

The pain of angina is due to the inability of the sclerotic or stenosed coronary arteries to provide adequate amounts of oxygen through adequate blood flow to the myocardium during time of increased oxygen demand. The pain is a dull or heavy feeling in the middle of the chest, which may move to either arm (usually the left), or up through the throat, into the jaw, and may radiate to the back. Precipitating factors for typical angina pectoris may be: strenuous physical exercise, emotional stress, drugs which increase the workload and oxygen demand on the heart, heavy meals or, possibly, exposure to rapid changes in temperature (hot & cold). The pain is usually relieved by rest or by stopping (eliminating) causative factors.

Atypical angina, also called variant angina or Prinzmetal's angina, is not induced by the commonly known predisposing factors. It may occur at rest and is not relieved by the common methods that will be discussed. This type of myocardial ischemia is thought to be due to coronary artery vasospasm (quick constriction of a vessel in a particular segment).

APPROACHES TO THE THERAPY OF ANGINA

1. Acute
   - Rest,
   - Nitroglycerin and,
   - Possibly, oxygen if hospitalized.

2. Chronic
   - Modification of lifestyle (diet, smoking),
   - Treatment of associated underlying diseases (MI, diabetes, HTN [hypertension], etc.).
   - Drug therapy
     - Nitrates,
     - Beta-blockers,
     - Calcium-channel blockers, or
     - Ranolazine

In this lesson, and the next, we will discuss a number of factors related to treatment of angina pectoris.

Primarily, we are seeking to (our goals are):
1. Describe the specific families of medications:
   a. Organic nitrates
   b. Beta - receptor blockers
   c. Calcium - channel blockers
   d. Ranolazine

2. Discuss therapeutic rationale
Background descriptions and classification of the disease are discussed in this lesson ("Part 1: Angina Pectoris--Review & Update"). Additionally, in this lesson, we provide a detailed synopsis of organic nitrate therapy.

In the next lesson ("Part 2: Angina Pectoris--Review & Update"), we will provide explanations and information regarding the other 3 classes of angina medications, along with summaries of therapeutic treatment rationale.

Angina pectoris ("strangling of the chest") occurs when myocardial oxygen demand exceeds myocardial oxygen supply, creating myocardial cell ischemia. The determinants of myocardial oxygen demand and myocardial oxygen supply are listed in Table 1 and diagrammed in Figure 1. During angina pectoris, the ischemic myocardial cells induce substernal discomfort or pain that patients typically describe as being dull (as opposed to sharp), heavy, crushing, squeezing, and/or choking. In many instances, the pain travels down the left arm but, in some cases, may travel down the right arm, down the back, or up the neck to the jaw. Patients often experience breathlessness during an episode.

Angina is often described in three manners: stable, unstable, and variant. Stable and unstable angina predominantly result from the development of atherosclerosis within coronary arteries. With stable angina, symptoms are predictably related to exertion or emotional stress and the symptoms are often relieved once the exertion has concluded or the emotional reaction has dissipated. If not, the patient may take a sublingual nitroglycerin product to relieve the pain. Angina attacks are rarely more than 20 minutes duration and are typically less than 5 minutes long. Unstable angina is said to be present when one has a change in his/her predictable stable angina pattern or has angina at rest in the absence of any emotional stress. Also, one is considered to have unstable angina the first time he/she has angina. Of the two angina types described here, unstable angina is more discerning because it may be a precursor to a more ominous acute coronary syndrome such as a myocardial infarction. If an EKG was obtained during an episode of stable or unstable angina, the EKG typically would exhibit ST-segment depression.

Variant angina, also known as Prinzmetal’s angina, is due to coronary vasospasm. Some patients’ coronary arteries have a predilection for vasoconstriction typically unrelated to atherosclerosis. Attacks are unrelated to exertion or emotion and can occur at rest. If an EKG is obtained during the chest discomfort of variant angina, the EKG typically would show ST-segment elevation.

This lesson focuses on stable angina, but will include relevant clinical comments related to unstable and variant angina.
Table 1. The Determinants of Myocardial Oxygen Demand and Supply

<table>
<thead>
<tr>
<th>Myocardial Oxygen Demand</th>
<th>Myocardial Oxygen Supply</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contractility</td>
<td>Oxygen content of blood</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Coronary artery blood flow</td>
</tr>
<tr>
<td>Wall tension</td>
<td>-Coronary vascular resistance</td>
</tr>
<tr>
<td>-Preload*</td>
<td>- Aortic pressure</td>
</tr>
<tr>
<td>-Afterload**</td>
<td></td>
</tr>
<tr>
<td>-Wall thickness</td>
<td></td>
</tr>
</tbody>
</table>

*The pressure exerted on the left ventricle immediately before ventricular systole. This pressure is related to left ventricular blood volume. Dilating veins or reducing blood volume reduces preload.

**The pressure exerted by the systemic arterial system on the left ventricle as it contracts. Dilating arteries reduces afterload.

Figure 1. Determinants of Myocardial Oxygen Demand and Myocardial Oxygen Supply
APPROACHES TO THE THERAPY OF ANGINA

General Comments

When a stable or unstable angina diagnosis is made, one should reduce cardiovascular risk factors that are present. Losing weight, when applicable, routine exercise, as well as eating a healthy diet, especially when a patient has dyslipidemia, are important. Blood pressure should be controlled. The current ACC/AHA (American College of Cardiology/American Heart Association) goal is for BP to be less than 130/80 mm Hg. When applicable, patients should quit smoking, and all patients should avoid second-hand smoke as well as polluted air. Effort should be made to control glucose concentrations and achieve a goal Hgb A1C in patients with diabetes mellitus, especially those with type 1. Vasoconstricting medications, such as those used in the treatment of migraine headaches like ergot derivatives and “triptans,” should be avoided. Finally, modest amounts of alcohol daily may be suggested in those patients with no history of alcoholism. Modest amount is defined as one drink a day for women and one or two drinks a day for men. A drink is defined as 12 oz. of beer, 4 oz. of wine, and 1 oz. of distilled spirits.

If the angina is known to be a result of atherosclerotic disease, inflicted patients should be placed on aspirin 81 mg daily. For patients allergic or intolerable to aspirin, clopidogrel 75 mg daily is a reasonable option. There is no advantage to using both aspirin and clopidogrel in a patient with chronic stable atherosclerotic disease; however, combined antiplatelet therapy can be advantageous in those who have recently suffered an acute coronary syndrome or received an intracoronary stent. Due to the fact that they can be thrombogenic and can negate the antiplatelet effects of aspirin, NSAIDs should be used sparingly, if at all, in patients with atherosclerotic disease. Statin therapy and an ACE-I (angiotensin - converting enzyme inhibitor) or ARB (angiotensin II receptor blocker), especially in the higher-risk patients, to reduce cardiovascular complications, should also be considered in patients with angina related to atherosclerotic disease. With respect to statin therapy, the fact that these patients have clinically evident disease makes high-intensity statin therapy (atorvastatin 40-80 mg daily or rosuvastatin 10-40 mg daily) preferred, especially in patients 75 years of age or younger. Moderate-intensity statin therapy might be initially tried in older patients. All patients should have annual influenza vaccinations. Based on data available at this time, the following therapies are not advocated for the sole purpose of reducing cardiovascular risk: vitamin C; vitamin E; beta-carotene; homocysteineby itself or with folate, vitamin B6, or vitamin B12; garlic; coenzyme Q10; selenium; chromium; and, in postmenopausal women, estrogens.

Medication Armamentarium

The general goal of antianginal pharmacotherapy is to reduce myocardial oxygen demand and/or increase myocardial oxygen supply. Medications cannot really increase the oxygen content of blood, but they can increase coronary artery blood flow by dilating coronary arteries, thus reducing coronary artery vascular resistance. Medications can also reduce contractility, heart rate, preload, and afterload; albeit, no one medication addresses all of these determinants in a positive manner.

Four families of medications currently exist to treat acute attacks of angina or prevent it from occurring; 1) organic nitrates; 2) beta-receptor blockers; 3) calcium channel blockers; and, 4) ranolazine. AS MENTIONED EARLIER, NITRATES WILL BE DISCUSSED IN THIS LESSON. THE OTHER THREE GROUPS WILL BE PRESENTED IN THE NEXT LESSON.
ORGANIC NITRATES

Organic nitrates are effective in both the acute treatment and prevention of angina by increasing coronary artery blood flow and by reducing preload and, to some extent, afterload. These latter two effects reduce wall tension. Organic nitrates may be used in all three types of angina. When using organic nitrates to prevent angina from occurring, it must be recognized that continuous around-the-clock use of these medications will result in tolerance and loss of their pharmacological effect. One possible explanation for this is that organic nitrates need sulfhydryl groups to become active and that the body’s continuous exposure to organic nitrates results in depletion of these groups. By allowing a patient to be nitrate-free for a period of time (at least 8 hours and preferably 12 hours) each day allows for the body to replenish sulfhydryl groups. A common misconception is that an oral isosorbide product can be used during the day and a nitroglycerin patch at night since they are different types of organic nitrates. This approach is ineffective because the receptors recognize all forms of organic nitrates as being the same.

From a clinical perspective in allowing a credible nitrate-free period each day, this means that immediate-release isosorbide dinitrate should be dosed no more than three times a day in non-concentric fashion. Non-concentric means that these three doses are not given every 8 hours but three times a day with doses separated by about 4 hours and the last dose given about 16 hours before the next day’s morning dose. Immediate-release isosorbide mononitrate can be given twice a day without inducing tolerance if the doses are separated by 7 hours. Sustained-release isosorbide mononitrate should be given only once a day. A sustained-release isosorbide dinitrate product also exists, but the once-a-day isosorbide mononitrate product has become the more commonly used sustained-release isosorbide product. If a sustained-release isosorbide dinitrate product is used, it should be dosed no more than twice a day with the dose separated by about 6 hours. The use of oral sustained-release nitroglycerin capsules has been considerably reduced with recognition of nitroglycerin tolerance. However, nitroglycerin patches are still regularly used. When nitroglycerin patches were first released, patients were instructed to place a patch on the body and keep it there for 24 hours, at which time the patch would be replaced by a newer one, meaning the patient was never nitrate-free and, indeed, the patches were eventually proven not to be effective when used in this manner. Once nitroglycerin tolerance became appreciated and it was recognized that such patches should be pulled off after being applied for 12 hours to allow for a nitrate-free period of time, patch efficacy was demonstrated. Patches should not be cut or reused.

Because of the availability of the patch, nitroglycerin ointment is not used as commonly as in the past. When it is used, ointment is dosed by the length (typically 0.5 to 2.0 inches) using application paper with a ruler marked on it. The ointment is squeezed out of a toothpaste-like tube and applied every 6 to 8 hours. This dosing approach does lead to some inconsistency with the dosing, mostly related to how one squeezes ointment out of the tube. That said, all nitroglycerin paste should be wiped off the patient’s body each day to allow for a 12-hour nitrate-free period. Two methods to enhance the absorption of nitroglycerin ointment into the body are to spread the ointment out as much as possible and cover it with cellophane. If the nitroglycerin ointment is on a patient but not covered over by cellophane, others should assure they quickly wash any part of their body that came into contact with the ointment to avoid experiencing any nitrate-related headaches. Table 2 has the various commonly-used organic nitrate products available, clinically relevant doses, and proper dosing intervals that should be used to avoid inducing nitrate tolerance.
For most patients with stable angina, it is most practical for the nitrate-free interval to be at night, when the patient is not exerting. However, some patients suffer from nocturnal angina or angina early in the morning upon waking. In these patients, the nitrate-free interval should be during the day, and the patient can take a dose of sustained-release isosorbide mononitrate at bedtime, or apply a nitroglycerin patch at bedtime (which is removed in the morning a few hours after awakening).

Table 2. Organic Nitrates, Dosage Form, Onset, Duration, and Typical Dosing

<table>
<thead>
<tr>
<th>Nitrate Product</th>
<th>Dosage Form</th>
<th>Onset (min)</th>
<th>Duration</th>
<th>Typical Dose</th>
<th>Dosing Frequency (Non-concentrically)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroglycerin</td>
<td>Oral, sustained-release</td>
<td>20-45</td>
<td>2-6 hours</td>
<td>6.5-9.0 mg</td>
<td>TID</td>
</tr>
<tr>
<td></td>
<td>2% Topical ointment</td>
<td>15-60</td>
<td>3-8 hours</td>
<td>0.5-2.0 inches</td>
<td>BID-TID</td>
</tr>
<tr>
<td></td>
<td>Transdermal patch</td>
<td>30-60</td>
<td>8-12 hours</td>
<td>0.4-0.8 mg/hour</td>
<td>Apply daily &amp; then remove after 12 hours</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>Oral, immediate-release</td>
<td>15-45</td>
<td>3-6 hours</td>
<td>10-40 mg</td>
<td>BID-TID</td>
</tr>
<tr>
<td></td>
<td>Oral, sustained-release</td>
<td>60-90</td>
<td>10-14 hours</td>
<td>40-80 mg</td>
<td>QD-BID</td>
</tr>
<tr>
<td>Isosorbide</td>
<td>Oral, immediate-release</td>
<td>30-60</td>
<td>3-6 hours</td>
<td>20 mg</td>
<td>BID</td>
</tr>
<tr>
<td>mononitrate</td>
<td>Oral, sustained-release</td>
<td>60-90</td>
<td>10-14 hours</td>
<td>60-120 mg</td>
<td>QD</td>
</tr>
</tbody>
</table>


Sublingual nitroglycerin tablets, spray, and powder are used to treat acute attacks of all three types of angina as well as to prevent stable angina if given about 5 minutes before an event known to precipitate angina in a patient. The onset of effect of these products is within 5 minutes and the duration of effect generally lasts 20-30 minutes. The sublingual 0.4 mg tablets are the mainstay, but the nitroglycerin spray (0.4 mg/puff) may have a role in patients who do not have the dexterity of their hands and fingers to open up and sort through the small sublingual nitroglycerin tablets placed in a small bottle. Unfortunately, the nitroglycerin spray is considerably more costly than the tablets. When using the spray, it is important to educate patients that they are to spray on or underneath the tongue and are not to inhale the spray. Most recently, packets containing 0.4 mg of nitroglycerin powder became available. The thought is that nitroglycerin powder provides a higher peak concentration relative to the other sublingual products but its price has currently limited its routine use in clinical practice. When the powder is used, it should be placed under the tongue and the patient should be instructed not to swallow until all of the powder has been dissolved. The patient should not spit or rinse the mouth for 5 minutes after taking the powder.

Common adverse effects associated with organic nitrates are lightheadedness, dizziness, headaches, and hypotension. Headaches can be treated with analgesics until tolerance to them occurs. Due to the fact that organic nitrates may induce hypotension, it should be suggested to patients that they sit down prior to using SL nitroglycerin and avoid standing after using a sublingual product for a period of time.
A serious drug interaction associated with organic nitrate use is that their pharmacological effects can be prolonged by phosphodiesterase type-V (PDE-V) inhibitors, the agents used to treat erectile dysfunction and pulmonary arterial hypertension. Organic nitrate use leads to the production of cGMP which induces the desired hemodynamic vasodilatory response of the nitrates. PDE-V metabolizes cGMP, so PDE-V inhibitors prolong the effects of cGMP and their concomitant use with organic nitrates could lead to an excessive drop in blood pressure. PDE-V inhibitors should not be used in people who routinely take organic nitrates. More specifically, one should not use organic nitrates for at least 12 hours after using avanafil, at least 24 hours after using sildenafil or vardenafil, and at least 48 hours after using tadalafl. One should wait at least 24 hours after an organic nitrate was used before using a PDE-V inhibitor. Organic nitrates also should not be used in patients receiving ticagrelor.

With respect to sublingual nitroglycerin tablets, these tablets are very volatile. The tablets should be kept in the original bottle with the cap tightly closed in an area that is dry and cool, but not in a refrigerator. The cotton contained within the bottle should be removed once the bottle is opened. Once a bottle is opened, consideration should be given to replacing the bottle and its contents after 6 to 12 months to assure the patient is using tablets that have not lost their potency. Potency should not be based on whether or not the patient perceives a burning of the tongue when using the tablets. The patient should be instructed to avoid swallowing oral secretions when using the tablets. With respect to dosing of SL nitroglycerin tablets, the ACC/AHA now advocates using SL nitroglycerin tablets in the following manner in patients with stable angina:5

If the patient’s chest pain is not the patient’s typical stable angina or it is worse, the patient may take a SL nitroglycerin tablet but medical attention should be sought immediately.

If the pain is the patient’s typical stable angina, the patient may take a SL tablet. The pain should improve with time. If the pain is improving but five minutes have passed, a second tablet may be taken. If the pain continued to improve but another five minutes have passed, a third tablet may be taken. If pain is still improving but remains at five minutes after the third tablet was given (15 minutes after the first SL tablet was given), medical attention should be sought immediately. During this scenario, if at any time the pain stopped improving or became worse, medical attention also should be sought immediately.

"Seeking immediate medical attention is generally accomplished by calling 9-1-1.

THIS ENDS “PART 1: ANGINA PECTORIS—REVIEW & UPDATE.” THE NEXT LESSON WILL INCLUDE DISCUSSION OF THE OTHER THREE GROUPS OF ANGINAMEDICATIONS, ALONG WITH DESCRIPTIONS OF OVERALL THERAPEUTIC RATIONALE.

Footnotes


**Bibliography**


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   - Nitroglycerin and,
   - Possibly, oxygen. if hospitalized.

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   - Modification of lifestyle (diet, smoking),
   - Treatment of associated underlying diseases (MI, diabetes, HTN {hypertension}, etc.).
   - Drug therapy
     - Nitrates,
     - Beta-blockers,
     - Calcium-channel blockers, or
     - Ranolazine

In this lesson, and the next, we will discuss a number of factors related to treatment of angina pectoris.

Primarily, we are seeking to (our goals are):

1. Describe the specific families of medications:
   a. Organic nitrates
   b. Beta – receptor blockers
   c. Calcium – channel blockers
   d. Ranolazine
2. Discuss therapeutic rationale
Background descriptions and classification of the disease were discussed in the previous lesson ("Part 1: Angina Pectoris---Review & Update"). Additionally, in this lesson, we provide a detailed synopsis of organic nitrate therapy.

In this lesson ("Part 2: Angina Pectoris---Review & Update"), we provide explanations and information regarding the other 3 classes of angina medications, along with summaries of therapeutic treatment rationale.

**BETA-RECEPTOR BLOCKERS**

Beta-receptor blockers (i.e., beta-blockers) that lack intrinsic sympathetic activity (ISA) are useful in the pharmacotherapy of angina by decreasing myocardial oxygen demand through reducing heart rate and contractility. Pure beta-blockers do reduce coronary blood flow because their pharmacologic activity can induce coronary vasoconstriction. This latter effect explains why beta-blockers, unless they also have the ability to block alpha-receptors such as labetalol and carvedilol, should be avoided in variant angina. Beta-blockers with ISA can actually increase heart rate since they are partial beta-receptor agonists and stimulate beta-receptors to some extent, therefore increasing myocardial oxygen demand; and thus, their use is undesirable to prevent stable angina in most instances.

When dosing beta-blockers to prevent angina, the dose can be increased until they are effective in prevention of angina without lowering the heart rate or blood pressure excessively. A reasonable goal for the lowering of heart rate is to achieve a rate that is at least in the lower 60's and ideally in the high 50's, assuming the patient can tolerate heart rates this low. Adverse effects associated with beta-blocker use include bronchospasm, worsening peripheral vascular disease and Raynaud disease, sexual dysfunction, and CNS disturbances. Many patients with COPD and some patients with asthma do tolerate being on a beta-blocker without experiencing any complications. Beta-blockers may be used in patients with diabetes mellitus, but the patient needs to be made aware that beta-blockers can mask the sympathomimetic response to hypoglycemia. Except for those proven to enhance the survival of patients with systolic heart failure (such as carvedilol and metoprolol succinate), beta-blockers should be avoided in patients with systolic heart failure. When used to treat cardiovascular disease, abrupt discontinuation of beta-blockers has precipitated angina and, in some instances, a myocardial infarction.

A listing of the more commonly-used beta-blockers and their pharmacological properties and general dosing are available in **Table 1**.
Therefore, dihydropyridines reflexively increase heart rate. Typically, calcium channel blockers are divided into three categories: verapamil, diltiazem, and the dihydropyridines. Two examples of commonly-used dihydropyridines are nifedipine and amlodipine. The pharmacological properties of the different classes of calcium channel blockers (as well as beta-blockers and organic nitrates) and their effects on myocardial oxygen supply and demand are available in Table 2. All three categories improve coronary artery blood flow by dilating coronary arteries. All categories dilate peripheral arteries and reduce afterload with dihydropyridines doing so to the greatest extent. None of them dilate veins and, as a result, have no impact on reducing preload. Verapamil and diltiazem directly reduce heart rate while dihydropyridines reflexively increase heart rate in response to their ability to dilate arteries. Therefore, one should be cautious with using a dihydropyridine in the absence of a

<table>
<thead>
<tr>
<th>Product</th>
<th>β1-Receptor Selective</th>
<th>α-Receptor Antagonism</th>
<th>ISAa</th>
<th>Typical Dose (mg)</th>
<th>Dosing Frequency</th>
<th>Predominate route of elimination</th>
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</thead>
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<td>Propranolol</td>
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<td>Pindolol</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>5-20</td>
<td>BID</td>
<td>Hepatic</td>
</tr>
</tbody>
</table>

ISA = Intrinsic sympathomimetic activity (see text for explanation).

a Available in a long-acting once-a-day preparation with a typical dose being 80-160 mg.

b This information relates to immediate-release metoprolol tartrate; an extended-release once-a-day metoprolol succinate product is also available with a typical dose being 50-100 mg.

c Available in a constant-release once-a-day preparation with a typical dose being 40-80 mg.

d Also causes peripheral vasodilation by stimulating nitric oxide release.


In the past, atenolol was a very commonly-used beta-blocker because it was relatively long-acting and beta1-selective. Beta1-selective agents are less apt to induce bronchospasm and peripheral vasodilation in the body and place patients at risk for experiencing symptomatic sinus bradycardia. In addition, a retrospective analysis has suggested that atenolol enhances morbidity and mortality. For these reasons, metoprolol use has become even more common, especially with the availability of the once-a-day extended-release succinate salt. Recall that metoprolol tartrate is given twice a day.

If hypertension is a concurrent concern with the angina, carvedilol or labetalol may be preferred since they have alpha-receptor blocking activity in addition to their beta-receptor blocking activity. As discussed above, since beta-blockers with ISA can increase myocardial oxygen demand because they increase heart rate, they are generally not considered in the pharmacotherapy of angina. Nebivolol is a beta-blocker that also can induce vasodilation. It does so by stimulating nitric oxide production, not by blocking alpha-receptors. Any clinical advantage that nebivolol has over traditional beta-blockers has yet to be clearly delineated.

**CALCIUM CHANNEL BLOCKERS**

Calcium channel blockers are also effective in the preventive treatment of angina. Typically, calcium channel blockers are divided into three categories: verapamil, diltiazem, and the dihydropyridines. Two examples of commonly-used dihydropyridines are nifedipine and amlodipine. The pharmacological properties of the different classes of calcium channel blockers (as well as beta-blockers and organic nitrates) and their effects on myocardial oxygen supply and demand are available in Table 2. All three categories improve coronary artery blood flow by dilating coronary arteries. All categories dilate peripheral arteries and reduce afterload with dihydropyridines doing so to the greatest extent. None of them dilate veins and, as a result, have no impact on reducing preload. Verapamil and diltiazem directly reduce heart rate while dihydropyridines reflexively increase heart rate in response to their ability to dilate arteries. Therefore, one should be cautious with using a dihydropyridine in the absence of a
beta-blocker since an increase in heart rate increases myocardial oxygen demand. Nearly all the calcium channel blockers reduce myocardial contractility to some extent with verapamil doing so to the greatest extent. Two calcium channel blockers that do not reduce contractility are amlodipine and felodipine. These two agents can be considered in the pharmacotherapy of angina in patients with systolic heart failure whereas the other calcium channel blockers should be avoided in such patients. Although not germane to the prevention of angina, verapamil and diltiazem block conduction within the AV node. A listing of commonly-used calcium channel blockers, their availability as immediate-release or sustained-release preparations, and their typical dosing are available in Table 3.

Calcium channel blockers can be used in stable, unstable, and variant angina. In fact, they are the drug of choice in the treatment of variant angina. The actual calcium channel blocker to use in a patient can be influenced by the patient’s other medical conditions. If a patient has atrial fibrillation, verapamil or diltiazem are often preferred because of their AV nodal effects. If a patient is already receiving a beta-blocker or has a low heart rate, a dihydropyridine is often preferred. Due to its long half-life and once-a-day dosing, amlodipine is the dihydropyridine most frequently used. Due to their association with enhanced mortality, immediate-release nifedipine use in patients with coronary artery disease should be avoided. All dihydropyridines are typically avoided in patients with hypotension.

Adverse effects of calcium channel blockers vary amongst the different agents. Constipation is most frequently associated with verapamil use. Dihydropyridines are associated with flushing, gingival hyperplasia, and leg edema. All calcium channel blockers have been implicated in causing gastroesophageal reflux and precipitating eczema.

With respect to drug interactions, diltiazem and verapamil can inhibit CYP 3A4 and can reduce the clearance of medications metabolized by this hepatic enzyme and, on occasion, have been associated with increasing digoxin serum concentrations by reducing the clearance of digoxin and/or increase digoxin bioavailability by inhibiting para-glycoprotein efflux pump activity.

Table 2. Pharmacological Comparison of Calcium Channel Blockers and Other Antianginals.

<table>
<thead>
<tr>
<th>Hemodynamic Parameter</th>
<th>Diltiazem</th>
<th>Dihydropyridines</th>
<th>Verapamil</th>
<th>Beta-blockers</th>
<th>Organic nitrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary blood flow</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↓</td>
<td>↑↑</td>
</tr>
<tr>
<td>Afterload -Normative</td>
<td>↓</td>
<td>↓↓↓</td>
<td>↓↓</td>
<td>sl↑</td>
<td>↓</td>
</tr>
<tr>
<td>-Hypertensive</td>
<td>↓↓↓</td>
<td>↓↓↓</td>
<td>↓↓↓</td>
<td>↓↓</td>
<td>↓</td>
</tr>
<tr>
<td>Preload</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>↑</td>
<td>↓↓↓</td>
</tr>
<tr>
<td>Heart rate</td>
<td>↓↓</td>
<td>↑a</td>
<td>↓↓</td>
<td>↓↓↓</td>
<td>↑a</td>
</tr>
<tr>
<td>AV node conduction</td>
<td>↓↓</td>
<td>0</td>
<td>↓↓</td>
<td>↓</td>
<td>0</td>
</tr>
<tr>
<td>Contractility</td>
<td>↓</td>
<td>↓b</td>
<td>↓↓</td>
<td>↓↓↓</td>
<td>↑a</td>
</tr>
</tbody>
</table>

*aThis increase is a reflexive reaction in response to peripheral arterial vasodilation.

*bNearly all dihydropyridines (the exceptions being felodipine and amlodipine) intrinsically reduce contractility; in theory, dihydropyridines may reflexively increase contractility in response to peripheral arterial vasodilation but this has not been demonstrated to be beneficial in the clinical setting.

Adapted from:
Table 3. Typical Dosing of Commonly-used Calcium Channel Blockers

<table>
<thead>
<tr>
<th>Medication</th>
<th>Immediate-Release (IR)?</th>
<th>Typical IR dosing (mg)</th>
<th>Sustained-release (SR)?</th>
<th>Typical SR dosing (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diltiazem</td>
<td>Yes</td>
<td>30-90 TID-QID</td>
<td>Yes*</td>
<td>120-360 QD or 60-180 BID</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Yes</td>
<td>80-120 TID</td>
<td>Yes</td>
<td>240-360 QD</td>
</tr>
<tr>
<td>Dihydropyridines (Nifedipine)</td>
<td>Yes</td>
<td>_b</td>
<td>Yes</td>
<td>30-90 QD</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>Yes</td>
<td>20-40 TID</td>
<td>Yes</td>
<td>30-60 BID</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>Yes</td>
<td>5-10 QD</td>
<td>No</td>
<td>5-10 QD</td>
</tr>
<tr>
<td>Felodipine</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td>5-10 QD</td>
</tr>
</tbody>
</table>

*Available as both a once-a-day preparation and a twice-a-day preparation; assure the correct preparation prescribed is being dispensed.

The newest FDA-approved medication in the pharmacotherapy of angina is ranolazine, even though, it was released more than 10 years ago. The exact mechanism by which ranolazine prevents angina is not fully understood. It is known that, in contrast to organic nitrates, beta-blockers, and calcium channel blockers, ranolazine does not treat angina by reducing heart rate or blood pressure. One thought is that ranolazine impedes the “late sodium current” and thus prevents the enhanced influx of sodium into myocardial cells that can occur during ischemia. With reduced intracellular sodium within ischemic cells, there is a reduced amount of sodium leaving the ischemic myocardial cells, and can allow this for calcium to enter ischemic myocardial cells. Calcium entering ischemic myocardial cells is harmful for several reasons, including disruption of myocardial relaxation and reduced coronary blood flow. Therefore, by reducing the influx of sodium, ranolazine ultimately reduces the influx of “harmful” calcium.

Ranolazine has been demonstrated to reduce angina episodes and prolong exertional activity duration in patients with stable angina. Ranolazine has not been demonstrated to be useful in the treatment of variant angina. Ranolazine comes as an extended-release tablet. Dosing is started at 500 mg BID and may be increased, if needed, to 1 gram BID.

Ranolazine does increase the QT interval and should be used cautiously, if at all, with other medications known to prolong the QT interval. A prolonged QT interval places a patient at risk of having a unique sinusoidal-shaped ventricular dysrhythmia known as torsade de pointes. Other adverse effects of ranolazine include headache, dizziness, GI upset, and constipation. Ranolazine is metabolized to a great extent by CYP 3A4 and to a small extent by CYP 2D6. It is contraindicated to use ranolazine with ketoconazole, itraconazole, clarithromycin, nefazodone, nelfinavir, ritonavir, indinavir, and saquinavir or enzyme inducers such as phenytoin, phenobarbital, carbamazepine, and rifampin. The dose of ranolazine should not exceed 500 mg BID in patients also receiving diltiazem, verapamil, erythromycin, or fluconazole. Ranolazine
does reduce DIGOXIN CLEARANCE.

**PHARMACOTHERAPEUTIC APPROACHES**

**Acute Attacks**

Sublingual nitroglycerin products are useful in the acute treatment of all three types of angina: stable, unstable, and variant. With respect to stable angina, acute attacks can be treated with a sublingual nitroglycerin product, giving a dose every 5 minutes for as many as three doses. As long as the pain is improving and has been relieved by the end of 5 minutes after the third dose of nitroglycerin, there is generally no need to seek medical attention. However, if the patient’s stable angina pain stops improving or gets worse, medical attention should be sought immediately. Also, if the initial angina pain is not the patient’s typical stable angina pain, medical attention should be sought immediately.

It should also be noted that the first time a patient experiences angina pain, medical attention should be sought immediately. Such an episode is considered unstable angina and the patient most likely has yet to be prescribed a SL nitroglycerin product. Also of note, chewing 325 mg of aspirin may be of benefit to the patient in such an instance.

**Chronic Prevention**

For the prevention of stable angina, beta-blockers are advocated by expert guidelines as the first pharmacotherapeutic option, especially if the patient has a history of a myocardial infarction or systolic heart failure. The beta-blocker selected should lack ISA (intrinsic sympathomimetic activity). The dose of beta-blocker can be increased as needed as long as the dose does not induce symptomatic bradycardia, hypotension, or other beta-blocker-associated adverse effects described earlier. If hypertension is a concurrent problem, a beta-blocker with alpha-blocking properties may be considered. If a patient is unable to receive a beta-blocker because of a contraindication or intolerance, consideration can be given to a non-dihydropyridine calcium channel blocker, assuming the patient does not have a reduced ejection fraction, since these agents can also lower heart rate as well as dilate coronary arteries. Recall that using a dihydropyridine in the absence of a beta-blocker may result in an increase in heart rate, an effect that is not desired in the treatment of angina.

A reasonable second drug to add to someone receiving a beta-blocker is a calcium channel blocker or an organic nitrate. Both can lower a patient’s blood pressure, but an organic nitrate has less propensity to do so. With respect to what calcium channel blocker to use, assuming the patient’s heart rate is already low due to maximizing the patient’s beta-blocker dose, a dihydropyridine such as amlodipine would be reasonable. With respect to what organic nitrate to use, the use of once-a-day sustained-release isosorbide mononitrate is a very worthy option. The dose of whichever medication is selected can be increased as needed for as much as the blood pressure will allow and/or the patient’s ability to tolerate the medication. If a low blood pressure prevents one from adding either medication, then ranolazine becomes a worthy consideration since it has minimal impact on the hemodynamic parameters. Ranolazine has traditionally been reserved as a latter selection due to its monthly cost relative to the other antianginal agents.

If a patient was originally on a calcium channel blocker because a beta-blocker could not be tolerated, adding an organic nitrate as the second agent is reasonable. Again, if hemodynamic issues prevent this, then ranolazine can be considered.

In some instances, a patient may be started on two medications initially since no one medication addresses all of the hemodynamic parameters in a positive manner that leads to
prevention of angina. Beta-blockers with an organic nitrate or with a calcium channel blocker may be considered here.

If a patient still has frequent attacks of angina despite therapeutic doses of two antianginals, a third antianginal can be added. If a patient is on a beta-blocker and an organic nitrate, adding a calcium channel blocker is reasonable but, again, one must realize that if the beta-blocker is dosed to achieve a low heart rate, the calcium channel blocker being added needs to lack the propensity to further lower the heart rate. Amlodipine is a very attractive option here. If hemodynamics limit the use of adding on a calcium channel blocker, ranolazine is a worthy consideration.

If angina continues to be an issue despite three medications, assuming all can be tolerated, all four medications may be used. That said, make sure the patient can tolerate the medications, the blood pressure and heart rate are not excessively low, and, if verapamil or diltiazem are being used, assure the dose of ranolazine does not exceed 500 mg BID.

**OTHER PHARMACOTHERAPEUTIC CONSIDERATIONS**

**Non-Pharmacological Treatments of Angina**

Non-pharmacological treatment of stable angina include coronary artery bypass surgery, percutaneous transluminal angioplasty with or without the insertion of an intracoronary stent, transmyocardial revascularization, and the use of enhanced external counter pulsation cuffs. It is beyond the scope of this lesson to further discuss these treatments.

**Prophylactic Use of SL Nitroglycerin**

If a patient knows an activity will precipitate angina, the patient may elect to use a SL nitroglycerin product in a prophylactic manner. The patient should be instructed to take a dose at least 5 minutes prior to initiation of the activity.

**Dual Antiplatelet Therapy**

If a patient receives coronary artery angioplasty followed by insertion of an intracoronary stent, the patient needs to be on both aspirin and a P2Y12 inhibitor such as clopidogrel, prasugrel, or ticagrelor for a period of time. This use of dual antiplatelet therapy protects the patient from thrombosis related to the exposed metal struts of the stent until this metal can be endothelialized. The duration of dual antiplatelet use is constantly being re-evaluated. At the time of this writing, for patients receiving a drug-eluting stent, it would be rare that a course of dual antiplatelet therapy would be less than 6 months in duration and, if the stent was inserted related to unstable angina, preferably be continued for at least 12 months. It should be noted that if a patient received a bare metal stent, dual antiplatelet therapy is needed for only a month in the absence of unstable angina but dual antiplatelet therapy for 12 months would also be preferred if the stent was inserted due to an episode of unstable angina. Patients who experience unstable angina and have angioplasty performed but no stent inserted or do not have angioplasty performed would also benefit from dual antiplatelet therapy for 12 months. In addition to the antiplatelet therapy, these patients should also receive daily aspirin and a statin and be considered for an ACE-inhibitor or ARB (angiotensin II receptor blocker). In theory, chronic antianginal pharmacotherapy would not be needed if the procedure was totally successful, but consideration would be given to antianginal pharmacotherapy if chest pain returned despite the procedure.
PHARMACOTHERAPY OF UNSTABLE ANGINA

A calcium channel blocker is the therapy of choice to treat variant angina. If this is insufficient, an organic nitrate may be added but not a beta-blocker since they can induce coronary vasospasm. If additional therapy is needed beyond an initial calcium channel blocker and an organic nitrate, a second calcium channel blocker may be added, preferably one that allows the patient to be ultimately on a dihydropyridine and either verapamil or diltiazem.

Footnotes


Bibliography


Activity Test

Angina Pectoris: Review and Update – Parts 1 & 2

Activity tests must be completed online at www.freeCE.com.
A passing grade of 70 or higher and completion of an online activity evaluation are required to earn credit.

1. Which hemodynamic action enhances myocardial oxygen delivery?
   a. Increasing afterload
   b. Dilating coronary arteries
   c. Reducing myocardial contractility
   d. Reducing heart rate

2. SL nitroglycerin is effective in acutely relieving chest pain due to:
   1. Stable angina  2. Unstable angina  3. Variant angina
   a. 1 and 2 only
   b. 1 and 3 only
   c. 2 and 3 only
   d. 1, 2, and 3

3. What should you counsel the patient when dispensing a sublingual nitroglycerin product?
   a. Inhale deeply as you spray a puff of nitroglycerin lingual spray on your tongue
   b. Remember to replace the cotton back into the bottle after you take out a SL nitroglycerin tablet from the bottle
   c. Start using a new nitroglycerin SL tablet bottle once you fail to experience a burning sensation when you take a tablet from an older bottle
   d. Do not store your SL nitroglycerin tablet bottle in the glove compartment of your car parked outside in the open during summer months

4. Factors that can precipitate an anginal attack include:
   a. Exercise
   b. Anxiety
   c. Stress
   d. Sedentary lifestyle
   e. a, b, c

5. Prinzmetal’s angina is also known as:
   a. Atypical angina
   b. Variant angina
   c. Stable angina
   d. a & b
   e. a, b, c

6. Best treatment option(s) for chronic angina include:
a. Beta-blockers  
b. Nitrates  
c. Calcium-channel blockers  
d. Ranolazine  
e. a, b, c or d

7. Variant angina is caused by:  
a. Stress  
b. Exercise  
c. Coronary vasospasm  
d. Elevated blood pressure  
e. None of these

8. The goal(s) of drug therapy for angina include:  
a. Reduce weight  
b. Decrease oxygen demand  
c. Decrease blood pressure  
d. Increase coronary artery blood flow  
e. None of these

9. Which nitroglycerin dosage form has quickest onset?  
a. Ointment  
b. Patch  
c. SL tablet  
d. Inhaler  
e. All of these

10. It is safe to use nitrates along with verdenafil.  
a. Yes  
b. No

11. Beta-blockers are useful in the treatment of stable angina by:  
a. Decreasing myocardial contractility  
b. Increasing wall tension  
c. Dilating peripheral arteries  
d. Increasing heart rate

12. Ranolazine:  
a. Increases blood pressure  
b. Enhances sodium influx into myocardial cells  
c. Reduces heart rate  
d. Prolongs the QT interval

13. In general, the initial pharmacotherapy to prevent stable angina should be:
a. Pindolol  
b. Nifedipine  
c. Metoprolol  
d. Isosorbide mononitrate  

14. Constipation is a common adverse effect of:  
a. Verapamil  
b. Atenolol  
c. Ranolazine  
d. Amlodipine  

15. A patient with stable angina is on metoprolol 50 mg BID and sustained-release isosorbide mononitrate 90 mg daily. The patient’s heart rate averages 58 bpm and blood pressure averages 102/72 but has no symptoms and feels fine; however, the patient still experiences exertional angina when gardening. Which do you suggest for chronic preventive treatment?  
a. Add amlodipine  
b. Add verapamil  
c. Add ranolazine  
d. Increase the dosing of the sustained-release isosorbide mononitrate to BID  

16. Metoprolol tartrate should NOT be used in patients with:  
a. Stable angina  
b. Unstable angina  
c. Variant angina  
d. None of these  

17. In addition to antianginal medications, what medication from the list below should a patient with stable angina typically be receiving?  
a. Warfarin  
b. Simvastatin  
c. Sumatriptan  
d. Ibuprofen  

18. A reasonable goal for the lowering of heart rate is to achieve a rate that is at least in the lower 60's and ideally in the high 50's, assuming the patient can tolerate heart rates this low.  
a. True  
b. False  

19. The newest FDA approved medication for treating angina is:  
a. Verapamil  
b. Tocix  
c. Ranolazine  
d. Cresaline  
e. Mictriacine
20. Which of these have been used for prevention of angina:
   a. Beta blockers
   b. Calcium channel blockers
   c. Organic nitrates
   d. All of these
   e. None of these