Module 3. Current practice of internal medicine.
Contents module № 1.
Theme 9. MANAGEMENT OF THE PATIENTS WITH STABLE ANGINA

Guidelines for students and interns

Модуль 3. Сучасна практика внутрішньої медицини.
Змістовний модуль №1.
Тема 9. ВЕДЕННЯ ХВОРОГО ЗІ СТАБІЛЬНОЮ СТЕНОКАРДІЄЮ

Методичні вказівки
для студентів та лікарів-інтернів

Рекомендовано
вченю радою ХНМУ.

Харків
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MANAGEMENT OF PATIENTS WITH STABLE ANGINA

General Outcome
The students should be able to manage a patient with stable angina, list and describe specific drugs in each category of anti-anginal and anti-ischemic medication and uses for each

The aim of this topic is to provide the student with an opportunity to:
• Provide a basic overview of the pathophysiology, diagnosis, and classification of angina.
• Evaluate guideline-based management strategies for the treatment of angina.
• Discuss the role of beta-blockers, calcium channel blockers, nitrates, metabolic medical agent and ivabradine in the treatment of angina.
• Develop an individualized pharmacotherapy and monitoring plan for the management of chronic stable angina, when given specific patient information.
• Develop an understanding of the principles of pharmacology of beta-blockers, calcium channel blockers, nitrates, metabolic medical agent and selective heart rate-lowering agents.

Specific Learning Outcomes:
Upon successful completion of this unit, the students should be able to:
1. List and describe the anti-anginal agent classifications.
2. Describe the mechanism of anti-anginal and anti-ischemic drugs action and main pharmacological effects.
3. List and describe anti-anginal and anti-ischemic drugs and give specific examples of each.
4. Describe the adverse effects and contraindications of beta-blockers, calcium channel blockers, nitrates, metabolic medical agent and ivabradine.

Specification of the theoretical question for training of “Clinico-pharmacological characteristics of anti-anginal and anti-ischemic medical agents”

Student must know:
1. How do antianginal drugs affect myocardial oxygen supply and demand, and how do these actions reduce chest pain?
2. Which antianginal drugs are used to treat the following types of angina, and what actions of these drugs make them suitable for a particular form of angina?
   a) chronic stable angina;
   б) printzmetal's variant angina;
   в) unstable angina.

   What are the mechanisms by which organic nitrate nitrodilator drugs dilate veins and how does this relieve angina?
2. What is drug tolerance and how does tolerance to organic nitrates affect dosing?
3. What are common side-effects to organic nitrates?
4. Which calcium-channels blockers are approved for angina and how do these drugs reduce anginal pain?
5. What preexisting conditions in patients can be made worse by administering calcium-channel blockers?
6. Why should calcium-channel blockers not be given with beta-blockers?
7. Why are beta-blockers useful antianginal drugs?
8. What are the mechanisms by which beta-blockers reduce heart rate and contractility (inotropy)?
9. Define the following characteristics for beta-blockers:
   a) selective vs. non-selective beta-blockade;
   b) intrinsic sympathomimetic activity;
   c) membrane stabilizing activity.
10. What are some common side-effects and contraindications for beta-blockers?

TESTS AND ASSIGNMENTS FOR SELF-ASSESSMENT BASIC LEVEL OF KNOWLEDGE: MULTIPLE CHOICE QUESTIONS
(CHOOSIE THE CORRECT ANSWER/STATEMENT)

1. A 63 y.o. woman complains of sneezing heart pain irradiating to the left arm and neck, dyspnea. On examination: AP 140/90 mm Hg, heart rate 86 bpm, heart boarders +1,5 cm left side, sounds are muffled, soft systolic murmur at apex and Botkin's area; sporadic extrasystoles. Liver isn't palpated, there are no edema. Blood test: WBC - 6, 7* 10^9/L, sedimentation rate-6 mm/hour? General cholesterol 6,4 mmol/l. What is the most probable diagnosis?
   A. Acute myocarditis.  
   B. Rheumatism, mitral insufficiency.  
   C. Climacteric myocardiodystrophia.  
   D. Ischemic heart disease, angina pectoris.  
   E. Hypertrophic cardiomyopathy.

2. A 61 y.o. man complained of sneezing and substernal pain on exertion. In the last 2 weeks such pain appeared at rest, with increased frequency, and couldn't be suppressed by 1 tablet of nitroglycerin. What is the most likely diagnosis?
   A. Angina pectoris of a new onset.  
   B. Myocarditis.  
   C. Stable angina pectoris of the III functional class.  
   D. Unstable angina pectoris.  
   E. Radiculitis.
3. A 52 y.o. patient with previously functional Class II angina complains of 5 days of intensified and prolonged retrosternal pains, decreased exercise tolerance. Angina is less responsive to Nitroglycerinum. Which of the following diagnosis is most likely?

A. Cardialgia due to spine problem.
B. Myocardial dystrophy.
C. IHD. Functional Class II angina
D. Myocarditis.
E. IHD. Unstable angina.

4. A patient with coronary artery disease was admitted to the cardiological department. For angina attack prevention a drug from the group of β-adrenoceptor blockers was administered. What drug is it?

A. Morphine hydrochloride.
B. Oxytocin.
C. Metoprolol.
D. Furosemide.
E. Atropine sulfate.

5. The patient has severe 3-vessel coronary artery disease and is referred for bypass surgery. The surgeons are concerned about his severely decreased LV function. Which of the following tests will NOT help predict improvement in cardiac function and survival after revascularization?

A. Dobutamine echocardiography.
B. Electron beam computed tomography.
C. Fluorodeoxyglucose positron emission tomography.
D. Persantine sestamibi imaging.
E. Rest-rest thallium.

**ANSWERS**

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<td>E</td>
<td>C</td>
<td>B</td>
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</table>
Introduction

Ischemic heart disease is the leading cause of death and morbidity all over the world, with a mortality rate higher than that of all cancers combined. The annual mortality rate for patients with chronic angina is approximately 2%, but is much higher in certain subsets of patients, particularly the elderly.

A definition of Angina:
Angina or Angina Pectoris, is used to describe a clinical syndrome of pressure like chest pain precipitated by activities such as exercise or emotional stress which increase myocardial oxygen demand. Classical stable angina is predictable in onset, reproducible and relieved by rest or glyceryl trinitrate (GTN). Although angina can be caused by other cardiovascular conditions which reduced myocardial perfusion is due to arterial narrowing resulting from underlying atherosclerotic coronary heart disease. A small minority of patients have objective evidence of myocardial ischemia in the absence of any obvious abnormality of the coronary arteries.

Stable angina tends to develop over a period of several weeks without major deterioration allowing assessment in the outpatient setting. This is in contrast to the more severe changes of plaque erosion and rupture occurring as part of the spectrum of acute coronary syndrome.

Angina can be graded by severity on a Canadian Cardiovascular Society (CCS) class scale of IV/

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
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<tbody>
<tr>
<td>Class 1</td>
<td>Ordinary activity such as walking or climbing stairs does not precipitate angina</td>
</tr>
<tr>
<td>Class 2</td>
<td>Angina precipitated by emotion, cold weather or meals and by walking up stairs</td>
</tr>
<tr>
<td>Class 3</td>
<td>Marked limitations of ordinary physical activity</td>
</tr>
<tr>
<td>Class 4</td>
<td>Inability to carry on any physical activity without discomfort- anginal symptoms may be present at rest</td>
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Angina is also associated with major social and economic burdens. Because of poor symptom control and hemodynamic, as well as other drug side effects, angina is commonly associated with a poor quality of life (QOL). No new class of drug has been available for angina treatment in more than two decades, and current medications frequently fail to provide adequate symptom control. Thus, the majority of patients are taking two or three antianginal medications. New agents that modulate myocardial metabolism have shown antianginal efficacy, a favorable side-effect profile, and an absence of hemodynamic effects.
Anti-anginals are pharmaceutical agents used to treat angina pectoris, a disease of the coronary arteries. The coronary arteries supply oxygen-laden blood from the left ventricle to all heart muscles including those of the ventricles themselves. Coronary arteries maintain cardiac function and are expected to adapt to sudden demands on the heart due to enhanced activity. Typically the arteries respond to this sudden demand by dilatation. However, it is possible that they may have developed atheromatous deposits that restrict the flow of blood even under normal conditions and more so under strenuous activity. The heart has to exert more to increase the blood flow through such atherosclerotic arteries. In this situation the heart is deprived of oxygen and feels suffocated, a condition called ischemic. Angina is the principal symptom of an ischemic heart creating a sudden, severe pain that originates in the chest and radiates through the left shoulder down the arm.

Myocardial ischemia is the result of imbalance between myocardial oxygen supply and demand. Anti ischemic drugs produce their beneficial effect by either improving myocardial O2 supply or decreasing demand or both.

Table 2.  
**Main causes of decreased myocardial oxygen supply or increased myocardial oxygen demands**

<table>
<thead>
<tr>
<th>Causes of decreased myocardial oxygen supply</th>
<th>Causes of increased myocardial oxygen demands</th>
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</table>
| 1. Progressive narrowing of epicardial coronary arteries by atherosclerotic (ASO) plaques.  
2. Sudden enlargement of ASO plaque.  
3. Sudden narrowing or complete occlusion of an epicardial coronary artery by an intracoronary thrombus following rupture or erosion of an ASO plaque.  
4. Coronary artery spasm usually in association with ASO disease e.g. vasospastic (Prinzmetal) angina.  
5. Microvascular disease: disease of the small intramyocardial arteries secondary to abnormalities in vasomotor tone as in syndrome X or secondary to coronary microemboli from thrombi or ruptured atherosclerotic plaque in epicardial coronary artery.  
2. Arterial pressure.  
3. Myocardial inotropic state (contractility).  
4. LV wall stress which is determined by the internal LV cavity dimensions and intraventricular pressure. LV dilatation will increase wall stress.  
5. An increase in LV muscle mass (LVH).  
6. Metabolic: free fatty acids, the major source of myocardial fuel require more oxygen to generate an equivalent amount of ATP when compared to glucose. |
The following are the major determinants of myocardial oxygen demand. Any increase of one or more of these factors will increase demand. Though atherosclerosis is the chief cause of coronary artery disease producing narrowing of coronary arteries, myocardial ischemia can occur in patients with normal coronary angiograms:

1. Coronary spasm.
2. Microvascular disease.
4. Pulmonary hypertension.
5. Left ventricular hypertrophy: hypertrophic cardiomyopathy, arterial hypertension.

Majority of these conditions are more common in women than in men.

Any factor that causes an imbalance between myocardial oxygen supply and demand can provoke ischemia. Myocardial oxygen requirements rise with increases in heart rate, contractility, or left ventricular wall stress. Myocardial oxygen supply is determined by coronary artery flow and myocardial oxygen extraction. Anti-anginal medications are the mainstay of anti-ischemic management and act to correct the balance between myocardial supply and demand by increasing coronary blood flow, reducing myocardial oxygen requirements, or both.

**Diagnosis**

Base the diagnosis on the history of retrosternal chest pain with a characteristic quality and duration. It may radiate to arms, neck, jaw, epigastrium or back. It is usually provoked by exercise or excitement and relieved by rest or GTN. Cold weather, a heavy meal or high altitude can precipitate angina. Variant (Prinzmetal) angina, is rare, it occurs at rest, is often more severe and prolonged and responds less well to GTN. Angina without chest pain may manifest as dyspnea on exertion. It is more likely to occur in those with diabetes or who have had a CABG.

**Atypical angina (vasospastic, Prinzmetal’s angina)** is a rare form of angina and is more commonly prevalent in women. Prinzmetal first described it. Unlike stable angina, coronary spasm has no relation with exercise but is the cause of myocardial ischemia. On the contrary, the pain is sometimes relieved with exercise. The pain usually comes while resting or sleeping. The electrocardiogram may show ST elevation. The pain is relieved by glycerine trinitrate. Specialist investigations using provocative tests (e.g., hyperventilation, cold-pressor testing, or ergometrine challenge) may be required to make the diagnosis. Ventricular arrhythmia and heart block may occur. Calcium channel blockers (CCBs) may prevent coronary spasm, but beta-blockers may worsen the
symptoms. However, patients may remain symptom-free for months or years. Like unstable angina, there is a subsequent risk of heart attack.

Investigations may be helpful in elucidating the cause of the angina and the severity of the coronary artery occlusion but they cannot refute a diagnosis based on a clear history.

Assessment

History and examination:
1. Ask about smoking and exercise.
2. Ask about other risk factors for CVD (family history, diabetes, hypertension, hyperchoesterolaemia and ethnic origin if relevant).
3. Check BP. Treat if 2 readings over 2 monthly intervals show it is = 140/90. Aim for <140/85. Blood pressure targets are lower (130/80) if the patient has established CVD, chronic renal disease or diabetes.
4. Check the heart for valvular disease. Any aortic systolic murmur needs assessment for aortic stenosis unless the patient’s general condition is too poor to consider even a valvotomy.
5. Check for evidence of arrhythmia, heart failure, and peripheral vascular disease.
6. Check weight, height and BMI.
7. Waist circumference may be used to assess central obesity.

Baseline investigations:
- Hb; CBC
- TFT, LFTs; CK; U&Es;
- fasting blood sugar;
- fasting lipid profile;

Investigations for confirming diagnosis
- Resting electrocardiogram (ECG)
- ECG stress testing
- Ambulatory ECG monitoring (Holter monitoring)
- Echocardiography at rest
- Stress echocardiography
- Myocardial perfusion scintigraphy
- Radionuclide angiography during exercise
- Coronary angiography
- Intravascular ultrasound

Clinical history and examination are very important. The speed with which the investigations are undertaken depends on the urgency, taking into account the age of the patient, the presence of other risk factors, the severity of chest pain, the likelihood of the diagnosis, and the findings on clinical examination. Chest x-ray helps to exclude congestive heart failure, valvular lesions, pericardial disease, or aortic dissection/aneurysm. However, the use of routine chest x-ray is not well established.
Blood tests should include tests for anemia, thyroid function (TFT), urea, electrolytes, lipid profile, glucose and cardiac enzymes, troponin, erythrocyte sedimentation rate (ESR) and high-sensitivity C-reactive protein (hsCRP). Resting electrocardiogram (ECG) is indicated in all cases as an initial test, although a normal ECG does not exclude CAD. Evidence of a prior Q-wave on ECG and evidence of left ventricular hypertrophy also increases the probability of angina. If the resting ECG is normal, depending on the likelihood of the diagnosis, treadmill stress testing is arranged.

The treadmill test is most valuable when the pretest probability is intermediate, for example, when a 50-year-old man has atypical angina and the probability of CAD is about 50%. When the probability of CAD is high, a positive test result only confirms the high probability of disease, and a negative test result may not decrease the probability of CAD enough to make a clinical difference. When the probability of CAD is very low, a negative test result only confirms the low probability of disease; a positive test may not increase the probability of disease enough to make a clinical difference. If there is high suspicion of CAD, then exercise testing could be combined with thallium testing (myocardial perfusion imaging [MPI]) or angiography. Exercise ECG (also known as a stress test or Exercise Tolerance Test (ETT); The exercise ECG as a key investigation. This is in order to single out those patients who might benefit from angioplasty or CABG.

**Reasons for not performing an exercise ECG:**
- the patient is physically incapable of performing the test;
- the patient has some other illness or condition which would make them unsuitable for coronary artery surgery or Percutaneous coronary intervention;
- the diagnosis is in doubt (an exercise ECG has low specificity for making the diagnosis of angina);
- symptoms are uncontrolled by medical treatment (such patients should be referred for angiography).

ECG shows Left Bundle Branch Block which makes Exercise ECG inappropriate

*Myocardial Perfusion scan*; may be requested by a Cardiologist for those patients unable to undergo ETT. Myocardial perfusion scintigraphy has been recommended as the initial diagnostic tool for people with suspected Coronary Artery Disease (CAD) for whom ETT poses particular problems. Echocardiography is usually not indicated in most patients, unless valvular disease or hypertrophic cardiomyopathy is suspected. Coronary angiography is very important in the diagnosis where myocardial ischemia is suspected and noninvasive testing is contraindicated.
The recommendations are for cardiac stress imaging as the initial test in the following situations:

1. Exercise ECG for the diagnosis of obstructive CAD.
2. Exercise myocardial perfusion imaging or exercise echocardiography when the patient has intermediate pretest probability of CAD or has either Wolff-Parkinson-White syndrome or more than 1mm of rest ST depression.
3. Exercise MPI or exercise echocardiography if there is a past history of revascularization.
4. If a patient is not able to exercise, then adenosine or dipyridamol MPI or dobutamine echocardiography is indicated if patient has either an intermediate pretest probability of CAD or a past history of revascularization.

When the probability of severe angina is low, noninvasive tests are most appropriate. However, when the pretest probability is high, direct referral for coronary angiography is a suitable choice. Stress imaging tests such as the radionuclide MPI test or two dimensional echocardiography at rest and during stress are valuable for the purpose of risk stratification and planning the best route of management. A normal thallium scan is highly indicative of a benign prognosis even in patients with known CHD. Coronary angiography is usually not indicated unless other measures show high risk. Stress echocardiography is also able to provide additional prognostic information.

Coronary angiography is most useful in the following situations:

1. If a patient suspected of CAD survived sudden cardiac death
2. Uncertain diagnosis after noninvasive tests
3. If the patient is unable to undergo noninvasive tests.
4. Patients in whom coronary artery spasm is suspected and provocative tests may be necessary.
5. Patients with a pretest probability of left main stem or three vessel disease.
6. Occupational requirement for a firm diagnosis.
7. To exclude anatomical anomalies in young patients as the cause of angina.
8. Those with atypical symptoms but a strongly positive exercise ECG.

Differential diagnosis of the symptoms

If all the above mentioned cardinal features are present, or even only the first two are quite typical, then the diagnosis of chronic stable angina is virtually assured. Often, however, the picture is not so clear-cut and other diagnoses must be considered (table 4).
### Table 3

**Definitions of stable angina and acute coronary syndromes**

<table>
<thead>
<tr>
<th></th>
<th>Prinzmetal Angina</th>
<th>Stable Angina</th>
<th>Acute Coronary Syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
<td></td>
<td>Unstable Angina</td>
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<tr>
<td></td>
<td>Similar symptoms as others.</td>
<td>Substernal chest pain (heaviness, tightness, pressure), nausea, diaphoresis, shortness of breath.</td>
<td>Same as stable angina but may be more intense</td>
</tr>
<tr>
<td></td>
<td>Precipitating factors: occur at rest, often in the morning hours</td>
<td>On physical examination, usually tachycardia with elevated blood pressure</td>
<td></td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td>Conditions that trigger vasospasm: - adrenaline surge - drug induced: cocaine</td>
<td>Risk factors that cannot be changed: heredity, gender (male &gt; female), race, age (men &gt; 45 y, women &gt; 55 y)</td>
<td>Same as stable angina</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk factors that can be modified: smoking, hypertension, hyperlipidemia, diabetes, low HDL</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Other contributing factors: obesity, lack of exercise, excessive stress</td>
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<tr>
<td><strong>Pathophysiology Vasospasm</strong></td>
<td></td>
<td>Atherosclerosis</td>
<td>Atherosclerosis or plaque rupture</td>
</tr>
<tr>
<td><strong>ECG changes</strong></td>
<td>ST ↑, ST ↓, T-wave inversion</td>
<td>ST ↑, ST ↓, T-wave inversion</td>
<td>ST ↑, ST ↓, T-wave inversion</td>
</tr>
<tr>
<td><strong>Cardiac enzymes</strong></td>
<td>No change</td>
<td>No change</td>
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</tbody>
</table>

### Table 4

**Alternative diagnosis to angina for patients with chest pain**

<table>
<thead>
<tr>
<th>Nonischemic Cardiovascular</th>
<th>Pulmonary</th>
<th>Gastrointestinal</th>
<th>Chest Wall</th>
<th>Psychiatric</th>
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</thead>
<tbody>
<tr>
<td>Acute dissective</td>
<td>Pulmonary embolus</td>
<td>Esophageal</td>
<td>Costochondritis</td>
<td>Anxiety disorders</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>Pneumothorax</td>
<td>Esophagitis</td>
<td>Fibrositis</td>
<td>Hyperventilation</td>
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<tr>
<td></td>
<td>Pneumonia</td>
<td>Spleen</td>
<td>Rib fracture</td>
<td>Panic disorder</td>
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<td></td>
<td>Pleuritis</td>
<td>Reflex</td>
<td>Stenocardiac arthritis</td>
<td>Primary anxiety</td>
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<td>Biliary</td>
<td>Herpes zoster</td>
<td>Affective disorders (e.g., depression)</td>
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<td></td>
<td></td>
<td>Colic</td>
<td>(before the rash)</td>
<td>Somatiform disorders</td>
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<td>Cholecytis</td>
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<td>Thought disorders (e.g., fixed delusions)</td>
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<td>Cholelithiasis</td>
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<td>Cholangitis</td>
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<td>Peptic ulcer</td>
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<td>Pancreatitis</td>
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Tests for risk assessment and prognosis in a patient with chronic stable angina

The following factors are associated with worse prognosis:

- One of the strongest and most consistent prognostic markers is the maximum exercise capacity. Poor exercise tolerance, either due to myocardial ischemia or left ventricular dysfunction, is a bad marker.
- Another important prognostic marker is related to exercise induced ischemia. ST-segment depression and elevation (in leads without pathological Q waves and not in aVR) best summarize the prognostic information related to ischemia.
- Left ventricular dysfunction or ejection fraction is less than 40%.
- Exercise stress test shows ST segment depression >2mm, poor exercise tolerance, or a fall of blood pressure.
- Myocardial perfusion test shows thallium uptake in the lungs.
- Angiography shows left main-stem involvement or multivessel disease, especially in the presence of left ventricular systolic dysfunction.
- Chest x-ray shows cardiomegaly, left ventricular aneurysm, or pulmonary venous congestion.
- A family history of myocardial infarction (MI) and diabetes is an independent predictor of death for coronary heart disease (CHD).
- Increasing age.
- Male gender, but after menopause females have a similar risk.

GENERAL MEASURES & TREATMENT OF STABLE ANGINA

Advise the patient:

(a) not to smoke. After 9 years, the risks for an exsmoker fall to those of a nonsmoker;
(b) to lose weight, if obese;
(c) to take adequate exercise. This means 30 minutes moderately intense exercise, e.g. brisk walking, 5 times a week. The 30 minutes may be divided into separate parts, but each bout of exercise should last at least 10 minutes;
(d) to eat a low saturated fat, Mediterranean diet, with oily fish twice a week;

* Driving. The patient should not drive while symptoms are uncontrolled. Group 2 licence holders (large lorries and buses) and holders of a pilot’s licence must inform the appropriate authority and stop driving/flying meanwhile.

* Vaccination: recommend influenza annually and pneumococcal vaccination once.

* Quality of life. Ask what effect the angina is having on the patient. Look especially for depression, erectile dysfunction and unnecessary invalidism.
1. Short term control of angina symptoms

Advise the patient about the symptoms of a myocardial infarction or unstable angina and the importance of calling an ambulance if chest pain persists for >15 minutes despite the use of GTN.

**Glyceryl trinitrate (GTN):**
(a) sublingual tablets: 500 mg per tablet; or
(b) sublingual spray: 400 mg per puff;

* When chest pain occurs, rest and take one or two tablets/sprays under the tongue if one or two tablets/sprays are not effective repeat the dose after 5 minutes, if necessary repeat after 10 minutes.
* GTN may also be administered a few minutes prior to encountering an anginaprecipitating stimulus (planned exertion).
* GTN may cause severe headaches which often become less severe with continued use.

GTN tablets can be discarded once pain is relieved thereby reducing the dose taken and occurrence of headache.

* If tablets are used advise about storage and expiry; keep in original darkened bottle and dispose of 8 weeks after opening.

If sublingual GTN is not tolerated/effective:
(c) Buccal tablets: 2mg, which may be more effective than sublingual preparations.

If angina occurs while the buccal tablet is in place, the dosage strength used should be increased to 3mg. The 5mg dosage strength should be reserved for patients with severe angina pectoris refractory to treatment with the lower dosage strengths.

* For patients suffering only occasional angina pectoris – the tablets may be administered on a p.r.n. basis to relieve the acute attack.
* The tablet may also be administered a few minutes prior to encountering an anginaprecipitating stimulus.

**Long term control of angina symptoms**

Each of these drug classes decreases cardiac workload and may increase coronary blood flow or improve its distribution and thus modify the imbalance between myocardial supply and demand. Although monotherapy is effective in some, the majority of patients require two or more antianginal agents to control their symptoms. The choice of first-line treatment remains controversial because no single class of drug has demonstrated unequivocal superiority. Long-acting nitrates, β-adrenergic blocking agents, and calcium channel blockers, either alone or in combination, have been proven effective in reducing the frequency of angina.

The medical treatment of angina has changed little in the past few years. Nitrates were first described for treatment of the condition by Brunton in 1867.
Beta-blockers were introduced for treatment in the 1960s, following the development of specific beta-antagonists by James Black. Pronethalol was the first beta-blocker, but because of its side effects it was replaced by propranolol. There has since been a proliferation of beta-blockers with different pharmacological properties such as duration of action, lipid solubility, and cardiac specificity. Beta-blockers have been shown in large trials to have clinical efficacy not only in the treatment of angina but also in hypertension, post-myocardial infarction, and heart failure.

The calcium antagonists were introduced in the 1970s for angina and are presumed to have their major impact by increasing coronary flow as a consequence of dilatation of the coronary vessels.

**Current treatment of chronic angina**

Current wisdom suggests that antianginal agents are first-line therapy, reserving revascularization procedures for patients who do not show an adequate response to pharmacologic therapy. Various drugs have been used to relieve acute attacks and others have been used prophylactically to prevent anginal episodes.

**The several classes of drugs commonly used for chronic angina, and include:**

- short- and long-acting nitrates;
- β-adrenergic blocking agents;
- calcium channel blockers;
- metabolic anti-anginal drugs;
- selective heart rate-lowering agents

**Organic nitrates.** Nitrates do not improve long-term morbidity and mortality and therefore are mainly used only for symptom control. An important point to remember about using nitrate therapy is the development of nitrate tolerance. The onset of tolerance can be as early as 24 hours in some patients. To prevent nitrate tolerance, maintaining a nitrate-free interval of 6-12 hours daily is crucial. During the nitrate-free period, patient may develop angina (as there are no nitrates in the body to protect them). Therefore, nitrates should never be used alone as the only anti-anginal therapy for patients. They should always be used with one or more of the other antianginal therapies, such as β-blockers or calcium channel blockers.

**Short- and**

Nitrates have been used to treat angina pectoris for over a century, and the efficacy of sublingual nitroglycerin in the relief of effort-mediated angina pectoris is unequivocal. Controversy exists, however, as to the mechanism of action of nitrates. There is also disagreement as to the utility of other forms of nitrate preparations in the relief of angina pectoris.

Two long-acting organic nitrates are currently used:

1. Isosorbide dinitrate (ISDN).
2. Isosorbide mononitrate (ISMN).

These drugs are available in a variety of formulations with different routes of administration (Table 5). They are prodrugs and undergo biotransformation in which nitrite ion (NO2⁻) is released and metabolized to nitric oxide (NO).

The nitrates are rapidly absorbed from the gastrointestinal tract, skin, and mucous membranes. Isosorbide dinitrate and nitroglycerin undergo extensive first-pass hepatic metabolism when given orally. Nitroglycerin has a plasma half-life of approximately one to four minutes. It undergoes hepatic and intravascular metabolism, yielding biologically active dinitrate metabolites that have a half-life of approximately 40 minutes.

Isosorbide dinitrate, although it has hemodynamic and antianginal effects, is rapidly metabolized, with a plasma half-life of approximately 40 minutes. Its major metabolites, isosorbide-2-mononitrate and isosorbide-5-mononitrate, are both biologically active, with half-lives of approximately two and four hours, respectively. Isosorbide mononitrate (isosorbide-5-mononitrate), does not undergo first-pass hepatic metabolism and is completely bioavailable.

**Mechanism of action:**

**Molecular mechanism of action.** Nitrates act through endothelial-independent pathway to relax all types of vascular smooth muscle cells to varying degrees.

The organic nitrates are prodrugs and must be biodegraded to have therapeutic effects. This biotransformation involves denitration of the nitrate, with the subsequent liberation of nitric oxide.

Nitric oxide stimulates guanylyl cyclase, which leads to the conversion of guanosine triphosphate to cyclic guanosine monophosphate, which in turn causes vasodilation through decrease in intracellular calcium level. The exact mechanism by which the organic nitrates undergo denitration and thus liberate nitric oxide remains controversial. In addition to exerting vasodilating effects, it reduces platelet adhesion and aggregation. Nitric oxide is also involved in the control of endothelial function and vascular growth as well as myocardial contractility. Therefore, the nitrates possess a unique combination of vascular effects that can favorably affect the mismatch between myocardial oxygen supply and demand in patients with coronary artery disease.

**A. Increase coronary blood supply.**

1. Dilatation of large coronary arteries and arterioles (>100 μm in diameter), this will lead to increased perfusion of ischemic zones. Nitrates dilate both normal and abnormal coronary arteries.
2. Relief of coronary artery spasm.
3. Dilatation of coronary collaterals and enhancement of collateral flow.
4. Redistribution of transmural coronary blood flow from subepicardial to subendocardial ischemic regions.
**B. Decrease myocardial oxygen consumption.**

This is the chief mechanism for relief of ischemia by nitrates. Systemic venous relaxation in the extremities and splanchnic circulation results in sequestration of the circulating blood volume away from the heart and lungs and fall in venous return and cardiac filling.

1. Venous dilatation with decreased LV filling pressure and decreased preload can reduce ventricular volume and decrease LV wall stress – a major determinant of myocardial oxygen consumption. The fall in preload is more pronounced with sitting or standing. Vasodilatation develops at low nitrate concentration and is near maximal at moderate dosage.

2. Arterial dilatation: nitrates dilate large and small arteries with fall in vascular impedance and decrease in arterial pressure, resulting in reduction in afterload.

**Other actions.**

1. Pulmonary arterial bed relaxation: beneficial in subjects with secondary pulmonary hypertension.

2. Antiplatelet action: decreased platelet activation resulting in inhibition of platelet aggregation and less thrombosis. Stimulation of platelet guanylate cyclase by nitrates prevents fibrinogen binding to platelet GP IIb/IIIa receptors.

**Contraindications.**

1. Patients who have taken sildenafil (Viagra) within 24 hours because of the risk of severe hypotension.

2. Patients with hypertrophic cardiomyopathy even those without a resting gradient across left ventricular outflow tract.

3. Patients with suspected right ventricular infarction because of risk of hypotension.

4. Use cautiously in patients with severe aortic stenosis or with volume depletion.

**Nitrate preparations**

**Nitroglycerin (NTG)**

- Available in many formulations, parenteral, sublingual, buccal, ointment and patch.
- It has a very short half-life of several minutes; cessation of an intravenous NTG infusion or removal of transdermal patch results in a rapid fall of NTG plasma level within 20 to 40 minutes.
- Veins take up NTG more avidly than arteries.

**Dosages.** *Sublingual NTG*: 0.3-0.6 mg, onset of action is 2-5 minutes and its duration is 20-30 minute. The usual tablet dose is 0.3 mg to 0.4 mg repeated every five minutes for a total of three doses. NTG tablets are both heat and light sensitive. They should be stored in a tightly capped dark bottle in the
• refrigeration. Prescription should be renewed every three to six months.
• NTG patch: 0.4-0.8 mg/h, the patch should be applied for only 12-14 hours each day.
• Oral NTG: has no reliable data supporting its effectiveness.
• Intravenous NTG: initiated at a rate of 10 mcg per minute through continuous infusion and increased by 10 mcg/min every 3-5 minutes until symptom relief or blood pressure response is noted.
• If no response is seen increments of 20 mcg/min can be used. If symptoms and signs of ischemia are not relieved, the dose should be increased until a blood pressure response is observed.
• Caution should be used when systolic blood pressure falls below 110 mmHg in previously normotensive patients or to a greater than 25% below the starting mean arterial blood pressure if hypertension was present.
• Maximal dose of 400 mcg/min should not be exceeded.

Table 5.

Long acting oral organic nitrate

<table>
<thead>
<tr>
<th>Isosorbide dinitrate (ISDN)</th>
<th>Isosorbide mononitrate (ISMN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The most widely used long acting nitrate.</td>
<td>• Onset of action is within 30 minutes, and the duration of action is six to eight hours.</td>
</tr>
<tr>
<td>• Available as short-acting and sustained-release formulation.</td>
<td>• It is completely bioavailable.</td>
</tr>
<tr>
<td>• Onset of action is within 15 to 30 minutes and the duration of action is three to six hours. There is low bioavailability from hepatic metabolism.</td>
<td>• The usual starting dose is 20 mg twice daily to be increased to 40 mg twice daily if necessary.</td>
</tr>
<tr>
<td>• Dosage: 10 to 40 mg three times daily. There is no added benefit with 60 and 120 mg doses.</td>
<td>• Seven hours interval between doses followed by 17 hours nitrate-free interval.</td>
</tr>
<tr>
<td>• Tolerance has limited the usefulness of ISDN as a chronic antianginal agent.</td>
<td>• Extended (sustained) release preparation is given once daily and lasts 12 hours.</td>
</tr>
<tr>
<td>• Development of tolerance occurs despite higher plasma concentrations of ISDN during maintenance therapy.</td>
<td>• A minimum of 60 mg per day is recommended, higher doses such as 120 or 240 mg daily may be necessary for sustained antianginal efficacy without tolerance. Sustained release preparation action lasts for 12 hours, nocturnal or rebound angina may develop.</td>
</tr>
<tr>
<td>• To prevent the development of tolerance, it is recommended to give ISDN at 8 AM, 1 PM and 6 PM. This regimen can offer antianginal protection for at least six hours.</td>
<td>• ISMN preparations (tablet size):</td>
</tr>
<tr>
<td>• Begin with a dose of 10 mg three times daily and advance to 40 mg three times daily as needed.</td>
<td>• Regular: 20, 40 mg</td>
</tr>
<tr>
<td></td>
<td>• Sustained release (SR): 25, 50 mg</td>
</tr>
<tr>
<td></td>
<td>• Extended release preparations are preferable. Starting dose is 30 mg once daily can be titrated to 120 mg once daily as needed.</td>
</tr>
</tbody>
</table>
Suggestions for nitrate dosing

- Start nitrate therapy with small doses and build up to maximally tolerated amount.
- Some individuals are extremely sensitive to nitrates; others experience little or no side effects.
- Headache and dizziness are the limiting symptoms with nitrate administration. They usually decrease or disappear over time.
- Many patients are underdosed e.g. 10 mg ISDN, 30 or 40 mg ISMN-SR or 0.2 to 0.4 mg/h of the NTG patch are less likely to be clinically effective doses.
- In congestive heart failure, the dosage of nitrates to achieve a significant hemodynamic effect is considerably higher than in patients with normal LV function. Patients with congestive heart failure tolerate large doses.
- In patients with primarily exertional angina, nitrates are given during the day when the patient is more active.
- In patients with nocturnal angina or congestive heart failure, therapy at night is advised.
- When given in adequate dosage, there is no difference in efficacy between ISDN, ISMN and transdermal NTG.

### Table 6. Common nitrate preparation

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Route of administration</th>
<th>Onset of action, minutes</th>
<th>Duration of action</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroglycerin</td>
<td>Sublingual tablet</td>
<td>2-5</td>
<td>15-30 min</td>
<td>0.15-0.9 mg</td>
</tr>
<tr>
<td></td>
<td>Sublingual spray</td>
<td>2-5</td>
<td>15-30 min</td>
<td>0.4 mg</td>
</tr>
<tr>
<td></td>
<td>Ointment</td>
<td>2-5</td>
<td>Up to 7 hours</td>
<td>2 percent, 15x15 cm (7.5 to 40mg)</td>
</tr>
<tr>
<td></td>
<td>Transdermal</td>
<td>30</td>
<td>8-14 hours</td>
<td>0.2-0.8 mg/hour</td>
</tr>
<tr>
<td></td>
<td>Oral sustained release</td>
<td>30</td>
<td>4-8 hours</td>
<td>2.5-13 mg</td>
</tr>
<tr>
<td></td>
<td>Intravenous</td>
<td>2-5</td>
<td>Drug infusion</td>
<td>5-200 mg/min</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>Sublingual</td>
<td>2-5</td>
<td>Up to 60 min</td>
<td>2.5-15 mg</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>30</td>
<td>Up to 8 hours</td>
<td>5-80 mg BID or TID</td>
</tr>
<tr>
<td></td>
<td>Spray</td>
<td>2-5</td>
<td>2-3 min</td>
<td>1.25 mg/day</td>
</tr>
<tr>
<td></td>
<td>Chewable</td>
<td>2-5</td>
<td>2-2.5 hours</td>
<td>5 mg</td>
</tr>
<tr>
<td></td>
<td>Oral slow release</td>
<td>30</td>
<td>Up to 8 hours</td>
<td>40 mg OD or BID</td>
</tr>
<tr>
<td>Drug</td>
<td>Route</td>
<td>Dosage Range</td>
<td>Duration</td>
<td>Dosing Schedule</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>-------------</td>
<td>--------------</td>
<td>-----------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Isosorbide mononitrate</td>
<td>Oral</td>
<td>30</td>
<td>6-8 hours</td>
<td>20-40 mg BID 60-240 mg/day</td>
</tr>
<tr>
<td>Isosorbide mononitrate, extended release</td>
<td>Oral</td>
<td>30-60</td>
<td>12 hours</td>
<td>30-120 mg once daily</td>
</tr>
<tr>
<td>Pentae erythroid tetranitrate</td>
<td>Sublingual</td>
<td>2-5</td>
<td>Not known</td>
<td>10 mg as needed</td>
</tr>
<tr>
<td>Eyrthritol tetranitrate</td>
<td>Sublingual</td>
<td>2-5</td>
<td>Not known</td>
<td>5-10 mg as needed</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>30</td>
<td>Not known</td>
<td></td>
</tr>
</tbody>
</table>

**BETA-ADRENERGIC BLOCKERS (BABS)**

In patients with IHD or history of myocardial infarction, b-blockers reduce recurrent cardiovascular events. In using b-blockers in patients with IHD, no b-blockers with intrinsic sympathomimetic activities should be used because their partial agonistic effect may increase instead of decrease myocardial workload.

Between beta-blockers and calcium channel blockers, b-blockers are generally considered the anti-ischemic agent of choice except in the case of Prinzmetal angina where beta-blockers are relatively contraindicated because of possible coronary vasospastic effects. Dosing beta-blockers in IHD is different from dosing in hypertension where achieving a target blood pressure is the goal. Our therapeutic target is a resting heart rate of 50 to 60 beats per minute (provided the patients’ blood pressure remains stable).

**Beta-blockers.**

- The only group of antiischemic drugs with documented efficacy in preventing reoccurrence of coronary events, myocardial infarction (MI) and sudden death following acute MI.
- BABs act as competitive inhibitors of catecholamines at beta-adrenergic receptors (BARs).
- BARs are divided into B1 (those in the myocardium) and B2 (present in smooth muscle cells, bronchi and other tissues). Epinephrine and nor-
epinephrine are equipotent at B1 receptors, whereas epinephrine is 10 to 50 fold more potent than nor-epinephrine at B2 receptors.

- Cyclic adenosine mono phosphate (cAMP) is the major second messenger of BAR stimulation leading to events that increase influx of calcium into the cell and activate glycogen phosphorylases.
- The metabolic effects of cyclic AMP including calcium overloading, high energy phosphate depletion, oxygen wastage by increased free fatty acid metabolism and increased arrhythmogenicity appear to play a role in catecholamine induced ischemic cell injury.

**Development of the beta-adrenoceptor antagonists.** The discovery and development of the b-adrenoceptor antagonists represents one of the most significant advances in the history of cardiovascular pharmacology and therapeutics Sir James Black is credited with leading the team that discovered the first clinically useful b-adrenoceptor antagonist, propranolol, which was developed specifically for the treatment of angina.

Black proposed that pharmacologic blockade of cardiac b-adrenoceptors would reduce heart rate and myocardial oxygen demand and thereby prevent angina of effort associated with activation of the sympathetic nervous system (eg, exercise, emotional stress, anxiety). This was a novel concept at that time (late 1950s, early 1960s) since the only effective antianginal drugs were the organic nitrates, such as nitroglycerin, whose therapeutic effects were attributed to vasodilation and increased coronary blood flow. Although there were no known b-adrenoceptor antagonists in existence, isoproterenol, a relatively pure b-adrenoceptor agonist that mimics the actions of norepinephrine and epinephrine on the heart, was available.

Black reasoned that isoproterenol must possess the requisite structural characteristics necessary for interacting with cardiac b-adrenoceptors. Using isoproterenol as a starting point, he had his chemists synthesize numerous molecules that were chemical derivatives of the b-adrenoceptor agonist, ultimately leading to the discovery of propranolol. Black was awarded the Nobel Prize in 1988, in part, for his role in the discovery of propranolol and the approach that he used.

**Classification of BABS.** More than 30 BABS are present worldwide. They are classified according to the following characteristics:

2. Lipid solubility-lipophily.
3. Intrinsic sympathomimetic activity (ISA).
4. Vasodilator properties.

Three distinct subtypes of b-adrenoceptors, termed b1, b2, and b3, have been identified. With regard to the actions of epinephrine and norepinephrine in the cardiovascular system, increases in heart rate and force of contraction are
mediated primarily via activation of b1-adrenoceptors in the heart, while vasodilation is mediated primarily by activation of b2-adrenoceptors in vascular smooth muscle.

Selectivity for b1-adrenoceptors is referred to as “cardioselectivity”, and represents an important pharmacologic property that can be used to distinguish among b-adrenoceptor antagonists. Other pharmacologic properties that differentiate the b-adrenoceptor antagonists include intrinsic sympathomimetic activity (ie, partial agonist), membrane-stabilizing activity (ie, local anesthetic like effects), and concomitant a-adrenoceptor blockade, though these properties are not required for efficacy in the treatment of angina. Important pharmacokinetic differences include variations in lipid solubility, bioavailability, half-life and elimination (renal vs. hepatic).

1. Beta-adrenergic specificity- selectivity

- Some BABs are more specific for B1 ARs, they are called cardio-selective BABs, examples are atenolol, metoprolol and bisoprolol. Bisoprolol is the most cardioselective BAB (table 6). Other BABs are non selective and block both B1 and B2 ARs. Examples are propranolol and nadolol.
- In low doses, B1-selective blockers may not block the B2-receptors that mediate dilatation of arterioles and bronchi and have a number of metabolic effects. Cardioselective BABs are relatively safer in the management of patients with COPD, diabetes and peripheral vascular disease (PVD). However, when given in large doses they block both B1 and B2 receptors.

   Advantage of B1-Selectivity
   - Glucose metabolism: no dose adaptation of oral hypoglycemics.
   - Lower risk of masking hypoglycemia.
   - Pulmonary function: safe use with COPD.
   - Peripheral vascular resistance: lower risk of cold extremities and erectile dysfunction.

2. Lipophility

- Lipid soluble BABs are metabolized by the liver, they have a short duration of action and tend to have central nervous system side effects. Examples are propranolol, metoprolol, carvedilol and timolol.
- Water soluble (lipid insoluble) BABs are excreted through the kidneys, they have a longer duration of action and less central nervous system side effects. Examples are atenolol, bisoprolol, and nadolol.

3. Intrinsic sympathomimetic activity (ISA)

BABs with this property slightly activate the BARs in addition to preventing the access of natural or synthetic catecholamines to the receptor. Drugs with partial agonist activity cause less slowing of the heart rate at rest and cause less depression of atroventricular conduction. Examples are pindolol.
4. Vasodilator properties
- Some BABs block both alpha and beta ARs and have direct vasodilator activity. Examples are labetalol and carvedilol. Bucindolol is a non-selective BAB with a direct vasodilator activity.

<table>
<thead>
<tr>
<th>Generation/Class</th>
<th>Compound</th>
<th>B1/ B2 Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>First/ Nonselective</td>
<td>Propranolol</td>
<td>2.1</td>
</tr>
<tr>
<td>Second/ Selective B1</td>
<td>Metoprolol</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>Bisoprolol</td>
<td>119</td>
</tr>
<tr>
<td>Third/ B-blocker-vasodilator</td>
<td>Carvedilol</td>
<td>7,3</td>
</tr>
<tr>
<td></td>
<td>Bucindolol</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>Nebivolol</td>
<td>293</td>
</tr>
</tbody>
</table>

**Pharmacokinetic properties.** Most b-adrenoceptor antagonists are well absorbed following oral administration, but many undergo firstpass hepatic metabolism; thus, the oral bioavailability of b-adrenoceptor antagonists is limited to varying degrees. The oral bioavailability of propranolol is approximately 25%-30% on average, but it is dose-related and subject to considerable variation among individuals.

Oral bioavailability of metoprolol (~50%) is also limited by first-pass metabolism. The elimination of propranolol and metoprolol may be decreased in the presence of liver disease or advanced age. Nadolol and atenolol are hydrophilic and are incompletely absorbed following oral administration. Bioavailability of nadolol (~35) and atenolol (~40%) is little influenced by hepatic metabolism and both drugs are excreted essentially unchanged in the urine. These drugs show less interpatient variation in plasma levels than propranolol and metoprolol, but their elimination may be reduced by renal disease. Half-lives range from about 4 hours for propranolol and metoprolol, to about 8 hours for atenolol, and up to 24 hours for nadolol.

Extended release oral dosage forms are available for propranolol and metoprolol. Propranolol, metoprolol, and atenolol may also be administered by intravenous injection. The pharmacodynamic effects of the b-adrenoceptor antagonists often extend well beyond the time predicted by their half-lives.

**Mechanism of anti-ischemic action of BABS**

**A. Decrease in myocardial oxygen requirements**
1. Slowing of heart rate.
2. Lowering of blood pressure.
3. Decrease in myocardial contractility.
4. Decrease in fatty acid utilization.
**B. Increase in myocardial oxygen supply**

1. Increase in diastolic perfusion and augmentation of coronary blood flow secondary to bradycardia.
2. Augmentation of collateral blood flow and redistribution of blood flow to ischemic areas.

**C. Other actions**

1. Stabilization of atherosclerotic plaque and preventing plaque rupture through reduction in vessel wall stress.
2. Decrease in microvascular damage.
4. Inhibition of platelet aggregation.

**Hemodynamic effects: myocardial oxygen demand.** Beta-adrenoceptor antagonists competitively inhibit the binding of endogenous catecholamines to β1-adrenoceptors in the heart and most evidence strongly suggests that their anti-ischemic effects are due to cardiac depression. Myocardial oxygen demand is determined in large part by heart rate and cardiac contractility. Increased heart rate and contractility result in increased myocardial oxygen consumption and, conversely, reductions in heart rate and contractility lead to a decrease in oxygen consumption. By inhibiting the actions of norepinephrine and epinephrine on the heart, the β-adrenoceptor antagonists reduce myocardial oxygen demand via a reduction in both heart rate and cardiac contractility and thereby attenuate the myocardial response to sympathetic nervous system stimulation that occurs, for example, with increased stress or exercise.

Though most β-adrenoceptor antagonists lower resting heart rate to some extent, the effect on exercise-induced tachycardia is much more pronounced. Thus, for a given degree of physical activity, myocardial oxygen consumption is diminished. It is important to note that the β-adrenoceptor antagonists do not change the point of imbalance between myocardial oxygen supply and consumption at which angina occurs; rather, they reduce the likelihood that this point is reached.

By mechanisms that remain poorly understood, β-adrenoceptor antagonists also decrease peripheral vascular resistance, which leads to a reduction in arterial blood pressure and afterload. Reduced afterload results in decreased left ventricular wall tension, which is another major determinant of myocardial oxygen demand.

This beneficial effect of the β-adrenoceptor antagonists may be partially offset, however, by an increase in left ventricular end-diastolic volume that occurs due to increased cardiac filling during diastole, but the net effect is to lessen oxygen demand.

**Hemodynamic effects: myocardial oxygen supply.** The heart is almost exclusively dependent on aerobic metabolism and an adequate supply of oxygen is critical to sustained cardiac activity. Myocardial oxygen supply is a function of both oxygen delivery and oxygen extraction from the blood. Since oxygen extraction from coronary blood is near maximal at rest, there is little reserve to meet increased demand due to increased cardiac activity. Thus, the most important determinant of myocardial oxygen supply is total coronary blood flow.
Since β-adrenoceptor antagonists are not coronary vasodilators, they have little propensity to increase coronary blood flow and myocardial oxygen supply. If anything, β-adrenoceptor antagonists may increase coronary vascular resistance by inhibiting the β2-adrenoceptor mediated vasodilator effects of endogenous catecholamines and leaving α-adrenoceptor-mediated vasoconstriction unopposed. Thus, the anti-ischemic effects of the β-adrenoceptor antagonists are largely due to their ability to reduce myocardial workload and decrease oxygen consumption, rather than to improve myocardial oxygen supply.

### Table 8.

<table>
<thead>
<tr>
<th><strong>A. Cardiovascular</strong></th>
<th><strong>B. Non-cardiovascular</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Systemic hypertension.</td>
<td>3. Anxiety (situational).</td>
</tr>
<tr>
<td>4. Heart failure with impaired LV systolic function.</td>
<td>4. Thyrotoxicosis.</td>
</tr>
<tr>
<td>5. Congestive cardiomyopathy.</td>
<td>5. Alcohol withdrawal.</td>
</tr>
<tr>
<td>7. Arrhythmias: sinus tachycardia, PVCs, supraventricular tachycardia, ventricular tachycardia, long QT syndrome.</td>
<td></td>
</tr>
<tr>
<td>8. Aortic dissection.</td>
<td></td>
</tr>
<tr>
<td>10. Mitral valve prolapse.</td>
<td></td>
</tr>
<tr>
<td>11. Digitalis intoxication.</td>
<td></td>
</tr>
</tbody>
</table>

Beta-adrenoceptor antagonists are a mainstay in the treatment of chronic, stable angina. While coronary blood flow (ie, oxygen supply) may be sufficient to meet myocardial oxygen requirements at rest in patients with fixed atherosclerotic lesions, the obstruction prevents blood flow from increasing during periods of increased oxygen demand. Under these conditions coronary blood flow is already at a maximal level in most patients, thus any increase in myocardial work can trigger an episode of acute angina. Precipitating factors include physical exertion, emotional stress or excitement, and temperature extremes. By decreasing heart rate, myocardial contractility, and afterload, β-adrenoceptor antagonists reduce myocardial workload and oxygen consumption at rest as well as during periods of exertion or stress. Oral β-adrenoceptor antagonists are widely used in long-term maintenance therapy to prevent acute ischemic episodes. Prophylactic use of these agents reduces the frequency and severity of acute anginal attacks. Because of their slow onset of action, oral β-adrenoceptor antagonists are not appropriate for terminating an acute attack of angina once it has begun; sublingual nitroglycerin is the agent most frequently
used under these conditions. Several b-adrenoceptor antagonists, including propranolol, metoprolol, and atenolol, have cardioprotective effects and have been shown to decrease mortality after myocardial infarction.

In patients with variant (Prinzmetal’s) angina, the major underlying cause of angina is vasospasm of one or more coronary arteries. Intense vasoconstriction decreases coronary blood flow, thereby reducing myocardial oxygen supply. Coronary vasospasm can occur in arteries with little or no atherosclerotic plaque and is not associated with an increase in myocardial oxygen demand. Indeed, variant angina may strike at any time of the day or night, including during periods of rest or sleep. In contrast to stable angina, variant angina is most often the result of an abrupt decrease in myocardial oxygen supply (ie, coronary blood flow) rather than an increase in myocardial oxygen demand. Unlike nitrates and calcium channel blockers, b-adrenoceptor antagonists do not directly dilate coronary arteries to increase coronary blood flow.

Moreover, blockade of vascular b-adrenoceptors inhibits the vasodilator actions of endogenous catecholamines and may exacerbate a-adrenoceptor-mediated vasoconstriction in coronary arteries. Thus, b-adrenoceptor antagonists may worsen coronary vasospasm and are not indicated for treatment of vasospastic angina.

Beta-adrenoceptor antagonists may reduce the risk of progression to acute myocardial infarction in patients with unstable angina. The pathophysiology of this condition is often complex and may involve several underlying factors superimposed upon one another, including rupture of atherosclerotic plaques and thrombus formation, constriction of coronary arteries, and increased myocardial oxygen demand. In these patients, the beneficial effects of the b-adrenoceptor antagonists are likely due to a reduction in myocardial oxygen consumption. If coronary vasospasm is the major underlying problem, nitrates or calcium channel blockers would be more effective and b-adrenoceptor antagonists should be used with caution.

Table 9. Contraindications of BABS

<table>
<thead>
<tr>
<th>Absolute</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cardiogenic shock.</td>
<td>1. Bronchial asthma or COPD.</td>
</tr>
<tr>
<td>2. Hypotension (SBP&lt; 85 mmHg).</td>
<td>2. Heart failure.</td>
</tr>
<tr>
<td>3. Acute pulmonary oedema.</td>
<td>3. Insulin dependent diabetes mellitus.</td>
</tr>
<tr>
<td>4. Signs of systemic hypoperfusion: mental deterioration, cold clammy skin, rising BUN.</td>
<td></td>
</tr>
<tr>
<td>5. Congestive heart failure with pulmonary crepitations more than one half of the chest or significant volume overload (until adequate diuresis).</td>
<td>4. Severe PVD.</td>
</tr>
<tr>
<td>6. Symptomatic bradycardia (heart rate &lt; 50/m) or more than grade I AV block in absence of pacemaker.</td>
<td></td>
</tr>
<tr>
<td>7. Patients receiving IV inotropes.</td>
<td></td>
</tr>
<tr>
<td>8. Status asthmaticus or bronchospasm requiring inhaled beta-agonists</td>
<td></td>
</tr>
</tbody>
</table>
In angina pectoris (chronic stable and unstable)

- Start with a small dose and build the dose over days, monitor heart rate and blood pressure.
- All types of BABs appear to be equally effective in exertional angina but there is interindividual variability in responsiveness.
- Evaluate anginal symptoms in 1 to 2 weeks.
- Starting dose of atenolol is 25 mg once daily which can be increased as tolerated to a maximum of 200 mg once daily (assuming the renal function is normal) until the resting heart rate is 50 to 60 beats/min and does not exceed 100 beats/min with ordinary activity.
- Starting dose of metoprolol is 25 mg BID, which can be increased to 200 mg BID as tolerated.
- The efficacy of BABs in relieving angina is dose-dependent.

It is important to be certain that adequate beta blockade has been attained. BABs dose is titrated to achieve the following goals:

1. Resting heart rate between 50 and 60 beat/min. Target heart rate for some patients with more severe angina can be less than 50 beats/min, as long as bradycardia is asymptomatic and heart block does not develop.
2. Blunting of postural increase in heart rate.
3. Blunting of peak heart rate and blood pressure during exercise, measured during exercise testing.
4. Reduction in the frequency and severity of angina and in use of sublingual nitroglycerin.

The following are cardioprotective doses proved effective in preventing sudden death and total cardiac deaths in patients after MI. The beneficial effect of smaller doses is unknown:
- Metoprolol 100-300 mg/d.
- Propranolol (non smokers) 160-240 mg/d
- Timolol 10-20 mg/d

BABs are not effective in Prinzmetal (vasospastic angina) and should not be used in this condition.

Avoid abrupt cessation of therapy when it is necessary to discontinue BABs. The dose should be reduced gradually over 2 to 3 weeks.

Adverse effects of BAB

1. Cardiac
   - Myocardial depression and precipitation of heart failure.
   - Profound bradycardia, sinus node dysfunction and AV conduction delay.
   - Hypotension.

2. Peripheral vascular effects
   - Cold extremities.
• Absent pulses, cyanosis.
• Raynaud's phenomenon.
• Worsening of claudication.

3. **Central nervous system effects**
   (more common with highly lipid soluble BABs such as propranolol and metoprolol)
   • Dreams, hallucinations, insomnia.
   • Depression.
   • Fatigue.
   • Impotence.

4. **Metabolic effects**
   • Enhancement of insulin induced hypoglycemia.
   • Masking manifestations (tachycardia) of hypoglycemia.
   • Hyperlipidemia: increase in plasma triglycerides and decrease in HDL-cholesterol secondary to inhibition of lipoprotein lipase activity.

5. **Rebound phenomenon**
   • Sudden discontinuation of BAB specially if it has been administered for a long time (> 3 weeks) can lead to profound elevation of blood pressure and tachycardia and may precipitate myocardial ischemia, or infarction.

6. **Ventilatory function**
   • Bronchospasm and increase airway resistance in asthmatics. **Calcium antagonists.** For the management of IHD, calcium channel blockers (verapamil, diltiazem, nifedipine, amlodipine) are generally considered in patients who have contraindications to b-blockers (i.e, Prinzmetal angina and other contraindications discussed previously). This is because in some post-MI clinical trials, calcium channel blockers increased mortality in patients with left ventricular dysfunction.

**Calcium channel blockers.** Calcium channel blocking agents (CCB) inhibit the entry of calcium into vascular smooth muscle cells and myocardial cells during the action potential.

CCBs are a heterogenous group of drugs with widely variable effects on heart muscle, sinus node function, atrioventricular (AV) conduction, peripheral blood vessels and coronary circulation.

**Classification**

1. **Dihydropyridines (DHP)**
   Include: Nifedipine, Amlodipine, Nicardipine, Felodipine, Nisoldipine, Isradipine.

2. **Nondihydropyridines**
   Include:
   • Phenylalkylamines: verapamil.
   • Benzothiazepines: diltiazem
Mechanism of anti-ischemic action

1. Increase coronary blood flow
   - Decrease coronary vascular resistance- coronary vasodilatation.
   - Increase collateral blood flow.
   - Decrease coronary spasm.
   The most effective in this action is nifedipine
2. Decrease myocardial oxygen demand
   - Bradycardia: most effective is verapamil. Nifedipine produces reflex tachycardia.
   - Reduction in blood pressure: all members lower blood pressure, the most effective is nifedipine.
   - Decrease in myocardial contractility. Most potent is verapamil.
3. Other actions
   Decreased platelet aggregation.
   DHP calcium antagonists are powerful vasodilators, they possess negligible negative inotropic and electrophysiologic effects. They are ineffective as antiarrhythmic agents.
   Verapamil is a moderately potent vasodilator but has a marked negative inotropic effect. It produces mild depression of sinus node function and of AV conduction. It is effective in the termination of AV nodal reenterant tachycardia.

Stable angina pectoris
CCBs are used as second line drugs and as effective alternatives or additional drugs in patients who remain symptomatic despite therapy with beta blockers and nitrates. They can be used as first-line antianginal drugs in patients with contraindications to beta blockers.

Coronary vasospasm and prinzmetal angina
CCBs are drugs of first choice in this syndrome because of their ability to block spontaneous and drug induced spasm.
Vasospastic angina is characterized by angina usually at rest specially in the morning with ST elevation and usually with preserved exercise capacity. Most patients have some degree of underlying epicardial CAD.
Coronary spasm and/or thrombosis play a major role in the pathogenesis of ischemia in most patients with angina at rest, regardless of the coronary anatomy.

Drug interaction with verapamil
- Beta-blockers
  Verapamil should not be given as IV bolus to patients receiving B-blockers. It is preferable to give oral preparation.
- Digoxin
  Verapamil should never be given to digitalized patient when digitalis toxicity is suspected. Serum digoxin levels may be increased by 50-70 % by verapamil.
- **Amiodarone**
  Verapamil is avoided in patients taking amiodarone because of depression of SA and AV nodes.
- **Oral Anticoagulants**
  Verapamil increases the effects of oral anticoagulants.
- **Quinidine**
  Plasma levels of quinidine may increase during the administration of verapamil. Marked hypotension may develop with IV verapamil.
- **Disopyramide**
  Added negative inotropic effect can result in heart failure.

**Contraindications**

**Contraindications for non-DHP (verapamil, diltiazem) CCBS**
1. Severe impairment of LV systolic function, CHF, or pulmonary oedema.
2. Sinus node dysfunction and AV block (second and third degree).
3. WPW with AF.

**Other contraindications to CCBs**
1. Cardiogenic shock.
2. Profound hypotension (SBP < 90 mmHg).
3. Pregnancy and lactation.
5. Rapid-release short acting nifedipine must be avoided in the absence of adequate concurrent beta-blockade in acute coronary syndromes.

**Adverse effects**
Four percent of patients discontinue CCBs because of side effects.
1. Hypotension and dizziness.
2. Oedema of ankles and lower limbs (more common with amlodipine).
3. Headache: more with DHPs.
4. Flushing and burning: more with DHPs.
5. Constipation common with verapamil.

**Combination therapy.** Combination therapy with drugs from different pharmacologic classes is often used in the long-term management of patients with angina. This strategy takes advantage of the diverse mechanisms of action of drugs from each category and offers several potential benefits. When used concurrently, b-adrenoceptor antagonists can inhibit the baroreceptor-mediated reflex tachycardia and positive inotropic effects that may sometimes occur with organic nitrates. Alternatively, organic nitrates increase venous capacitance and can thereby offset b-adrenoceptor antagonist-mediated increases in left ventricular end-diastolic volume. Moreover, organic nitrates are coronary vasodilators and, as such, may prevent the increase in coronary vasomotor tone that may potentially result from blockade of vascular b-adrenoceptors.
Dihydropyridine calcium channel blockers are also potent coronary vasodilators and provide similar advantages with regard to coronary vascular resistance in patients treated simultaneously with β-adrenoceptor antagonists. As with nitrates, dihydropyridines may also cause reflex tachycardia that can be alleviated by β-adrenoceptor antagonists. Concurrent use of β-adrenoceptor antagonists with the non-dihydropyridine calcium channel blockers, verapamil and diltiazem, is much more limited due to the potential for severe cardiac depression and must be used with great caution.

In the long-term management of ischemic heart disease, β-adrenoceptor antagonists, with their antianginal effects, may also be combined with vasculo-protective drugs such as anti-platelet agents (aspirin, clopidogrel), angiotensin-converting enzyme inhibitors, and HMG-CoA reductase inhibitors to reduce the risk of ischemic vascular events.

**Metabolic antianginal drugs**

*Drugs*
- **Perhexiline**
- **Trimetazidine**
- **Ranolazine**
- **Etomoxir**
- **Nicorandil**

This group exerts its anti-ischemic effect through metabolic action and have little or no effect on coronary hemodynamics.

They do not affect blood pressure, pulse rate or LV systolic function.

They have considerate potential as adjunctive therapy for angina, particularly in patients refractory to standard therapy. They may be a primary therapeutic option in certain circumstances.

These agents (trimetazidine, ranolazine, and perhexiline) have documented anti-ischemic effects. They are, in theory, useful in patients with angina secondary to hypertrophic cardiomyopathy, aortic stenosis, and cardiac syndrome X (microvascular disease) due to their anti-ischemic effects in the absence of vasodilatation.

They may be of potential benefit in heart failure as some can improve myocardial function.

**Myocardial metabolism**

Sixty to ninety percent of the energy generated by the normal adult heart is from free fatty acids (long-chain free fatty acid, LCFA). LCFA entry into the mitochondria is facilitated by the enzyme carnitine-palmityl-transferase (CPT).

Carbohydrate metabolism contributes only to about 10-40% of energy generated by the healthy human adult heart.
Fatty acids require approximately 10-15% more oxygen to generate an equivalent amount of ATP when compared to glucose.

Suppression of FFA uptake and/or oxidation stimulates an increase in myocardial glucose utilization.

**Perhexiline**

It acts by shifting myocardial substrate utilization from fatty acids to carbohydrates through inhibition of CPT, resulting in increased glucose and lactate utilization.

Perhexiline can cause hepatic toxicity and peripheral neuropathy, but this risk can be reduced by maintaining a low plasma concentrate between 150 to 600 ng/mL.

The mechanism for toxicity appears to be due to phospholipids accumulation, which is a direct consequence of CPT inhibition.

The drug improves angina frequency and exercise capacity.

It is used as adjunctive treatment for refractory angina in patients not suitable for, or awaiting, coronary intervention. It is given as a short-term therapy (less than 3 months).

Serum level monitoring is necessary when perhexiline is administered.

Dose: 100 mg twice daily with subsequent plasma guided dose titration.

**Trimetazidine**

It exerts no significant negative inotropic or vasodilator properties.

It reduces the rate of FFA oxidation (free fatty acid), with a concomitant increase in glucose oxidation rates during ischemia, but the exact molecular mechanism of action is unclear. The metabolic effect of trimetazidine is mediated by inhibition of mitochondrial long-chain 3-ketoacyl Co A thiolase, a fundamental enzyme that operates in the FFA beta-oxidative chain. As a result, myocardial glucose oxidation is increased and substrate utilization is shifted from fatty acid to carbohydrate metabolism.

It has a favorable side-effect profile.

In clinical trials (meta-analysis) trimetazidine demonstrated a significant reduction in anginal frequency in patients with stable angina, but only a non-significant trend towards prolongation of the duration of treadmill exercise.

It improves resting ventricular function in patients with CAD and various degrees of contractile impairment.

It has no short or long term mortality benefit when infused intravenously immediately post-MI for 48 hours.

Though the clinical efficacy of trimetazidine has been demonstrated, yet, there is uncertainty regarding its role, particularly its safety profile at higher doses in management of CAD. It remains a potential treatment for the future.

Dose: two forms
- Short acting: 20 mg three times a day.
- Slow release (MR): 35 mg twice a day.
**Ranolazine**

It stimulates glucose oxidation and act as a partial fatty-acid-oxidation inhibitor. It inhibits fatty-acid oxidation during the periods of elevated plasma FFA levels associated with myocardial ischemia.

It has a significant antianginal effects both as monotherapy and in combination with other antianginal agents.

Two studies using high doses of ranolazine (up to 1500 mg twice daily) in patients with chronic stable angina either as monotherapy (MARISA study) or as background antianginal therapy (CARISA study) showed that ranolazine significantly increased duration of exercise, time to angina and fewer anginal episodes compared to placebo. There was minor prolongation of QT interval.

Long term safety, particularly with relation to QT prolongation is not known.

**Etomoxir**

It was initially introduced as a potential antidiabetic agent on the basis of its hypoglycemic effects.

It is potent CPT inhibitor (Carnitine palmitoyl-transferase enzyme inhibition)

It is an experimental drug.

In experimental animals, it reduces oxygen consumption during ischemic recovery and prevented depression of myocardial function.

Etomoxir administered 80 mg/day to patient with heart failure, improved LV ejection fraction and clinical status.

**Nicorandil**

A vasodilator that opens ATP-sensitive potassium channels in blood vessels and heart muscle.

Possibly its action is through enhancing ischemic preconditioning, a process whereby one episode of ischemia makes the heart more tolerant to subsequent episodes.

It may have also anti-adrenergic actions by inhibition of norepinephrine release.

It resulted in a 17% reduction in the relative risk of nonfatal MI or unplanned hospitalization for angina (IONA trial, 2001).

Nicorandil can be a useful adjuvant to the treatment of patients with chronic angina

**ACE inhibitors.** In patients who have chronic stable angina and left ventricular dysfunction, ACE inhibitors should be used to reduce the progression of left ventricular dysfunction and prevent future cardiovascular events (more discussion to follow in heart failure lecture).

Recent clinical trials have demonstrated that the use of certain ACE inhibitors (ie, Ramipril) in patients with hypertension, diabetes, or IHD, even with normal left ventricular dysfunction, can reduce future cardiovascular events. The issue of
tissue versus non-tissue ACE inhibitors is discussed here, but the issue is controversial. Therefore, as long as patient blood pressure can tolerate, ACE inhibitors should be added. If patients cannot tolerate ACE inhibitors due to cough, an angiotensin receptor blocker (ARB) can be used instead.

**Antiplatelet agents.** Examples of antiplatelet agents are aspirin, clopidogrel, and glycoprotein IIb/IIIa receptor antagonists. Aspirin and clopidogrel can be used across the spectrum of IHD. Glycoprotein IIb/IIIa receptor antagonists are used in patients with ACS only, as part of their in-hospital regimen.

**Aspirin.** There is strong evidence that the use of aspirin in IHD can reduce future cardiovascular events. Therefore, unless absolutely contraindicated, patients across the spectrum of IHD should receive aspirin, 81-325 mg orally, once a day, indefinitely.

**Clopidogrel.** Clopidogrel has been demonstrated to reduce cardiovascular events in IHD, and may be slightly more effective than aspirin (based on one study). Clopidogrel is to be used in patients who cannot tolerate aspirin for primary and secondary prevention of MI. In patients who have coronary stent placement, clopidogrel should be used in combination with aspirin for 12 months after stent placement to prevent stent thrombosis. There are also clinical data demonstrating that the early initiation of aspirin and clopidogrel combined therapy in patients with unstable angina or NSTEMI is better than aspirin alone in reducing recurrent cardiovascular events. Data on combination use of aspirin and clopidogrel beyond 12 months is not available.

**Glycoprotein IIb/IIIa receptor antagonists.** Glycoprotein IIb/IIIa receptor antagonists are currently only available in intravenous forms and therefore only used for managing ACS in hospitals. They are used during percutaneous coronary intervention to prevent acute platelet aggregation and thrombosis. The 2 small molecules glycoprotein IIb/IIIa inhibitors (tirofiban and eptifibatide) can also be used for medical stabilization of patients.

**Specific treatment endpoints.** Specific endpoints are to ensure blood pressure,140/90 mm Hg (according to JNC VII guidelines, blood pressure goal is ,140/90 mm Hg and in patients with diabetes or chronic kidney disease, it is 130/80 mm Hg), a resting heart rate of 50 or 60 beats per minutes, and to improve exercise tolerance.

Monitoring parameters and monitoring frequency. Monitoring parameters include blood pressure, heart rate, and episodes of symptoms and side effects of individual pharmacologic agents. Since this is a stable angina case, the patient can be encouraged to obtain a home blood pressure monitoring device to check his own blood pressure and heart rate several times a week and during symptoms. The patient should have regular follow-up visits with his physicians. The patient should report any increase in symptoms or intolerable side effects to drugs immediately.

**Patient counseling.** In general, patients with any form of IHD should receive education regarding symptoms of ACS and seeking prompt medical assistance as appropriate. Also, patients should be educated to modify their lifestyles and properly manage their risk factors.
At this point, the guidelines for treatment of chronic stable angina are summarized:

- Every patient should receive aspirin, 81-325 mg daily, indefinitely (if allergic to aspirin, may use clopidogrel, 75 mg daily).
- Patients who have coronary stents should receive aspirin and clopidogrel together for 12 months, then back to aspirin alone (dose of aspirin is 325 mg for the first month, then 81 mg thereafter).
- All patients should have sublingual nitroglycerin for relief of chest pain as needed.
- Add b-blockers, then titrate until resting heart rate reaches approximately 50 to 60 beat per minute.
- If use of b-blockers are contraindicated or if patient has Prinzmetal angina, use calcium channel blockers.
- Add long-acting nitrates if angina is frequent (make sure a 6- to 12-hour nitrate-free interval is incorporated into the regimen).
- Never use nitrates alone without b-blockers or calcium channel blockers as an antianginal.
- A combination of b-blockers, and calcium channel blockers (and nitrates) may be used for severe disease (titrate to the most optimal dose based on heart rate, blood pressure, and symptoms).

Use lipid lowering drugs:

- All patients with angina pectoris should have a lipid profile done. Diet modifications and use of lipid lowering drugs are indicated for lowering total cholesterol to <200 mg/dl and LDL cholesterol to <100 mg/dl.
- If baseline LDL cholesterol is > 100 mg/dl, LDL lowering drug therapy should be initiated in addition to therapeutic lifestyle changes. When LDL lowering therapy is used in high-risk or moderately high-risk persons, intensity of therapy should be sufficient to achieve a 30-40% reduction in LDL cholesterol levels. Reduction of LDL cholesterol to <70 mg/dl with high-dose statin therapy can be considered for CV risk reduction.
- Drug combinations (eg. statin-ezetimibe combination) are beneficial for patients on lipid lowering therapy who are unable to achieve LDL-C < 100 mg/dL or LDL-C < 70 mg/dL.
- If triglycerides are 200-499 mg/dl, non-HDL cholesterol should be maintained to <130 mg/dl. Fibrate and niacin therapy can be useful options to reduce non-HDL cholesterol.
- If triglycerides are > 500 mg/dl, fibrates or niacin should be used to lower the triglyceride in order to reduce the risk of pancreatitis; these should be initiated before LDL cholesterol lowering therapy.
- If HDL cholesterol is < 40 mg/dl, consider niacin or fibrate therapy
## Table 10

### Drugs: dosage guidelines

<table>
<thead>
<tr>
<th>Class</th>
<th>Example</th>
<th>Initiating dose</th>
<th>Usual maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A) For prevention of MI and death</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid lowering drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(e.g. statins)</td>
<td>Atorvastatin</td>
<td>10 mg once daily</td>
<td>10-80 mg once daily</td>
</tr>
<tr>
<td></td>
<td>Fenofibrate</td>
<td>145 mg (nanobead formulation) or 200 mg (micronized capsule formulation) or 160 mg (micronized tablet formulation) once daily</td>
<td>145 mg (nanobead formulation) or 200 mg (micronized capsule formulation) or 160 mg (micronized tablet formulation) once daily</td>
</tr>
<tr>
<td>Antiplatelet drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>75-162 mg once daily</td>
<td>75-162 mg once daily</td>
</tr>
<tr>
<td></td>
<td>Clopidogrel</td>
<td>75 mg once daily</td>
<td>75 mg once daily</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitors</td>
<td>Ramipril</td>
<td>2.5-5 mg daily</td>
<td>10 mg daily</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>Telmisartan</td>
<td>40 mg/day</td>
<td>40-80 mg/day</td>
</tr>
<tr>
<td><strong>B) For symptom relief</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sublingual nitrates</td>
<td>Nitroglycerin</td>
<td>0.3 mg-0.8 mg every 5 minutes till cessation of pain</td>
<td>0.3 mg-0.8 mg every 5 minutes till cessation of pain</td>
</tr>
<tr>
<td>Oral nitrates</td>
<td>Isosorbide dinitrate</td>
<td>10-60 mg/day</td>
<td>30-120 mg/day</td>
</tr>
<tr>
<td></td>
<td>Isosorbide mononitrate</td>
<td>30-60 mg/day</td>
<td>60-120 mg/day</td>
</tr>
<tr>
<td>Transdermal nitrates</td>
<td>Nitroglycerin</td>
<td>5 mg once daily</td>
<td>5-10 mg once daily</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Metoprolol XR</td>
<td>50-100 mg/day</td>
<td>100-200 mg/day</td>
</tr>
<tr>
<td></td>
<td>Atenolol</td>
<td>25-50 mg once daily</td>
<td>50-100 mg once daily</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Diltiazem</td>
<td>90 mg/day</td>
<td>90-180 mg/day</td>
</tr>
<tr>
<td></td>
<td>Amlodipine</td>
<td>2.5-5 mg once daily</td>
<td>5-10 mg once daily</td>
</tr>
<tr>
<td>Cytoprotective drugs</td>
<td>Trimetazidine</td>
<td>20 mg three times daily</td>
<td>20 mg three times daily</td>
</tr>
<tr>
<td></td>
<td>Trimetazidine modified release</td>
<td>35 mg twice daily</td>
<td>35 mg twice daily</td>
</tr>
<tr>
<td>Potassium channel openers</td>
<td>Nicorandil</td>
<td>5-10 mg twice daily</td>
<td>10-20 mg twice daily</td>
</tr>
</tbody>
</table>
**Drugs: Side-effects & contraindications**

<table>
<thead>
<tr>
<th>Class</th>
<th>Main side-effects</th>
<th>Contraindications/Special precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lipid lowering drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(e.g. atorvastatin)</td>
<td>Intestinal irritation, liver enzyme elevation, skeletal muscle damage</td>
<td>Hypersensitivity, active liver disease or unexplained persistent elevations of liver enzymes, pregnancy and lactation</td>
</tr>
<tr>
<td>(e.g. fenofibrate)</td>
<td>Hepatitis, cholelithiasis, myalgia, myasthenia, rhabdomyolysis</td>
<td>Hypersensitivity, hepatic/severe renal dysfunction including biliary cirrhosis, patients with persistent liver function abnormality, gallbladder disease, pregnancy and lactation</td>
</tr>
<tr>
<td><strong>Antiplatelet agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(e.g. aspirin)</td>
<td>Diarrhoea, gastrointestinal bleeding, prolongation of bleeding time</td>
<td>Hypersensitivity, history of gastrointestinal bleeding, patients with bleeding disorders, nasal allergies, patients with chicken pox, influenza or flu symptoms, patients with gastric distress, ulcer or bleeding problems, pregnancy (3rd trimester)</td>
</tr>
<tr>
<td>(e.g. clopidogrel)</td>
<td>Diarrhoea, rash, pruritus &amp; abdominal discomfort, Neutropenia and thrombotic thrombocytopenic purpura are rare compared to ticlopidine</td>
<td>Hypersensitivity, active pathological bleeding such as peptic ulcer or intracranial hemorrhage, patients at risk of increased bleeding from trauma, surgery or other pathological conditions, patients who have lesions with a propensity to bleed (e.g. ulcers), hepatic impairment</td>
</tr>
<tr>
<td><strong>Nitrates</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(e.g. nitroglycerin, isosorbide dinitrate)</td>
<td>Headache, dizziness, flushing, postural hypotension</td>
<td>Hypersensitivity, shock, hypotensive collapse (systolic pressure below 100 mm Hg), volume depletion from diuretic therapy, use with phosphodiesterase inhibitors</td>
</tr>
<tr>
<td><strong>Beta-blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(e.g. metoprolol)</td>
<td>Bradycardia, fatigue, impotence</td>
<td>Hypersensitivity, severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent</td>
</tr>
</tbody>
</table>
Percutaneous coronary intervention (PCI) is recommended in following group of patients:

- Two- or three-vessel disease with significant proximal LAD CAD, who have anatomy suitable for catheter-based therapy & normal LV function & who have untreated diabetes.
- Significant left main coronary disease who are not candidate for CABG.
- One- or two-vessel CAD without significant proximal LAD CAD but with a large area of viable myocardium and high-risk criteria on non-invasive testing.
- One- or two-vessel CAD without significant proximal LAD CAD who have survived sudden cardiac death or sustained ventricular tachycardia.
Percutaneous transluminal coronary angioplasty (PTCA) was originally introduced as a balloon angioplasty, a procedure that involved using a catheter-borne balloon that was inflated at the site of coronary stenosis. The scope of this procedure has widened to include the use of stents, atherectomy and laser therapy.

The following are the important indications for angioplasty:

- Stable angina in patients with suitable coronary anatomy who are uncontrolled on or intolerant of medical treatment.
- Two- or three-vessel disease with significant proximal left anterior descending artery disease, in patients who have normal anatomy suitable for catheter-based therapy, normal left ventricular function, and who do not have treated diabetes.
- Unstable angina not responding to medical treatment.
- Unstable angina or AMI followed by a positive exercise test.
- AMI complicated by cardiogenic shock.
- AMI where thrombolytic drugs are contraindicated.
- One- or two-vessel disease without a significant disease of proximal left anterior descending artery but with a large area of viable myocardium and high-risk criteria on noninvasive testing.

Disadvantages. Angioplasty has similar mortality to coronary artery bypass grafting (CABG), with 1% mortality for the treatment of single-vessel disease, and 2% when more than one vessel is dilated. About 3% of people need an emergency heart bypass due to damage to the coronary artery during angioplasty. Almost one third of patients experience restenosis within 3 months and again require angioplasty. Of those who have angioplasty on more than one vessel, almost half have restenosis of one or more vessels. Almost one fifth of patients who have angioplasty require heart bypass within 3 years.

STENTS

A coronary stent (scaffold) is an artificial support device in the coronary artery to keep the vessel open. It was developed to overcome the two primary limitations of balloon angioplasty: sudden closure of the coronary artery and late restenosis. Stents prevent narrowing of the coronary artery by providing a scaffolding lattice to tack back the inner surface of the coronary artery. It prevents late restenosis by mechanically enforced remodeling and resetting of the vessel size of the stented segment. In 20% to 40%, restenosis gradually occurs.

There are several different coronary stents available, and the scaffolding lattice of each stent differs markedly in configuration. Coronary artery stenting is currently applicable only to relatively large arteries (>3mm diameter). The stents can be categorized into the mesh stents, characterized by strong and extensive scaffolding of the vessel wall (Wallstent, Palmaz-Schatz, and AVE...
Micro) and the coil stents, characterized by a low metallic surface area and predominantly transverse strut orientation (Gianturco-Roubin, Wiktor, Multilink, and Cordis). Drug-eluting stents (DESs) are now used and have been shown to dramatically reduce the risk of restenosis compared with bare metal stents. In the Sirolimus-Eluting Coronary Stent (SIRUS) Trial, 1058 patients undergoing elective coronary stent implantation were randomized to a bare stent or the sirolimus DES. The patients were followed-up for a year. The sirolimus stent reduced the restenosis rate by 75%, from 36.3% to 8.9%, and reduced the rate of repeat revascularization from 28.4% to 13%. No significant advantage was found with regard to mortality and MI.

Coronary stenting usually follows balloon angioplasty, which requires inserting a guide catheter at the ostium of the coronary artery through the femoral artery. The guide wire is then manipulated beyond the lesion, after which the balloon catheter is inserted over it. When this catheter is positioned at the site of blockage, it is slowly inflated to widen the coronary artery and is then removed.

The stent-mounted catheter is then threaded into the artery. When this is correctly positioned in the coronary artery, the balloon is inflated, expanding the stent against the wall of coronary artery. The balloon catheter, guide wire, and guide catheter are then removed, leaving the stent. A cardiac angiography follows to ensure that the stent is keeping the artery open. Aspirin is taken for few days before the procedure in the dose of 300mg a day. There is a small risk that the stented artery may close. Thrombosis, bleeding, and artery damage are rare complications.

**Coronary artery bypass grafting (CABG)** New minimally invasive operative procedures that do not require cardiopulmonary bypass may extend its use to patients who are at greater risk of surgery. Arterial grafts can be used not only from the internal mammary artery but also from the right gastroepiploic artery, inferior epigastric artery, and radial artery. Arterial grafts have many advantages over saphenous vein grafts. They have a reduced propensity to develop atherosclerosis. Reviews of patients treated with internal mammary artery grafting of left anterior descending artery have shown improved long-term survival, a lower long-term incidence of angina, and higher graft patency rates. Fourteen percent of coronary bypass operations are now reoperations. Repeat grafting is associated with higher operative risk (3%). Symptom-free patients, without complication, can be expected to return to work in 4 to 8 weeks.

**The important indications for CABG are as follows:**

- Patients with significant left main artery disease. One- or two-vessel disease without significant proximal left anterior.
- Descending artery disease but with a large area of viable myocardium and high-risk criteria on noninvasive testing.
Patients with three-vessel disease; the surgical benefit is better with left ventricular dysfunction (ejection <50%).

Patients with two-vessel disease with significant proximal left anterior descending artery disease and left ventricular dysfunction (ejection <50%).

Patients with one- or two-vessel artery disease without proximal left anterior descending artery disease who survived sudden cardiac death or sustained ventricular tachycardia.

Patients who have not been successfully treated by medical therapy. Some patients are suitable for either procedure (CABG or PCTA).

Overall there is no evidence of a major difference between the two over 3 to 5 years in the risk of death or heart attack. Occasionally, it is difficult to dilate all stenosed segments of the coronary artery at a single attempt of angioplasty, and restenosis occurs within 6 months in about one third of patients. Therefore, patients initially treated with angioplasty needed more repeat procedures to restore blood circulation (30–50%) than did bypass patients (5–10%).

Newer revascular techniques and their advantages:

Coronary atherectomy devices

Since PTCA does not remove the plaque but acts by splitting and shifting the plaque and stretching the coronary artery, this led to the development of new devices that remove the plaque and also cause fewer traumas to the deeper components of the arterial wall.

Atherectomy devices include directional, rotational atherectomy, transluminal extraction, and excimer laser angioplasty. The directional coronary atherectomy is a nonballoon interventional device. It is a cutting device, as it cuts the plaque and leaves smooth lumen. It is a suitable procedure when lesions are ostial, eccentric, or present at bifurcations. Its contraindications include small vessel size, calcified lesions, lesion angulation, and proximal tortuosity of the vessel.

Rotational atherectomy ablates plaque material. Percutaneous rotational atherectomy uses a high-speed metal burr coated with diamond clips to abrade and destroy plaques into fine microparticles.

This technique is suitable for harder calcified, fibrotic lesions.

It is contraindicated in patients with left ventricular dysfunction and in those with visible thrombus.

Transluminal extraction atherectomy (TEC) increases luminal size by cutting material and aspirating it. The system comprises a conical cutting head with two stainless steel blades bound to the distal end of a hollow flexible torque tube. A suction bottle, which collects the excised lesions, and a battery-powered motor drive unit are attached to the proximal end of the tube. The is useful in lesions in which thrombus or debris has to be removed from the artery.
Coronary laser angioplasty

Coronary laser angioplasty involves using excimer laser systems. It is a pulsed laser, that is, the energy is released in short bursts of ultraviolet light separated by relatively long periods of silence, during which laser emission is switched off. This procedure is indicated in saphenous vein graft lesions, long lesions, ostial lesions, and total occlusions. Its contraindications include bifurcation lesions, highly eccentric lesions, severe lesion, angulation, vessel tortuosity, and prior dissection.

Transmyocardial laser revascularization (TMR)

Transmyocardial laser revascularization with the aid of a laser makes small channels into the myocardium, which lead to improved exercise tolerance. The procedure is performed in the operating theater (with carbon dioxide or holmium: yttrium-aluminumgarnet [YAG] laser) or by a percutaneous approach. Although this technique gives symptomatic improvement in chronic stable angina, no definite benefits have been shown in terms of increasing myocardium perfusion.

Spinal cord stimulation

This method involves accurate placement of the stimulating electrode in the dorsal epidural space, usually at the C7-T1 level. This method is proposed for patients with chronic stable angina refractory to medical, catheter intervention, and surgical therapy.

Summary

- Stable angina pectoris is a common and disabling disorder
- With proper management, the symptoms can usually be controlled and the prognosis substantially improved
- As a minimum, each patient should have a carefully taken history and physical examination, and assessment of risk factors and a resting electrocardiogram
- Short-acting nitrates should be offered either sublingually or via spray formulation to all angina patients
- Patients should be prescribed lipid lowering drugs if they have an abnormal lipid profile (LDL-cholesterol > 100 mg/dl, triglyceride > 200 mg/dl, HDL-cholesterol < 40 mg/dl)
- Aspirin 75-162 mg/day should be administered indefinitely to all angina patients, unless contraindicated
- RAAS blockers (ACE inhibitors & ARBs when ACE inhibitors is intolerant) should be used indefinitely, unless contraindicated, in all patients with left ventricular ejection fraction < 40%.
- If there are no other contraindications, a selective beta-blocker is the drug of choice for providing symptom relief. Other effective alternatives include long-acting nitrates, calcium channel blockers, potassium channel openers and cytoprotective drugs.
Beta blockers should be used indefinitely in all patients who had MI, acute coronary syndrome, or left ventricular dysfunction with/without heart failure symptoms unless contraindicated.

Combination is recommended when a single drug is ineffective. Third drug can be added after proper evaluation & when only if optimal 2 drugs regimens is insufficient.

Revascularization (CABG or PCI) is indicated in angina patients who are not controlled by medical therapy & when there are anatomically suitable lesions.

Revascularization relieves the symptoms of angina & reduces the risk of mortality particularly in recommended sub-groups of patients.

10. TESTS AND ASSIGNMENTS FOR SELF-ASSESSMENT
FINAL LEVEL OF KNOWLEDGES

1. Which of the following best describes variant or Prinzmetal’s angina?
   A. Angina at rest, often in early morning, associated with sinus tachycardia (ST) elevation.
   B. Angina at rest, often in early morning, associated with ST depression.
   C. Angina with effort, often in early morning, associated with ST elevation.
   D. Angina with effort, often in early morning, associated with ST depression.

2. Which of the following mediators are associated with acute coronary syndromes?
   A. Adenyl cyclase, growth hormone, and parathyroid hormone.
   B. Insulin-like peptides, thyroxin, and melatonin.
   C. Pancreatic growth factor, serotonin, and adenosine monophosphate.
   D. Thromboxane A₂, serotonin, and adenosine diphosphate.

3. Which of the following contributes to the beneficial effect of nitroglycerin?
   A. Decrease of ventricular compliance.
   B. Dilation of systemic veins.
   C. Increase of left ventricular preload.
   D. Increase of left ventricular afterload.

4. How do slow calcium-channel blockers produce relaxation of vascular smooth muscle?
   A. Fragmenting thick filaments.
   B. Making no net change of influx of calcium.
   C. Reducing influx of calcium to the cell.
   D. Reducing influx of calcium to the lysosome organelle of the mitochondrion.
5. β-blockers (β-adrenergic agents) are used in the treatment of angina because:

A. They decrease variables such as heart rate and myocardial contractility.
B. They increase afterload and preload.
C. They increase sinus node automaticity.
D. They increase sympathetic tone to the myocyte.

ANSWERS

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LIST OF SUGGESTED READING

Навчальне видання

Модуль 3. Сучасна практика внутрішньої медицини.
Змістовний модуль №1.
Тема 9. Ведення хворого зі стабільною стенокардією

Методичні вказівки
для студентів та лікарів-інтернів

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виготовників і розповсюджувачів видавничої продукції серії ДК № 3242 від 18.07.2008 р.
Module 3. Current practice of internal medicine.
Contents module № 1.
Theme 9. Management of the patients with stable angina
Guidelines for students and interns