1. **What is the most common cause of angina?**

   Angina is the sensation of discomfort experienced during periods of myocardial ischemia or myocardial infarction. It may occur when myocardial oxygen demand exceeds myocardial oxygen supply. Myocardial ischemia and angina are most commonly the result of significant stenosis of one or more coronary arteries. Typically, coronary artery stenosis that is 70% or more of the coronary artery diameter is flow restricting and may cause angina. In patients with chronic stable angina, myocardial ischemia results when myocardial oxygen demand increases, such as during physical exertion. Coronary vasoconstriction, particularly at the site of a preexisting stenosis, can also contribute to myocardial ischemia and produce angina.

2. **What other conditions can cause anginal pain?**

   - Aortic stenosis
   - Hypertrophic cardiomyopathy
   - Hypertensive crisis
   - Tachyarrhythmias and tachycardia (such as caused by hyperthyroidism)
   - Coronary artery anomaly
   - Severe anemia (as a result of decreased oxygen-carrying capacity of the blood)
   - Severe hypoxemia
   - Coronary vasospasm (Prinzmetal’s angina or cocaine induced)
   - Cardiac syndrome X

3. **How is chronic stable angina classified or graded?**

   The most commonly used system is the Canadian Cardiovascular Society system, in which angina is graded on a scale of I to IV. These grades and this system are described in Box 14-1.

4. **What are the three primary antianginal medications used for the treatment of chronic stable angina?**

   - Beta-blockers
   - Nitrates
   - Calcium channel blockers

5. **What are the principal issues regarding the use of beta-blockers?**

   The most commonly used beta-blockers are metoprolol and atenolol, although many others are used. Both generic and brand names are available for many of these agents. Beta-blockers’ principal effects are negative chronotropic (slow heart rate) and, to a variable extent, negative inotropic (decrease cardiac contractility). Both these actions serve to decrease cardiac oxygen demand. Beta-blockers are usually started at a low dose, then titrated upward as tolerated. Primary side effects include excessive bradycardia, prolongation of the PR interval and heart block, exacerbation of congestive heart failure, and exacerbation of severe reactive airway disease. Thus, generally they are not initiated in patients with baseline bradycardia, significantly prolonged PR interval (more than 220–240 msec), acute decompensated heart failure as a result of systolic dysfunction, and severe reactive airway disease. In general, the dose is titrated to control of symptoms or resting heart rate in the 60s (beats/min).
6. When should one primarily use a peripherally acting calcium channel blocker (amlodipine or felodipine), and when should one use a calcium channel blocker that has effects on both the heart and the periphery (verapamil, diltiazem)?

Amlodipine and felodipine are used primarily as second- or third-line antianginal agents in patients already on beta-blockers (and often, also long-acting nitrates). They act mainly as vasodilators, lowering blood pressure and likely having some coronary vasodilating effects. Verapamil and diltiazem, in addition to having vasodilating effects, also have negative chronotropic and negative inotropic effects and can block atrioventricular (AV) conduction. Thus, they may be used instead of beta-blockers in patients with severe reactive airway disease. Generally they are not used in patients already on beta-blockers and are contraindicated in patients with depressed ejection fractions (less than 40%) because of their negative inotropic effects and because studies in the 1980s suggested a worse outcome with their use in such patients.

7. When does one prescribe a long-acting nitrate?

Long-acting nitrates are often prescribed along with beta-blockers as the initial treatments in patients with chronic stable angina (Table 14-1). A nitrate-free interval, usually overnight, is necessary to prevent the development of tolerance to these agents. Once-a-day, long-acting nitrate preparations are ideal in terms of avoidance of nitrate tolerance and patient compliance.

8. When should one consider using ranolazine?

Ranolazine is a newer antianginal agent unlike previous agents. It does not work by affecting heart rate or blood pressure or by coronary artery vasodilation. Its mechanism of action is still not completely understood. In clinical trials (MARISA, CARISA, ERICA), it leads to a modest
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<tr>
<td>Beta-blockers</td>
<td>Negative chronotropy</td>
<td>Extreme bradycardia</td>
<td>Resting bradycardia</td>
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<td>Negative inotropy</td>
<td>AV node block and PR prolongation</td>
<td>Prolonged PR interval (&gt;220–240 msec)</td>
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<td>Exacerbation of acute heart failure</td>
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<td>Bronchospasm</td>
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<td>Long-acting nitrates</td>
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<td>Prolonged PR interval (&gt;220–240 msec)</td>
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<td>Calcium-channel blockers:</td>
<td>Peripheral vasodilation</td>
<td>Extreme bradycardia</td>
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<td>verapamil and diltiazem</td>
<td>Coronary vasodilation</td>
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<td></td>
<td>Negative chronotropy</td>
<td>Blood pressure reduction</td>
<td>Ejection fraction &lt; 40%</td>
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<td></td>
<td>Negative inotropy</td>
<td>Exacerbation of chronic and acute heart failure</td>
<td>Usually, patients already on beta-blockers</td>
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<tr>
<td>Calcium-channel blockers:</td>
<td>Peripheral vasodilation</td>
<td>Blood pressure reduction</td>
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<td>amlodipine and felodipine</td>
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increase in exercise tolerance (approximately 30 seconds) and decreases in angina and sublingual nitroglycerin (SL NTG) use. It is generally a third-line agent in patients with continued significant angina despite traditional antianginal therapy. Its major side effect is QT prolongation. Thus, it should not be used in patients with baseline QT prolongation or those on other medications that can prolong the QT interval. Patients initiated on this drug should have their QT duration monitored periodically with 12-lead electrocardiograms (ECGs). The usual starting dose is 500 mg orally twice a day (PO BID), which can be increased to 1000 mg PO BID. Generally this drug should be prescribed only by cardiologists.

9. Should everyone with chronic stable angina be prescribed sublingual nitroglycerin (or nitroglycerin spray)?
Yes. This is the standard of care. Patients should be instructed on how to use SL NTG—generally one pill every 5 minutes up to a maximum of three tablets. Patients with chronic stable angina should be instructed to call 911 and seek immediate medical attention if their angina is not relieved after three pills or 15 minutes (or after one pill or 5 minutes in the case of patients with a history of acute coronary syndrome [ACS]).

10. Which patients with chronic stable angina should be referred for stress testing or cardiac catheterization?
The two purposes of stress testing are diagnosis of coronary artery disease (CAD) and prognosis in patients with presumed or known CAD. If the pretest likelihood of CAD is extremely high (e.g., a 64-year-old man with multiple cardiac risk factors and classic exertional anginal symptoms has a pretest probability of CAD of at least 94%), there is little diagnostic value in stress testing, because even a negative stress test would not significantly change the true probability that the patient has CAD. For example, in patients with a pretest probability of having CAD of 90%, a negative exercise stress test lowers the post-test probability of CAD to only 83%.

Many experts and the American College of Cardiology/American Heart Association (ACC/AHA) guidelines on chronic stable angina advocate in many cases obtaining a stress test for prognostic reasons—if the stress test reveals low-risk findings, then the patient can be managed medically, whereas if the stress test reveals high-risk findings, the patient is referred for cardiac catheterization. Although this latter strategy is often used, it is important to note that percutaneous coronary intervention has never been shown to reduce the risk of myocardial infarction (MI) or death in patients with chronic stable angina. Referral for cardiac catheterization is appropriate if the patient’s symptoms cannot be adequately controlled with antianginal medications, the patient develops unstable symptoms, or the patient has a depressed ejection fraction (less than 40%).

Stress testing performed for diagnostic purposes is usually performed with the patient off antianginal therapy, whereas stress testing performed for prognostic purposes may sometimes be performed with the patient on antianginal agents.

11. What other medications, besides antianginal medications, should patients with chronic stable angina be prescribed?
- Sublingual nitroglycerin, as described earlier
- Aspirin (75–325 mg qD)
- Statin therapy to lower low-density lipoprotein (LDL) cholesterol levels to less than 70 to 100 mg/dl
- Angiotensin-converting enzyme (ACE) inhibitor if diabetic, hypertension, chronic kidney disease, and left ventricular ejection fraction is less than 40%, unless contraindicated
- Clopidogrel after an episode of acute coronary syndrome and after bare-metal stent implantation, usually for 1 year, and after drug-eluting stent implantation for at least 1 year. Other newer antiplatelet agents that block the P2Y12 platelet receptor may be used instead
of clopidogrel at the physician’s discretion. The CHARISMA study, which assessed long-term clopidogrel use (in addition to aspirin) in patients with atherosclerosis or with high-risk features, demonstrated no overall benefit of this strategy, although it did show a trend toward benefit in those with preexisting atherosclerosis. However, this latter finding in this subgroup analysis was not statistically significant, and the general approach to indefinitely treating all patients with atherosclerosis with long-term dual antiplatelet treatment has not been embraced by most of the medical community.

- Annual influenza vaccination

12. Is chelation therapy of any benefit in patients with coronary artery disease?
   No.

BIBLIOGRAPHY, SUGGESTED READINGS, AND WEBSITES