



PHARMACY CONTINUING EDUCATION FROM WF PROFESSIONAL ASSOCIATES

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“Part 1: Angina Pectoris: Review & Update”

September 2018



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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 (Part 1), and the next, we will discuss a number of factors related to treatment of angina pectoris. 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.

This lesson is intended for pharmacists & technicians in all practice settings. The program ID # for this lesson is 0798-0000-18-225-H01-P for pharmacists, and 0798-0000-18-225-H01-T for technicians.

This lesson furnishes 1.25 (0.125 CEUs) contact hours of credit.

Participants completing this lesson by August 31, 2021 may receive full credit. Release date for this lesson is September 1, 2018. This is knowledge-based continuing pharmacy education.

To obtain continuing pharmacy education credit for this lesson, you must answer the questions on the quiz (70% correct required) and return the answers. Should you score less than 70%, you will be asked to repeat the quiz. Computerized records are maintained for each participant.

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The objectives of this lesson are such that upon completion participants will be able to:

For Pharmacists:

- 1. List determinants of myocardial oxygen demand & myocardial oxygen supply.
2. Describe the pharmacology of antianginal medications.
3. Prepare a pharmacotherapeutic plan to prevent stable angina & variant angina from occurring.
4. Identify common adverse effects of antianginal drugs.
5. Counsel patients when dispensing SL nitroglycerin drugs.

For Technicians:

- 1. List determinants of myocardial oxygen demand & myocardial oxygen supply.
2. Describe the pharmacology of antianginal medications.
3. Identify common adverse effects of antianginal drugs.

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## 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”<sup>1</sup>) 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.**

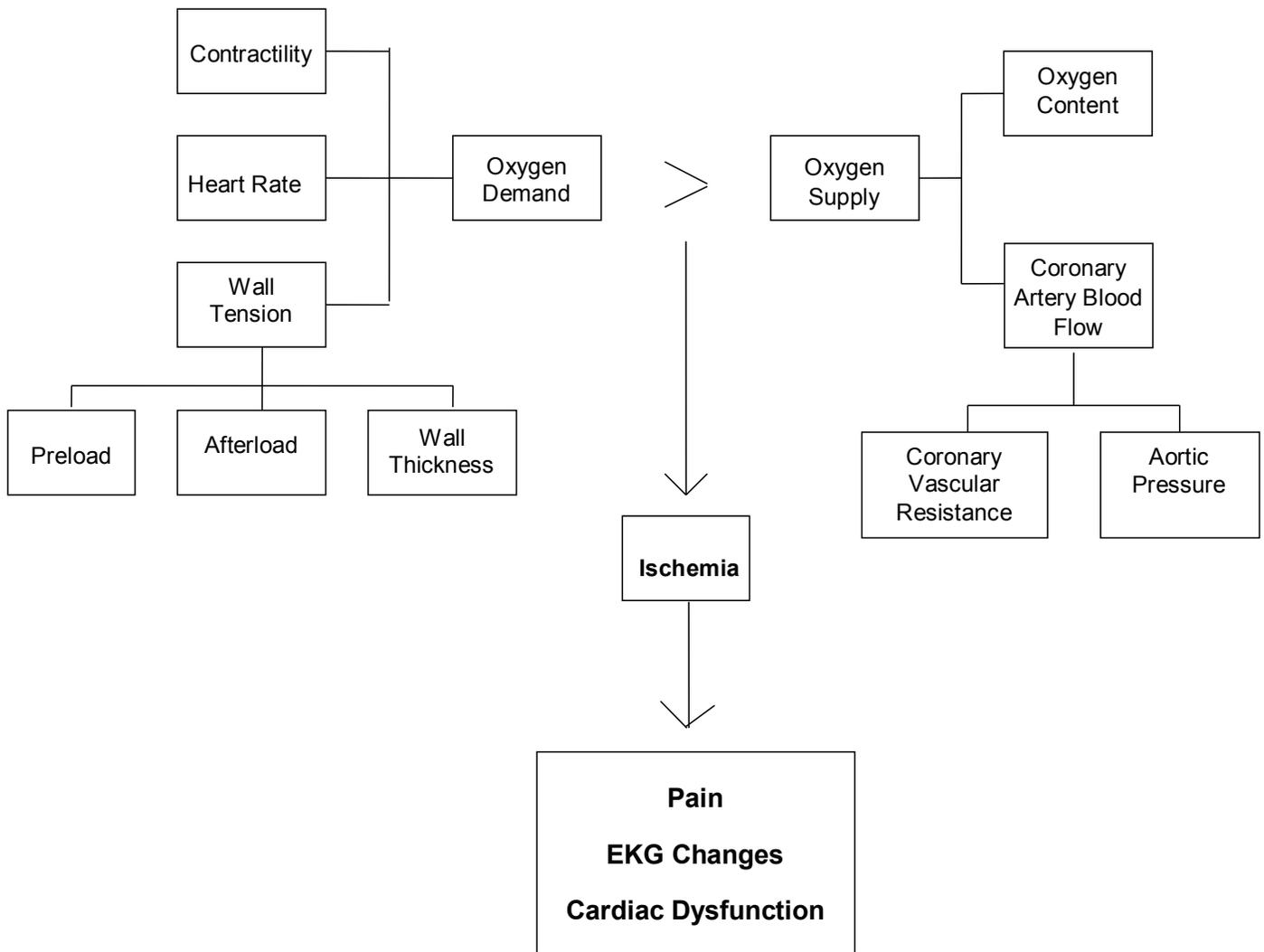
**Table 1. The Determinants of Myocardial Oxygen Demand and Supply**

Myocardial Oxygen Demand	Myocardial Oxygen Supply
Contractility	Oxygen content of blood
Heart rate	Coronary artery blood flow -Coronary vascular resistance - Aortic pressure
Wall tension -Preload* -Afterload** -Wall thickness	

\*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.<sup>2</sup> 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, inflected 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.<sup>3</sup> 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; homocysteine by itself or with folate, vitamin B6, or vitamin B12; garlic; coenzyme Q10; selenium; chromium; and, in post-menopausal 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**

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

Adapted from: Abrams J. The role of nitrates in coronary heart disease. Arch Int Med. 1995;155:357-64. Lexicomp Drug Information Handbook, 26th edition. Wolters Kluwer:2017.

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 tadalafil. 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 riociguat.

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.<sup>4</sup> 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:<sup>5</sup>

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.<sup>a</sup>

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 5 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.

<sup>a</sup>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 DISCUSSIONS OF THE OTHER THREE GROUPS OF ANGINA MEDICATIONS, ALONG WITH DESCRIPTIONS OF OVERALL THERAPEUTIC RATIONALE.**

## Footnotes

1. Netter FH. The CIBA collection of medical illustrations. Volume 5: heart. West Caldwell, NJ:CIBA Medical Education: 1978:223.

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Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2012;126: e354-471.

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**I am a Technician**

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**LESSON EVALUATION**

Please fill out this section as a means of evaluating this lesson. The information will aid us in improving future efforts. Either circle the appropriate evaluation answer, or rate the item from 1 to 7 (1 is the lowest rating; 7 is the highest).

1. Does this lesson meet the learning objectives? (Circle your choice).

- |  |     |    |
|--|-----|----|
| List determinants of myocardial oxygen demand & supply   | YES | NO |
| Describe pharmacology of antianginal drugs               | YES | NO |
| Prepare a pharmacotherapeutic plan of anginal prevention | YES | NO |
| Identify adverse effects of antianginal drugs            | YES | NO |
| Counsel patients regarding SL nitroglycerin products     | YES | NO |

2. Was the program independent & non-commercial? YES NO

	Low Relevance					Very Relevant		
3. Relevance of topic	1	2	3	4	5	6	7	

4. What did you like **MOST** about this lesson? \_\_\_\_\_

5. What did you like **LEAST** about this lesson? \_\_\_\_\_

6. How would you improve this lesson? \_\_\_\_\_

**Please Mark the Correct Answer(s)**

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