

Approach to STEMI and NSTEMI



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Abstract

Acute coronary syndrome (ACS) refers to any constellation of clinical symptoms that are compatible with acute myocardial ischemia. ACS is divided into ST-elevated myocardial infarction (STEMI), non-ST elevated myocardial infarction (NSTEMI), and unstable angina (UA). STEMI results from complete and prolonged occlusion of an epicardial coronary blood vessel and is defined based on ECG criteria. NSTEMI usually results from severe coronary artery narrowing, transient occlusion, or microembolization of thrombus and/or atheromatous material. NSTEMI is defined by an elevation of cardiac biomarkers in the absence of ST elevation. The syndrome is termed UA in the absence of elevated cardiac enzymes. History, physical examination, ECG, biochemical markers, ECHO all remain important tools to make an appropriate diagnosis. The management of ACS should focus on rapid diagnosis, risk stratification, and institution of therapies that restore coronary blood flow and reduce myocardial ischemia.

Introduction

Acute coronary syndrome (ACS) represents the clinically manifest acute myocardial ischemia. Acute ischemia is usually, but not always, caused by atherosclerotic plaque rupture, fissuring, erosion, or a combination with superimposed intracoronary thrombosis, and is associated with an increased risk of cardiac death and myonecrosis. ACS comprises non ST elevation ACS (NSTEMI-ACS), Unstable angina (UA) and ST elevation MI (STEMI). The CREATE REGISTRY¹ data revealed that NSTEMI ACS patients take a long time to reach hospital in India, and the frequency of NSTEMI exceeds that of STEMI in contrast to the West. It is important to note that mortality of STEMI and NSTEMI are comparable after six months.² A large number of guidelines are available from different societies. In this article a systematic approach to ACS (UA, NSTEMI AND STEMI), will be discussed.

UA/ NSTEMI

Clinical presentation

Acute chest pain is one of the most common reasons for

presentation to the emergency, however only 15-20% patients with chest pain actually have ACS after evaluation.³⁻⁵ In view of missed diagnosis (2% patients approximately)³ and atypical presentation of ACS patients,⁴ a proper approach is very important. Approach to diagnosis of patients with acute coronary syndrome (ACS) is indicated in Figure 1.

The following clinical presentations are usually included in unstable angina,⁶

- Prolonged (> 20 min) anginal pain at rest.
- New onset (de novo) severe angina (class III of the classification of Canadian Cardiovascular Society (CCS)).⁷
- Recent destabilization of previously stable angina with at least CCS III angina characteristics (crescendo angina) or
- Post MI angina.

The typical clinical presentation of NSTEMI ACS is retro sternal pressure or heaviness ("angina") radiating to the left arm, neck or jaw which may be intermittent (usually lasting several minutes) or persistent. There are several atypical symptoms and these include epigastric pain, recent onset indigestion, stabbing chest pain, chest pain with pleuritic symptoms, or increasing dyspnea.

Atypical complaints are often observed in younger and older patients, in women, and in patients with diabetes.

Detailed history and physical examination : History of presenting symptoms and standard risk factors (Age, DM, HTN, smoking, family history, anginal episodes, dyspnoea, aspirin intake, past history of similar episodes, CAD, dyslipidemia etc) has to be taken and evaluated.

The clinical examination is frequently normal. The presence of tachycardia, heart failure or haemodynamic instability must prompt the physician to expedite the diagnosis and treatment of patients. It is important to identify clinical circumstances that may precipitate or exacerbate NSTEMI- ACS, such as anemia, infection, fever and metabolic or thyroid disorders. An important goal of physical examination is to exclude non-cardiac causes of chest pain and non-ischemic

cardiac disorders (e.g. pulmonary embolism, aortic dissection, pericarditis, valvular heart disease) or extra cardiac causes.

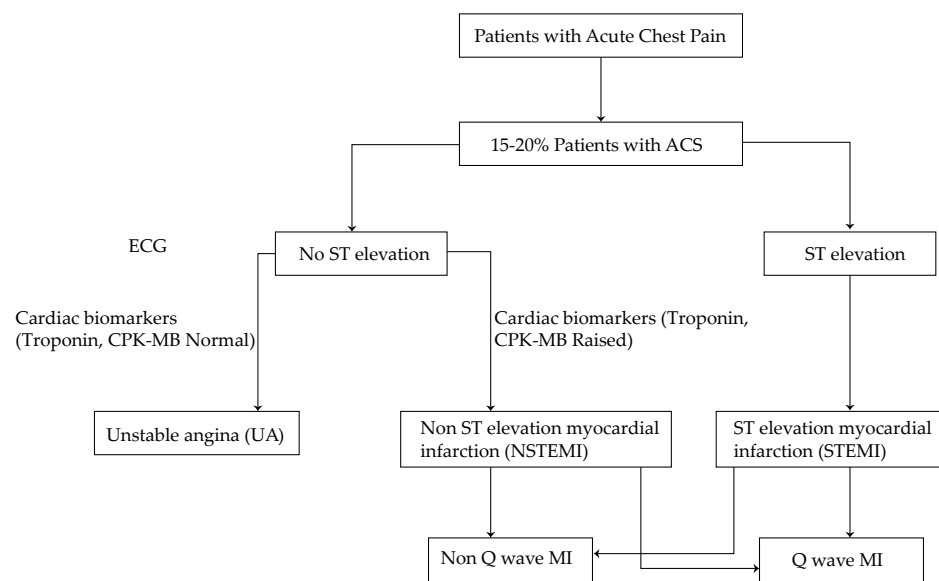


Fig. 1 : Approach to diagnosis of patients with acute coronary syndrome (ACS)

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Electrocardiogram (ECG)

In NSTEMI ACS, ECG may show ST segment deviation, T wave changes or may remain normal. In several studies, around 5% patients with normal ECG who were discharged from the emergency department were ultimately found to have acute MI or UA.⁸ ST segment shifts and T wave changes are the ECG indicators of unstable CAD. The number of leads showing ST depression and the magnitude of ST depression are indicative of the extent and severity of ischemia and correlate with the prognosis.⁹ ST depression of > 2 mm carries an increased mortality risk. Inverted T waves, especially if marked (greater than or equal to 2mm (0.2 mv) also indicate UA/ NSTEMI. Q waves suggesting prior MI indicate a high likelihood of IHD.

Biochemical Markers

Cardiac troponin (CTn) is the biomarker of choice because it is the most sensitive and specific marker of myocardial injury/necrosis available. Troponin levels usually increase after 3-4 hours. If the first blood sample for CTn is not elevated, a second

Table 1 : The TIMI risk score for NSTEMI-ACS

Characteristics	Points
Historical	
Age ≥ 65	1
≥ 3 risk factors for CAD (DM,HTN, SMOKING,HIGH CHOLESTEROL,FAMILY HISTORY)	1
Known CAD (Stenosis ≥ 50 %)	1
Aspirin use in past 7 days	1
Presentation	
2 anginal events in < 24 hrs	1
ST – segment deviation ≥ 0.5 mm	1
↑ Cardiac markers	1
Risk Score = Total Points	(0-7)

sample should be obtained after 6-9 h, and sometimes a third sample after 12 to 24 hours is required. Troponin level may remain elevated up to 2 weeks. Elevated CTn values signal a higher acute risk and an adverse long term prognosis.¹⁰ Creatine Kinase MB is less sensitive and specific for the diagnosis of NSTEMI ACS. However, it remains useful for the diagnosis of early infarct extension (reinfarction) and peri-procedural MI because of its short half life. NT-Pro BNP is helpful in assessing left ventricular failure patients.

Echocardiography

Echocardiography and Doppler examination should be done after hospitalization to assess the global left ventricular function and any regional wall motion abnormality. Echocardiography also helps in excluding other causes of chest pain.

Risk Stratification at presentation

NSTEMI ACS includes a heterogeneous group of patients with a highly variable prognosis. The risk stratification (Table 1) is necessary for prognosis assessment and treatment. A simple TIMI risk score¹¹ has been validated and can be used.

A TIMI score <3 usually indicates a low risk and a TIMI score = 3-4 indicates intermediate risk, where as score of 5-7 is high risk.

In general, patients having multiple coronary risk factors, advanced age, rest angina, clinical left ventricular (LV) dysfunction, prior history of percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABGS) or patients with dynamic ST-T changes and elevation of troponin or CK-MB indicates myocyte necrosis and a high risk. There are other risk models based on PURSUIT trial¹² and GRACE registry.¹³

Management : Approach to management of NSTEMI is shown in Figure 2. Patients who are awaiting hospitalization are advised to chew non-enteric coated aspirin (162 to 325 mg) and use sublingual nitrate for pain relief.

Approach to Management of NSTEMI

Patients with definite or probable NSTEMI-ACS who are stable should be admitted to an inpatient unit for bed rest with continuous rhythm monitoring and careful observation for recurrent ischemia. High risk patients, including those with continuing discomfort and/or haemodynamic instability, should be hospitalized in a coronary care unit (CCU) and observed for at least 24-48 hours.

Fibrinolytic (thrombolytic) therapy using streptokinase, urokinase, tenecteplase or any other agent should not be used in patients with UA and NSTEMI. These agents can prove harmful. Glycoprotein IIb/IIIa agents like abciximab, tirofiban and eptifibatid are mostly useful in patients undergoing percutaneous coronary interventions (PCI).

Anti-ischemic and analgesic therapy

Oxygen is useful for initial stabilization particularly in those with hypoxemia.

Topical, oral or intravenous nitrates are recommended for pain relief. Intravenous nitroglycerin (NTG) is particularly helpful in those who are unresponsive to sublingual NTG, in hypertension and in those with

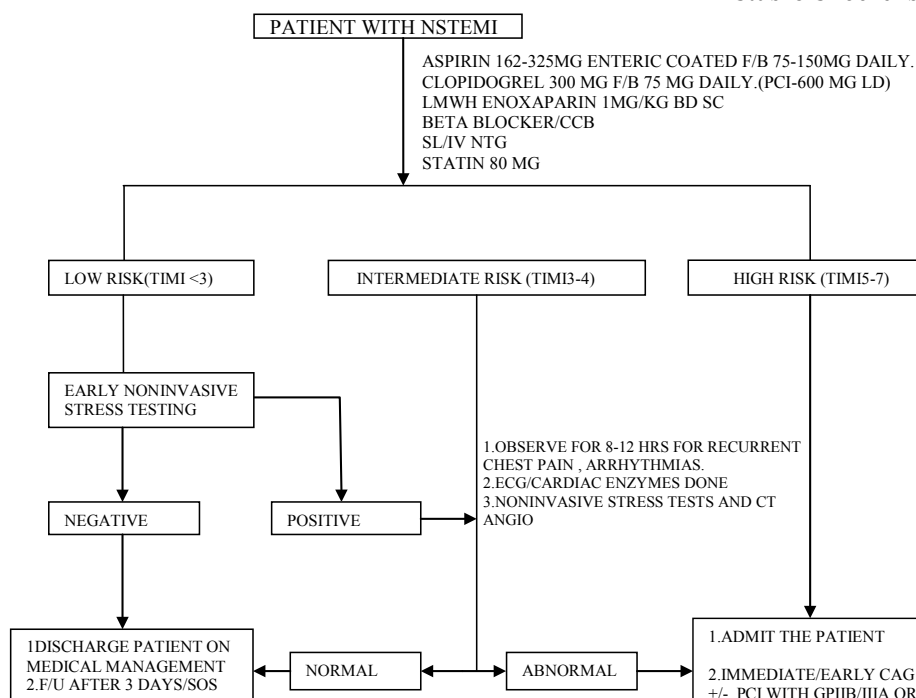


Fig. 2 : Approach to Management of STEMI

Table 2 : The indications for urgent coronary angiography

Refractory angina (e.g. evolving MI).

- Recurrent angina despite intense antianginal treatment (associated with ST depression (≤ 2 mm) or deep negative T waves).
- Clinical symptoms of heart failure or haemodynamic instability ('Shock').
- Life threatening arrhythmias (ventricular fibrillation or ventricular tachycardia).

heart failure. Nitrates should be used with caution if systolic blood pressure is below 100 mm of Hg.

The nonsteroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors should not be administered for pain relief. It can cause increased risk of cardiovascular events.¹⁴ Note of caution is also raised about use of morphine in UA/NSTEMI.

Oral beta blockers are useful for pain relief. The use of intravenous beta blockers should be avoided particularly in unstable patients. Calcium channel blockers are of utility in vasospastic angina and in patients with contraindications to beta blockade. Other antianginal drugs like ivabradine, trimetazidine, ranolazine and nicorandil have a very limited role to play. They have no survival benefit.

Antiplatelet agents

Aspirin should be administered to all patients unless contraindicated and as mentioned earlier, initial dose of chewed non-enteric aspirin from 162 to 325 mg is recommended. The subsequent dose of aspirin can be 75 to 100mg daily on a long term basis. GI bleeding appears to increase with higher doses.

Clopidogrel is recommended in all patients with an immediate dose of 300 mg followed by 75 mg daily. In patients considered for a PCI, a loading dose of 600 mg is advised to achieve more rapid inhibition of platelet function. Clopidogrel should be maintained for at least 12 months unless there is an excessive risk of bleeding.

TRITON TIMI- 38 trial¹⁵ has shown that in patients with ACS undergoing PCI, prasugrel significantly reduced the incidence of ischemic events, both in short and long term but was associated with an increased risk of bleeding, particularly in patients with age > 75 yrs, weight <60 kg and patients with h/o TIA/stroke or h/o intracranial haemorrhage.

Another new promising reversible anti-platelet drug is Ticagrelor. It is not available for use in India at present.

Early ACS trial¹⁷ did not find upstream use of GP IIb/IIIa agents beneficial in ACS.

Anticoagulants

Anticoagulation is recommended for all patients in addition to antiplatelet agents.^{3,4} An increasing number of agents are available and include unfractionated heparin (UFH), low molecular weight heparin (LMWH), fondaparinux and bivalirudin. The choice of anticoagulation depends on the risk of ischemic and bleeding events and choice of the initial management strategy (e.g. urgent invasive, early invasive or conservative).

Enoxaparin (1mg/kg bw twice daily) is a preferred anticoagulant and is a good option in patients treated conservatively or by invasive strategy. Enoxaparin can be stopped within 24 h after an invasive strategy whereas it should be administered up to hospital discharge (usually 3 to 5 days) in conservative strategy.

Fondaparinux is recommended on the basis of most favourable efficacy/ safety profile and the recommended dose is 2.5 mg daily.¹⁸ This agent causes least bleeding complications. An additional UFH in standard dose of 50-100 U/kg bolus is necessary during PCI due to slightly high incidence of catheter thrombosis.

Bivalirudin is currently recommended as an alternative anticoagulant for urgent and elective PCI in moderate or high risk NSTEMI ACS.¹⁹ Bivalirudin reduces the risk of bleeding as compared with UFH/LMWH plus GP IIb/IIIa inhibitor but needs bolus of heparin additionally during PCI to prevent stent thrombosis.

Statins and other drugs

Statins are recommended for all NSTEMI ACS patients, irrespective of cholesterol levels, initiated early after admission, with the aim of achieving LDL C levels <70 mg/dL. Atorvastatin is usually the preferred agent, at a dose of 80mg per day. ACE inhibitors are indicated in patients with reduced LV systolic function. ARB's are indicated in those patients who are intolerant to ACE inhibition.

Coronary revascularization

Revascularization for NSTEMI ACS is performed to relieve angina, ongoing myocardial ischemia and to prevent progression to MI or death. The indications for revascularization and the preferred approach, PCI or CABGS depend on the extent and severity of the lesions, the patient's condition and co-morbidity (Tables 1 and 2).²⁰

The indications for urgent coronary angiography and invasive strategy are shown in Table 2.

Conservative and Invasive Strategy

RCT's have shown that an early invasive strategy reduces ischemic end points mainly by reducing severe recurrent ischemia and the need for re-hospitalization and revascularization.²¹ This strategy reduces cardiovascular death and MI up to 5 years of follow-up.²² High risk/unstable patients benefit most from the early revascularization therapy and these patients should be promptly treated in advanced centers.

The mode of revascularization is usually based on the severity and distribution of the CAD. The PCI is usually performed for the culprit lesion using drug eluting stents. Significant lesions in multiple vessels can be treated either in the same sitting or in a staged fashion as considered appropriate. CABG is usually advised for complex CAD not amenable to PCI, left main with triple vessel disease, total occlusions and diffuse disease. It is important to consider the bleeding risk as these patients are on aggressive antiplatelet therapy. The benefits of CABG are greatest after several days of stabilization with medical treatment and stopping the antiplatelet agents.

Long term management

Patients with NSTEMI ACS after the initial phase carry a high risk of recurrence of ischemic events. Therefore, active secondary prevention is an essential element of long term management. Life style alterations, weight reduction, blood pressure control, management of diabetes, lipid intervention, antiplatelet agents, beta blockers, ACE inhibitors (or ARB) remain extremely important.

STEMI

Recent articles have described the evidence-based diagnosis and management of acute ST segment elevation myocardial

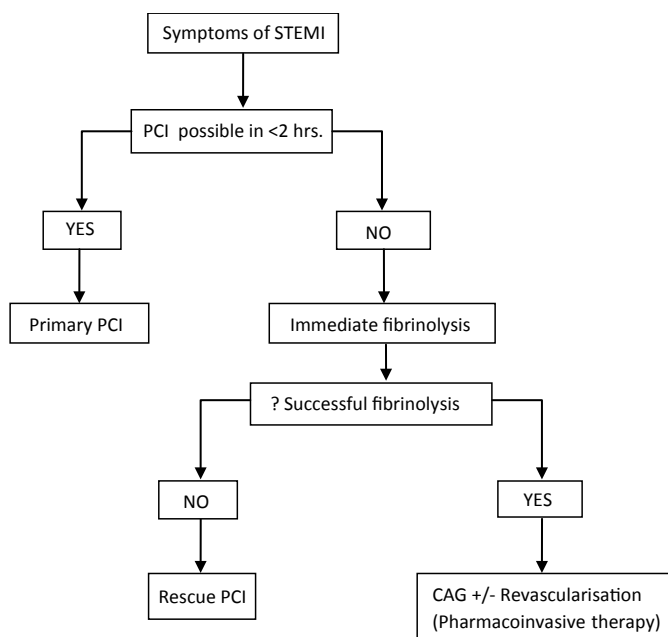


Fig. 3 : Approach to Management of STEMI

infarction (STEMI).²³⁻²⁶ While these are erudite and exhaustive, this article attempts to provide an approach for making decisions for the optimal management of patients with STEMI.

Diagnosis of STEMI

Early diagnosis is the key to early treatment of STEMI. A history of chest pain or discomfort lasting 10-20 minutes should raise the suspicion of acute STEMI in susceptible individuals (middle-aged male patients, particularly if they have risk factors for coronary disease)

Diagnosis of STEMI is based on any two of the following :

1. Chest pain.
2. ECG changes or new LBBB.
3. Raised biomarkers.

STEMI patients may experience a range of symptoms varying from crushing retrosternal or left sided chest pain /discomfort with associated typical symptoms to isolated dyspnoea, syncopal attacks, malaise and breathlessness. Elderly, diabetics and patients on NSAIDs may suffer silent myocardial infarction. These patients are commonly found to have cardiogenic shock, hypotension, arrhythmias and conduction blocks and acute left ventricular failure.

A 12-lead ECG must be performed as soon as possible. If the initial ECG is not suggestive of STEMI but the patient continues to have symptoms, repeat ECGs must be obtained (every 15 minutes or so). While markers of myocardial necrosis are useful in corroborating the diagnosis, it must be emphasized that they may not be elevated early after the onset of symptoms.

In doubtful cases, echocardiography may be a useful adjunct in making the diagnosis, particularly among young patients without prior history of coronary disease.²⁶

Management of STEMI

Figure 3 depicts an approach to management of STEMI. Killip class is prognostically useful. The following characteristics have been most consistently associated with adverse outcomes in patients with STEMI.²⁷⁻²⁹

- i. Older age (age ≥ 75 years)
- ii. Higher Killip class (class III or IV)
- iii. Lower systolic blood pressure (< 100 mm Hg)
- iv. Higher heart rate (> 100 /min)
- v. Anterior MI

The greater the number of risk factors, the higher is the risk. Therefore, after instituting initial treatment (which may include fibrinolytic therapy), such patients are best transferred to hospitals with coronary care units and catheterization laboratory facilities.

Initial Treatment

The first treatment that should be given is 325 mg of (preferably) non enteric-coated aspirin to be chewed. All patients should receive aspirin.³⁰ Clopidogrel should be administered at a loading dose of 300 to 600 mg to all patients.³¹⁻³² Patients undergoing primary PCI should receive a 600 mg loading dose.³³

All patients should receive medications to relieve pain. These may include opioid analgesics (morphine sulfate intravenously) where available. Sublingual or intravenous nitrates should be administered if systolic blood pressure is ≥ 120 mm Hg. If systolic BP is ≥ 100 mm Hg but less than 120 mm Hg, nitrates must be administered cautiously. Non-steroidal anti-inflammatory drugs (NSAIDs, other than aspirin) should not be given for analgesia.³⁴

Reperfusion therapy is the cornerstone of STEMI management and should be instituted in all patients presenting within 12 hours of onset of symptoms.^{30,35} The most efficacious reperfusion therapy available is timely primary PCI,³⁶ but it may not be the most effective in the Indian context, given the relative paucity of PCI-capable centers. Moreover, since most of these centers are located in urban areas, the distances involved in transporting patients from rural areas become prohibitive. Fibrinolytic therapy therefore remains the most practicable reperfusion strategy for India. The most recent data from India suggests that only about 8% of patients with STEMI receive primary PCI.³⁷ Nearly 60% of patients receive fibrinolysis with streptokinase as initial treatment. It should be emphasized that even among urban/semi-urban dwellers (only 17% of patients enrolled in the CREATE registry were from rural areas), a third of patients did not receive any form of reperfusion therapy.³⁷ Patients presenting to PCI-capable centers should of course be treated with timely primary PCI if the door-to-balloon time is anticipated to be less than 2 hours from the time of arrival at the hospital.²⁶ It should be recognized that door-to-balloon times may be greater than 2 hours even in PCI-capable centers during off-duty hours, weekends and holidays, and immediate fibrinolysis may be the better option when delays are anticipated. Such hospitals should implement processes to minimize and monitor door-to-balloon times. Indication for primary PCI is shown in Table 3.

Choice of Fibrinolytic Agent

Traditionally, streptokinase has been the most commonly used fibrinolytic agent in India. Recently, there is some favorable evidence for the use of tenecteplase in Indian settings.³⁸⁻³⁹ Tenecteplase has the advantage of being fibrin-specific, can be given as a bolus dose, and has a lower incidence of hypersensitivity reactions. TIMI 3 flow in the infarct related coronary artery may also occur more frequently with tenecteplase when compared to streptokinase. Tenecteplase should be administered at a dose of 0.5 mg/kg body weight.⁴⁰

Table 3 : Indications for primary PCI (STEMI)

1. Patients presenting within 12 hours of symptom onset and anticipated time from first medical contact to balloon inflation of 2 hours or less (including the time taken for transport)
2. Contraindications to fibrinolytic therapy
3. Patients presenting 12-24 hours of symptom onset with ongoing symptoms/signs of ischemia or hemodynamic instability

Transport of Patients to Centers with CCUs and/or PCI Capability

The delay to reach hospital can be shortened by institution of systems to initiate pre-hospital evaluation and fibrinolysis. Pre-hospital fibrinolytic therapy has clearly shown to improve outcomes and has compared favorably with primary PCI.⁴¹

Recent studies in Europe and North America have suggested that transport of patients to PCI-capable centers may be a better strategy than immediate fibrinolytic therapy.⁴² Such a strategy may however not be suitable for most parts of India because of the distances involved and the insurmountable logistics of transport. Nevertheless, it may be possible for small geographic units (urban or rural) to develop systems for the provision of efficient services for transporting patients to designated PCI-capable centers. Recent data from India suggests that only 6% of patients with STEMI travel to hospital by ambulance.³⁷

After administration of fibrinolytic therapy several situations may necessitate transfer of patients to centers with CCUs and/or PCI capabilities. These are listed in Table 4.

Antiplatelet Treatment

Aspirin and clopidogrel should be administered initially as discussed. As maintenance dose aspirin (75-100 mg) and clopidogrel (75 mg) should be given.

As per the latest ACC/AHA Focused Updates, Glycoprotein IIb/IIIa antagonists may be selectively used in patients undergoing primary PCI in the setting of dual antiplatelet therapy with UFH or bivalirudin as the anticoagulant in the catheterization laboratory, at the time of the procedure where large thrombus burden is there or patient has received inadequate thienopyridine loading.

There is no role of administering these agents within the context of a strategy to bridge the time delay before primary PCI (facilitated PCI).⁴⁵ Abciximab, eptifibatid and tirofiban appear to be similarly effective and may be used depending upon local preferences and availability.²⁵

Antithrombotic Therapy

Following treatment with both fibrin-specific and non fibrin-specific fibrinolytic agents, there is strong evidence for the use of antithrombotic agents for reducing reinfarction or recurrent ischemia.^{35,46} Recent studies suggest that low molecular weight heparins (LMWH) may be better than unfractionated heparin (UFH) for this purpose.⁴⁶⁻⁴⁸ The LMWHs enoxaparin or reviparin may be administered for up to 8 days post-MI. Fondaparinux has recently been shown to reduce the occurrence of death or reinfarction while concomitantly reducing the risk of major bleeding, and may therefore be considered among patients undergoing treatment with streptokinase.⁴⁹ There is no role for bivalirudin among patients receiving fibrinolytic therapy.

Patients undergoing primary PCI should receive periprocedural UFH²⁶ or bivalirudin.⁵⁰ Fondaparinux (without added UFH) may increase the risk of catheter thrombosis.

Table 4 : Indications for transfer of patients (after fibrinolytic therapy) to centers with CCUs and/or PCI capabilities

1. Patients in cardiogenic shock or those who are at high risk of developing cardiogenic shock^{†43}
2. Failed fibrinolytic therapy
3. High-risk patients^{†44}

[†]Age >70 years, systolic blood pressure <120 mmHg, heart rate >110/min or <60/min, and increased time since onset of symptoms.⁴³

[‡]Patients with ST elevation ≥2 mm in anterior leads or ≥1 mm in inferior leads who have at least one of the following high-risk factors: systolic blood pressure < 100 mm Hg, heart rate >100/min, Killip class II or III, ST-segment depression of ≥2 mm in the anterior leads, or ST-segment elevation of ≥1 mm in right-sided lead V4 (V4R).⁴⁴

[†]PCI may then be performed as and when needed or as part of a pharmaco invasive strategy

Patients not receiving any reperfusion therapy Fondaparinux may be the preferred agent among patients who have not received any reperfusion therapy.⁵¹

Beta Adrenergic Antagonists

Oral beta-blockers should be administered in the first 24 hours to patients who do not have heart failure, a low output state, are not at increased risk of developing cardiogenic shock,⁴³ or do not have other contraindications to beta-blocker therapy. ACE inhibitors and ARBs' care should be taken to avoid hypotension.

ACE inhibitors improve survival in patients who have reduced left ventricular ejection fraction (LVEF ≤40%) and those who are in heart failure following STEMI.²⁶ Benefits are proportionately lower among low risk patients. ACE inhibitors should be started in the first 24 hours after STEMI in the absence of contraindications.⁵²⁻⁵³ ARBs may be used in patients who do not tolerate ACE inhibitors.²⁶

Routine use of intravenous or oral nitrates does not improve outcomes in patients with STEMI. Nitrates may be used for pain relief. There is no role for the routine use of calcium antagonists, intravenous magnesium, antiarrhythmic agents or glucose-insulin-potassium infusions, and may be associated with adverse outcomes in some cases.²⁶ High dose statins should be initiated as early as possible during hospital stay as part of secondary prevention measures. The dose of statin to be used in Indian patients is not clear, but lowering LDL levels to ≤80mg/dL may be a useful target.

Management Post-fibrinolytic Therapy

Several studies have suggested that routine angiography and PCI of the infarct related artery may reduce the rates of reocclusion or reinfarction.⁵⁴⁻⁵⁷

Recent data clearly suggests that Pharmaco-invasive therapy has an important place in improving the prognosis of patients after thrombolysis. Unlike facilitated PCI where patients are immediately taken up for PCI after thrombolysis. It is increasingly been demonstrated that patients after a successful thrombolysis should be transferred to facilities with a cardiac cath laboratory for coronary angiography and, if need be, a PCI with stent deployment.

However, because of the resource intensiveness of this strategy and the absence of an effect on survival in several studies most guidelines still favor a more conservative approach consisting of revascularization guided by the results of risk-stratification by early exercise stress testing. Angiography (and

revascularization) should of course be performed in the event of spontaneous ischemia or the development of mechanical complications.

After the acute phase of STEMI, therapeutic lifestyle changes (including smoking cessation, exercise and dietary modification) and drugs for secondary prevention assume critical roles in improving outcomes in the medium and long-term. Patient counseling and education are key to maintaining adherence to therapy in the long run.

For patients being discharged home, emphasize the following:

Timely follow-up with primary care provider. Compliance with discharge medications, specifically aspirin and other medications used to control symptoms and need to return to the physician for any change in frequency or severity of symptoms.

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