

**PRACTICAL
GUIDELINES FOR
MANAGEMENT
OF
CHRONIC STABLE
ANGINA PECTORIS**

Preface

Coronary heart disease (CHD) has assumed epidemic proportions in India. By the year 2010, 60% of the world's heart disease is expected to occur in India. Angina pectoris is the commonest initial manifestation of CHD. About half of MI patients have had preceding angina. Management of this disabling disease is important for improving the quality of life of the patient as well as to reduce the risk of cardiovascular events & mortality.

The ever increasing data available in the dynamic field of cardiology makes it difficult for the physician to make appropriate decisions in his day-to-day practice. The aim of this booklet is to present the reader with lucid, user-friendly & concise practical management guidelines for angina pectoris; with a major focus on the medical management of the disease. The information in this booklet has been compiled from the various guidelines i.e. *2006 European Society of Cardiology guidelines on the management of stable angina pectoris; ACC/AHA 2002 guidelines update for the management of patients with chronic stable angina & 2007 Chronic angina focused update of ACC/AHA 2002 guidelines for the management of patients with chronic stable angina.*

July 2009

Angina pectoris

The term 'angina pectoris' is used for *chest discomfort due to myocardial ischaemia* associated with coronary artery disease.

Angina pectoris occurs when there is an imbalance between myocardial perfusion and the demands of the myocardium. This almost always occurs as a result of narrowing of the coronary arteries due to atherosclerosis. Usually, a coronary artery must be narrowed by at least 50-70% in luminal diameter before blood flow is inadequate to meet the metabolic demands of the heart with exercise or stress.

Classification of angina pectoris

- Anginal symptoms are regarded as **stable** if they have been occurring over several weeks without major deterioration. They typically occur in conditions associated with increased myocardial oxygen consumption (e.g. during exercise).
- Angina is said to be **unstable** if pre-existing angina worsens (i.e. it becomes more frequent, more prolonged, and more severe and/or occur at a lower threshold or at rest) abruptly for no apparent reason or when new angina develops at a relatively low work load or at rest. This form of angina is often associated with rupture of the atherosclerotic plaque and subsequent clot formation within the coronary artery.
- Angina is **variant** or of the **Prinzmetal** type if it develops spontaneously with ST elevation on the electrocardiogram. This is usually due to an increase in coronary tone or spasm and usually occurs at rest.

This booklet outlines the guidelines for the pharmacological management of chronic stable angina pectoris.

Risk factors for angina pectoris

Non-modifiable

- Age
- Male gender
- Family history of coronary heart disease
- Past history of cerebrovascular or peripheral vascular disease

Modifiable

- Smoking
- High intake of alcohol
- Hyperlipidaemia
- Hypertension
- Diabetes
- Stress
- Obesity

Symptoms

Anginal symptoms have four cardinal features

a. Location

Discomfort is typically located in the retrosternal region (central chest region) and may radiate to both sides of the chest and the arms (more commonly the left) as far as the wrist, and to the neck and jaw. Quite frequently, the pain starts in one of the other areas and only later spreads to the central chest.

b. Relationship to exercise

Angina is provoked by exercise (or other stress) and is quickly relieved by rest or by using nitroglycerin. Emotions may also cause angina.

c. Character

Feeling of pressure or a strangling sensation in the chest. The intensity may vary from a slight localised discomfort to severe pain.

d. Duration

Symptoms usually spontaneously resolve within 1-3 minutes after discontinuation of exercise but may last up to 10 minutes or even longer after very strenuous exercise. Anginal pain provoked by emotion may be relieved more slowly than that provoked by physical exercise.

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.

Alternative diagnosis to angina for patients with chest pain is as follows:

Nonischemic				
Cardiovascular	Pulmonary	Gastrointestinal	Chest Wall	Psychiatric
Aortic dissection	Pulmonary embolus	Esophageal	Costochondritis	Anxiety disorders
Pericarditis	Pneumothorax	Esophagitis	Fibrositis	Hyperventilation
	Pneumonia	Spasm	Rib fracture	Panic disorder
	Pleuritis	Reflux	Sternoclavicular arthritis	Primary anxiety
		Biliary	Herpes zoster	Affective disorders
		Colic	(before the rash)	(e.g., depression)
		Cholecystitis		Somatiform disorders
		Cholelithiasis		Thought disorders
		Cholangitis		(e.g., fixed delusions)
		Peptic ulcer		
		Pancreatitis		

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

Treatment

Life style changes, drugs and interventional techniques all play a part in the treatment of angina pectoris

Aims of treatment

- To improve prognosis by preventing myocardial infarction and death
- To minimize or abolish symptoms

General management

- Stop smoking
- Limit alcohol intake
- Lose weight, if overweight
- Increase physical activity within the patient's limitation (30-60 min, 7 days/week or minimum 5 days/week)
- Limit intake of food rich in fat and cholesterol. Encourage a high intake of fruits and vegetables
- Control stress and use relaxation techniques
- Control other concomitant disorders such as diabetes, hypertension, anaemia & dyslipidemia

Drug therapy

For prevention of myocardial infarction (MI) and death

- *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
- *Reduce risk of thrombosis*
 - Aspirin 75-162 mg/day should be administered indefinitely to all angina patients, unless contraindicated
 - Clopidogrel should be used when aspirin is absolutely contraindicated
- *RAAS blockers*
 - Angiotensin converting enzyme (ACE) inhibitors should be used indefinitely, unless contraindicated, in all patients with left ventricular ejection fraction $\leq 40\%$ and in those with hypertension, diabetes, or chronic kidney disease.
 - Angiotensin receptor blockers (ARBs) are recommended for patients who have hypertension, have indications for but are intolerant to ACE inhibitors, have had a myocardial infarction with left ventricular ejection fraction $\leq 40\%$.
 - Angiotensin receptor blockers may be considered in combination with ACE inhibitors for heart failure due to left ventricular systolic dysfunction.
 - Aldosterone blockade is recommended for use in post-MI patients without significant renal dysfunction or hyperkalemia who are already receiving therapeutic doses of an ACE inhibitor and a beta blocker, have a left ventricular ejection fraction $\leq 40\%$, and have either diabetes or heart failure.

For symptom relief

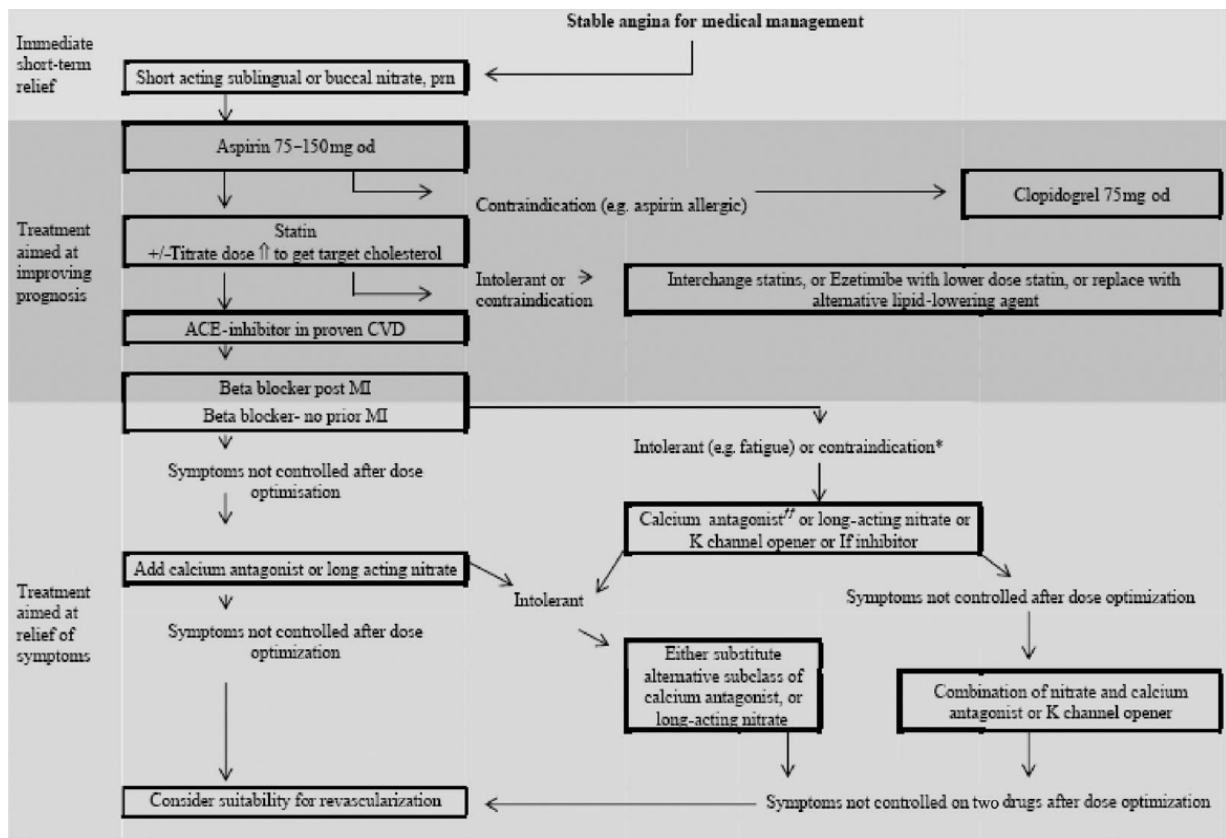
- *Nitrates:* (e.g. nitroglycerin, isosorbide dinitrate) Sublingual and spray formulations of nitrates provide rapid relief of symptoms and are used for treatment of acute attacks of angina pectoris. Oral and transdermal formulations of nitrates are used to prevent anginal attacks and should be taken regularly
- *Beta blocker.* (e.g. metoprolol, atenolol): It is beneficial to start and continue beta blocker therapy indefinitely in all patients who have had MI, acute coronary syndrome, or left ventricular dysfunction with/without heart failure symptoms, unless contraindicated
- *Calcium channel blockers (CCBs):* {e.g. diltiazem, verapamil (non-dihydropyridine CCBs), amlodipine (dihydropyridine CCBs)}.
- *Cytoprotective drugs:* e.g. trimetazidine
- *Potassium channel openers:* e.g. nicorandil

Choice of antianginal agent

- All patients should be offered short-acting nitrates either sublingually or via spray formulation. These drugs are used not only to treat an acute episode but also when an anginal attack is anticipated, e.g. prior to exercise.
- Test the effects of a beta blocker, titrate to full dose, consider the need for 24 hr protection against ischemia

- If beta blocker is not tolerated or is of poor efficacy shift to monotherapy with CCB, long-acting nitrates or nicorandil
- If the effects of beta blocker monotherapy are insufficient, add a dihydropyridine CCB
- Metabolic agents may be used as an add-on therapy or as a substitution therapy when conventional drugs are not tolerated

Figure 1: Algorithm for medical management of stable angina



Combination therapy

- Indicated when single agent is ineffective
- Provides balanced and complementary anti-anginal effect
- Provides attenuation of side-effects
- Offers enhanced patient compliance (in case of fixed-dose combinations)
- Beta-blockers are frequently combined with nitrates or dihydropyridine calcium channel blockers (e.g. atenolol plus amlodipine)
- Beta-blockers should be combined with verapamil and diltiazem with caution, because extreme bradycardia or heart block may occur
- Triple drug therapy should be considered only if optimal 2 drugs regimens are insufficient, with careful evaluation of the additional drugs

Drugs: dosage guidelines

Class	Example	Initiating dose	Usual maintenance dose
A) For prevention of MI and death			
Lipid lowering drugs (e.g. statins) (e.g. Fibrates)	Atorvastatin Fenofibrate	10 mg once daily 145 mg (nanotablet formulation) or 200 mg (micronized capsule formulation) or 160 mg (micronized tablet formulation) once daily	10-80 mg once daily 145 mg (nanotablet formulation) or 200 mg (micronized capsule formulation) or 160 mg (micronized tablet formulation) once daily
Antiplatelet drugs	Aspirin Clopidogrel	75-162 mg once daily 75 mg once daily	75-162 mg once daily 75 mg once daily
Angiotensin converting enzyme inhibitors	Ramipril	2.5-5 mg daily	10 mg daily
Angiotensin receptor blocker	Telmisartan	40 mg/day	40-80 mg/day
B) For symptom relief			
Sublingual nitrates	Nitroglycerin	0.3 mg-0.8 mg every five minutes till cessation of pain	0.3 mg-0.8mg every five minutes till cessation of pain
Oral nitrates	Isosorbide dinitrate	10-60 mg/day	30-120 mg/day
	Isosorbide mononitrate	30-60 mg/day	60-120 mg/day
Transdermal nitrates	Nitroglycerin	5 mg once daily	5-10 mg once daily
Beta-blockers	Metoprolol XR	50-100 mg/day	100-200 mg/day
	Atenolol	25-50 mg once daily	50-100 mg once daily
Calcium channel blockers	Diltiazem	90 mg/day	90-180 mg/day
	Amlodipine	2.5- 5 mg once daily	5-10 mg once daily
Cytoprotective drugs	Trimetazidine	20 mg three times daily	20 mg three times daily
	Trimetazidine	35 mg twice daily	35 mg twice daily

	modified release		
Potassium channel openers	Nicorandil	5-10 mg twice daily	10-20 mg twice daily

Drugs: Side-effects & contraindications

Class	Main side-effects	Contraindications/Special precautions
Lipid lowering drugs		
(e.g. atorvastatin)	Intestinal irritation, liver enzyme elevation, skeletal muscle damage	Hypersensitivity, active liver disease or unexplained persistent elevations of liver enzymes, pregnancy and lactation
(e.g. fenofibrate)	Hepatitis, cholelithiasis, myalgia, myasthenia, rhabdomyolysis	Hypersensitivity, hepatic/severe renal dysfunction including biliary cirrhosis, patients with persistent liver function abnormality, gallbladder disease, pregnancy and lactation
Antiplatelet agents		
(e.g. aspirin)	Diarrhoea, gastrointestinal bleeding, prolongation of bleeding time	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 (3 rd trimester)
(e.g. clopidogrel)	Diarrhoea, rash, pruritus & abdominal discomfort. Neutropenia and thrombotic thrombocytopenic purpura are rare compared to ticlopidine	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
Nitrates		
(e.g. nitroglycerin, isosorbide dinitrate)	Headache, dizziness, flushing, postural hypotension	Hypersensitivity, shock, hypotensive collapse (systolic pressure below 100 mm Hg), volume depletion from diuretic therapy, use with phosphodiesterase inhibitors
Beta-blockers		
(e.g. metoprolol)	bradycardia, fatigue, impotence	Hypersensitivity, severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent

		pacemaker is in place), diabetes, bronchospastic disease
Calcium channel blockers		
(e.g. diltiazem, amlodipine)	Headache, pedal edema	In case of non-dihydropyridine calcium channel blockers (e.g. diltiazem) – Hypersensitivity, Sick sinus syndrome except in the presence of a functioning ventricular pacemaker, second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, hypotension (< 90 mm Hg systolic), acute myocardial infarction and pulmonary congestion documented by x-ray on admission In case of dihydropyridine calcium channel blockers (e.g. amlodipine) – Hypersensitivity
Angiotensin converting enzyme inhibitors		
(e.g. Ramipril)	Renal dysfunction, cough, hyperkalemia, angioedema, nausea	Bilateral renal artery stenosis, hypersensitivity, renal dysfunction, hepatic failure, surgery, anaesthesia, pregnancy
Angiotensin Receptor blocker		
(eg. Telmisartan)	Headache, dizziness, back pain, fatigue and nausea, hyperkalemia	Pregnancy, bilateral renal artery stenosis, hypersensitivity
Cytoprotective drugs		
(e.g. trimetazidine)	Headache, gastric discomfort	Hypersensitivity
Potassium channel openers		
(e.g. nicorandil)	Headache, dizziness, flushing, hypotension	Hypersensitivity, cardiogenic shock, left ventricular failure with low filling pressures, hypotension.

Myocardial revascularization

- Coronary artery bypass grafting (CABG) is recommended in following group of patients:
 - Significant left main coronary artery disease (LM CAD) or its equivalent (i.e. severe stenosis of ostial/proximal segment of left descending and circumflex coronary arteries),
 - Three-vessel disease particularly in patients with abnormal left ventricular (LV) function (ejection fraction < 50 %) or with early or extensive reversible ischemia on functional testing
 - 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 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

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 \leq 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

Treatment mnemonic: the 10 most important elements of stable angina management

- A** = **A**spirin and **A**nti-anginal therapy
- B** = **B**eta-blocker and **B**lood pressure
- C** = **C**igarette smoking and **C**holesterol
- D** = **D**iet and **D**iabetes
- E** = **E**ducation and **E**xercise

Further Reading

1. Guidelines on the management stable angina pectoris of the European Society of Cardiology. *Eur Heart J.* 2006;27:1341-81
2. ACC/AHA 2002 guidelines update for the management of patients with chronic stable angina. *Circulation.* 2003;107:149-58
3. 2007 Chronic angina focused update of ACC/AHA 2002 guidelines for the management of patients with chronic stable angina. *Circulation* 2007;116:2762-72

Updated as on July 2008