GUIDELINES FOR THE MANAGEMENT OF CARDIOVASCULAR DISEASES IN INDIA

Part 1

Ministry of Health & Family Welfare

Govt. of India, New Delhi

Contents

The cardiovascular diseases are very important cause of morbidity and mortality in India. There is increase in incidence and prevalence of cardiovascular disease in this country. The healthcare burden of this menace is enormous. To fight this growing burden of cardiovascular epidemic government of India under the leadership of Dr. Jagdish Prasad, Director General, Health Services, constituted a special task group of experts for preparation of the guidelines of cardiovascular disease. The task group under the leadership of Prof. (Dr.) Upendra Kaul, Executive Director & Dean of Cardiology (Fortis Group of Hospitals) prepared the initial guidelines for the following diseases

1. Congenital Heart Disease.
2. Acute coronary syndrome/Non ST elevation MI
3. ST elevation myocardial infarction (STEMI)

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REVIEW OF STGs

The draft guidelines were forwarded to many experts for critical review, suggestions and amendments. The following experts have reviewed these draft guidelines. The sub group would like to place on record their useful contribution and acknowledges their efforts.

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CONSENSUS DOCUMENT ON CONGENITAL HEART DISEASE

1.0 INTRODUCTION

This brief document will provide a broad outline for selected congenital heart diseases. It needs to be recognized that there are unlimited possibilities because of the enormous variety of congenital heart diseases. Therefore only a few common situations will be discussed here. Guidelines have been recently developed and published through consensus among all leading pediatric cardiologists in India and these references are listed below. They cover most common situations and provide a ready reference.

1. Shrivatsava S, Saxena A, Iyer KS, Radhakrishnan S, Kumar RK, Maheswari S, Pediatric Cardiac Society of India Recommendations for Timing of Surgery/Catheter Intervention in Left-to-Right Shunts, Indian Heart J 2006; 58: 169-171.

2. Working group on management of congenital heart diseases in India, Consensus on Timing of Intervention for Common Congenital Heart Diseases. Ind Pediatr 2008;45:117-126.

3. Working group on management of congenital heart diseases in India, Drug Therapy of Cardiac Diseases in Children, Ind Pediatr 2009;46:310-338.

4. Kumar RK, Sandoval J, Consensus Statements on Pulmonary Hypertension Associated with Congenital Heart Disease: Advanced pulmonary vascular disease: The Eisenmenger syndrome, Cardiol Young 2009; 19(E-Suppl. 1): 39-44.

5. Kumar RK, Shrivastava S, Pediatric Heart Care in India, Heart 2008;94;984-990.

The following book is specially written for the Indian situation:

Kumar RK, Prabhu SS, Ahamed Z, IAP Specialty Textbook of Pediatric Cardiology, Jaypee brothers, New Delhi, India, 2008.

The following three conditions will be covered here

1. Cyanotic congenital heart defects

2. Left to right shunts

3. Acute rheumatic fever

2.0 Cyanotic Heart Disease:

1. Introduction: Disease categories

2. Cyanotic Spells and their management

3. Timing of intervention for common lesions

2.1 Disease Categories:

Cardiac conditions that result in cyanosis are extremely diverse. The management guidelines are unique to every lesion. Even within lesions there are numerous categories that require individualized attention. For example Tetralogy of Fallot has numerous anatomic variations that can seriously influence how the condition is managed. Broad principles have been listed in published guidelines (reference 3).

Common lesions in broad categories of cyanotic congenital heart disease (CCHD) that include conditions associated with reduced pulmonary blood flow, CCHD with increased pulmonary blood flow and CCHD associated with pulmonary hypertension are discussed in the published reference.

2.2 Cyanotic Spells:

Since cyanotic spells are common to a variety of CCHD conditions associated with reduced pulmonary blood flow, it will be discussed in greater detail here:

Hyper cyanotic or Cyanotic spell is a pediatric emergency, which requires prompt recognition, and intervention to prevent disabling cerebro-vascular insults and to save lives. A cyanotic spell needs to be taken seriously not just because of the immediate threat but also because it indicates the need for early operation.

How to recognize a spell?

- Commonly seen below 2 years [peaks between 2 months to 6 months]
- Onset is usually spontaneous and unpredictable
- Occurs more often in early morning, although can occur at anytime in the day.
- Infant cries incessantly, are irritable and often inconsolable.
- Tachypnea is prominent and a cardinal feature. Typically these infants have a pattern of
- Deep and rapid breathing without significant subcostal recession.
- Cyanosis deepens as the spell progresses.
- Later gasping respiration and apnea ensues, which leads to limpness and ultimately
- Anoxic seizures.

- Can last from minutes to hours.
- Auscultation reveals softening or disappearance of pulmonary ejection murmur.
- Occasional patient can have profound bradycardia.

Cardiac lesions which produce spells

- Tetralogy of Fallot.
- TOF with Pulmonary atresia.
- Tricuspid atresia and PS.
- DORV with VSD and PS.
- D-TGA or L-TGA with VSD and PS.
- Single ventricle with PS.
- Atrioventricular septal defect with PS.

Management of spells

1. Check airway and start oxygen. If child is uncomfortable with mask or nasal cannula, deliver oxygen via tube whose end is held ½ - 1 inch away from nose. This corresponds to delivering 80% oxygen.

2. Knee - chest position.

3. Obtain a reliable intravenous access.

4. Sedate child with subcutaneous morphine 0.2 mg/kg/dose]or i/m ketamine [3-5 mg/kg/dose] if the access is not obtainable expeditiously.

5. Soda -bicarbonate 1- 2 ml/kg given as 1:1 dilution or can be diluted in 10 ml/kg of isolyte-P which is given bolus as the initial resuscitating fluid.

6. Correct hypovolemia (10ml/kg fluid bolus of isolyte P or dextrose normal saline).

7. Keep the child warm.

8. Start beta -blockade. Beta blockade is fairly safe unless a specific contraindication like bronchial asthma or ventricular dysfunction exists. It should always be given with heart rate monitoring.

Medications and dosages:

- IV metoprolol 0.1 mg/kg, given slowly over 5 min.
- Can repeat every 5-min for a maximum of 3 doses.
- Can be followed by infusion 1-2 mcg/kg/min
- Monitor saturation, heart rates & BP
- Aim to keep heart rate below 100/min.

Other options

- I/v esmolol: 500mcg/kg over 1 min as loading dose, 50 mcg/kg/min for 4 minutes; if desaturation persists without a significant decrease in heart rate the loading dose will need to be repeated and the infusion rate can be increased in 50 mcg/kg/min increments until 300mcg/kg/min; this infusion should be maintained at the rate that produces the desired result. Esmolol is relatively expensive but has the advantage of being very short acting.
- I/v propranolol [0.1 mg/kg].If desaturation persists and there is still no significant trend towards improvement despite maximum beta blockage
- Start vasopressor infusion.

  Methoxamine given i/v at dose of 0.1mg-0.2 mg/kg /dose or i/m (0.1- 0.4

  mg/kg/dose). Phenylepherine: 5ug/kg as bolus and then 1-4 ug/kg/min as infusion.

- If spells are persistent, consider paralyzing the child, elective intubation and ventilation and plan for surgery, which can be corrective or palliative [BT shunt]
- If convulsions occur- consider IV diazepam 0.2 mg/kg or IV midazolam 0.1-0.2 mg /kg/dose, as slow push.

Appropriate and timely management of cyanotic spells can save lives and prevent CNS insults.

After a Spell:

- After a spell is successfully managed, a careful neurological examination is mandatory. In case of suspicion of neurologic insult during a spell, a CT scan is to be done to assess the presence and extent of cerebral infarcts.
- Initiate maximally tolerated beta-blockade (propranolol 0.5-1.5 mg/kg/dose 8hourly or 6 hourly). The dose can be titrated by the heart rate response. Beta blockade may help improve restiniled segmental analysis by 2D echo for complete diagnosis.
- Plan towards early corrective or palliative operation (depending on the age and anatomy).
- Correct anemia by packed cell transfusion. Hemoglobin levels < 12 gm/dl merit correction through a blood transfusion in children with cyanotic spells; Continue therapeutic (if anemic) or prophylactic iron therapy (if not anemic).

Preventing a Spell in a Child with a Cyanotic Congenital Heart Defect

Parents of patients diagnosed to have a cyanotic congenital heart defect should be counseled if the possibility of occurrence of a spell is anticipated:

- Explain to them the circumstances when a spell may occur.
- Avoid dehydration.
- Rapid control of temperature whenever fever occurs
- Encourage early surgical repair

Obtaining IV access in a cyanotic child can precipitate spells. Difficulty in obtaining access can potentially be avoided by sedating child with IM ketamine [3-5 mg/kg] and/or by using local anesthetic skin ointment before attempting for venous access or blood sampling.

2.3 Timing of Intervention in common cyanotic heart diseases:

Broad guidelines have been published (reference 3). Numerous anatomic variations dictate specific decisions for individual patients. Additionally the paucity and variable capabilities of centers capable of infant and newborn heart surgery in India will need to be recognized (reference 5). All these factors make decision making in individual patients quite complicated and highly individualized.

3.0 Left to right shunts:

1. Introduction: Timing and indications of surgical or catheter-based intervention

2. Medical management while awaiting surgery or intervention

The timing of surgical or trans-catheter intervention for left to right shunts is a critical decision and one of the most important tasks the pediatric cardiologist is asked to perform. Simply stated, the decision about when to intervene requires carefully balancing the results of the procedure with the natural history of the conditions. The extraordinary variety of conditions associated including unlimited combination of defects complicates the decision making process. Further, during the last 30 years there have been numerous advances in the field of pediatric cardiology and pediatric cardiac surgery. These advances have enabled improved results from operations and trans-catheter interventions and have allowed the procedures to be performed early. In addition, we now have information on the natural history of many congenital heart conditions. An increasing number of studies are being published on the long-term results of operations and interventions for congenital heart disease. Because of the wealth of information available to us the decision about when to intervene in CHD" now involves careful consideration of a number of variables that influence natural history and procedural outcome. There are no simple rules for the numerous CHD conditions and the decision making process has to be individualized for every patient.

Detailed guidelines for individual left to right shunts are provided in reference number 1 and 2.
These are fairly contemporary and represent a consensus of national experts.

While awaiting surgery or catheter intervention, medications need to be administered. Specific guidelines have been developed for this purpose and are published (reference number 4) through a consensus of national experts.

4.0 ACUTE RHEUMATIC FEVER (RF) AND RHEUMATIC HEART DISEASE (RHD):

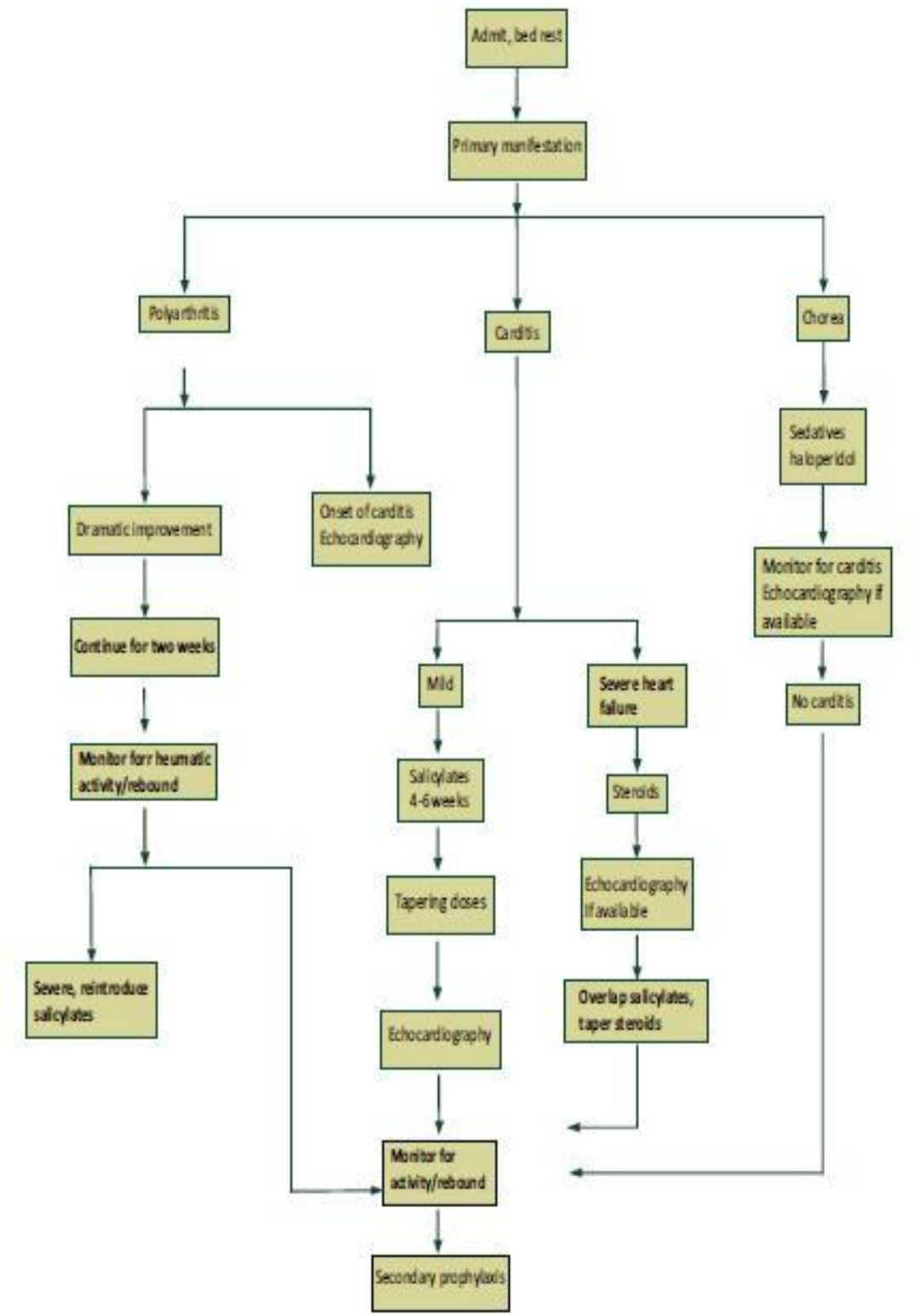
In the past 4-5 decades there have been modest advances in our understanding of the disease process. There have been minor changes in the diagnostic criteria and management practices for RF have also largely remained unchanged for the last 20-30 years. However, there have been important changes in the epidemiology both in India and the rest of the world. There appears to have been a sharp decline in RF and RHD in parts of India that have shown improving indices of human development. Physicians living in these parts of India need to be mindful of the prospect of over-diagnosis of RF. For most of India, however, the disease is still quite common and it is important to not miss the initial episode of RF because secondary penicillin prophylaxis still remains the most effective way of preventing RHD.

The algorithm displayed in the next page summarizes the initial management of RF.

Consensus guidelines have been published (see reference below):

Saxena A, Kumar RK, Gera RPK, Radhakrishnan S, Misra S, Ahamed ZA (writing committee members), Consensus guidelines on pediatric acute rheumatic fever and rheumatic heart disease, Indian Pediatrics, 2008;45:565-573.

Figure 1 : Algorithm for initial Management of RF



CONSENSUS DOCUMENT FOR THE DIAGNOSIS AND TREATMENT OF NON-ST ELEVATION ACUTE CORONARY SYNDROME

1.0 INTRODUCTION AND SCOPE OF THE DOCUMENT :

Acute Coronary syndrome (ACS) has evolved as a useful operational term to refer to clinical symptoms that are compatible with acute myocardial ischemia. Non-ST elevation (NSTE) ACS comprises unstable angina (UA) and NSTE myocardial infarction (NSTEMI). The aim of the treatment in ACS is to prevent myocardial necrosis, fatal or non-fatal myocardial infarction (MI), recurrent hospitalization and resultant morbidity and mortality. The CREATE registry[1] data revealed that NSTE-ACS patients take a long time (median 420 minutes) to reach to the hospital in India. Surprisingly, the incidence of NSTE ACS patients was less in this registry in contrast to reports from the west where NSTE ACS is more frequent than STEMI. It is important to note that the mortality of STEMI and NSTE ACS is comparable after 6 months [2]. The adverse events in NSTE ACS continue over days and weeks in contrast to STEMI where most events occur before or shortly after the presentation. A large number of detailed guidelines are available from American College of Cardiology (ACC) / American Heart Association (AHA)[3] and European Society of Cardiology[4]. An expert consensus document on the management of ischemic heart disease (IHD) in India is also available[5]. The current document evaluates and summarizes the currently available evidence on the management of NSTE ACS to assist the Indian physicians in selecting the best management.

2.0 DIAGNOSIS OF NSTE ACS :

All patients presenting to a health care provider with symptoms suggestive of ACS should be considered as high priority. For the purpose of this document, an arbitrary division is made to categorize the health care facilities available in India for care of ACS patients (table 1). In big cities centers with varying degree of sophistication are usually available. On the other hand, in parts of India (especially rural) even the basic facilities are not available. Every health care centre should have a functioning ECG machine available 24 hours a day. Health workers at these centers should be trained to interpret the ECG so that treatment can be initiated without delay. Telemedicine (fax, e-mail, and internet) is advancing in our country and a networking between the centers can be of great value.

2.1 Definition of terms:

The term, NSTE-ACS includes UA and NSTEMI. These two conditions are closely related whose pathogenesis and clinical manifestations are similar but of differing severity. The clinical presentation depends on the severity of stenosis and the degree of thrombosis. In patients where ischemia is severe, there can be myocardial damage with the release in troponin I (TnI), troponin T (TnT), or CK-MB and the condition is referred to as NSTEMI. If there is no evidence of enzyme elevation, the condition is labeled as UA. It is important to remember that the appearance of biomarkers may be delayed by up to several hours after the onset of ischemic symptoms. The distinction between the terms UA or NSTEMI is retrospective. It is also common to describe patients as Trop T- ve NSTE ACS (UA) or Trop T +ve NSTE ACS (NSTEMI).

2.2 Clinical presentation of NSTE ACS:

The clinical presentation of NSTE ACS encompasses a wide variety of symptoms. An accurate history recording is very important. The important points in the history include nature of anginal symptoms, prior history of IHD, sex (male), older age and an increasing number of traditional risk factors. The following clinical presentations are usually included in NSTE ACS[(3)].

- Prolonged (> 20 min) anginal pain at rest.
- New onset (de novo) severe angina (class III of the classification of Canadian Cardiovascular Society (CCS)[(6)].
- Recent destabilization of previously stable angina with atleast CCS III angina characteristics (crescendo angina) or
- Post MI angina.

The typical clinical presentation of NSTE ACS is retrosternal pressure or heaviness (“angina”) radiating to the left arm, neck or jaw which may be intermittent (usually lasting several minutes) or persistent. These complaints may be accompanied by other symptoms such as diaphoresis, nausea, abdominal pain, dyspnea, and syncope. 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.

2.3 Clinical assessment of NSTE ACS:

Physical examination: 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 NSTE- ACS, such as anaemia, 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.

Electrocardiogram (ECG): The resting 12 lead ECG is the first diagnostic tool. It should be recorded as soon as possible and immediately interpreted by a qualified physician. The finding of persistent ST elevation suggests STEMI which requires a different treatment. ECG recordings should be repeated at least at 6 and 24 h, and in the case of recurrence of chest pain/symptoms. ECG should be compared with any previously available recordings.

In NSTE ACS, ECG may show ST segment deviation, T wave changes or may remain normal. It should be emphasized that a completely normal ECG does not exclude the possibility of NSTE ACS. 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[(7)]. 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[(8)]. ST depression of > 2 mm carries a increased mortality risk. Inverted T waves, especially if marked (greater than or equal to 2mm (0.2 MV) also indicate UA/ NSEMI). Q waves suggesting prior MI indicate a high livelihood of IHD. The utility of ECG becomes less if ECG is abnormal due to pre-existing intraventricular conduction defect or left ventricular hypertrophy (LVH).Ischemia in the left circumflex coronary artery territory is frequently missed in the common 12 lead ECG. It may be detected in lead V4-R, V3- R as well as in leads V7 – V9. These leads should be recorded if clinically indicated.

Biochemical markers : Several biomarkers have been investigated in recent years to be used for diagnosis and risk stratification. Cardiac troponin (CTn) is the biomarker of choice because it is the most sensitive and specific marker of myocardial injury/ necrosis available. Unfortunately, there is a lack of understanding of many of the analytical and clinical issues that govern the use of this

important biomarker. The diagnostic cut off for MI using cardiac troponins should be based on the 99th percentile of levels among healthy controls as recommended by the consensus committee[9]. All laboratories need to validate their values. The diagnosis of NSTE- ACS should never be made only on the basis of cardiac biomarkers, the elevation should always be interpreted in the context of clinical presentation. Troponin levels usually increase after 3-4 hours. If the first blood sample for CTn is not elevated, a second sample should be obtained after 6-9 h, and sometimes a third sample after 12-24 hours is required. Troponin level may remain elevated upto 2 weeks. Troponin elevation can occur in cardiac and non cardiac conditions including chronic renal failure. In NSTE ACS, elevated CTn values signal a higher acute risk and an adverse long term prognosis. The elevated troponin level is also useful for selecting appropriate treatment. Creatine Kinase MB is less sensitive and specific for the diagnosis of NSTE ACS. However, it remains useful for the diagnosis of early infarct extension (reinfarction) and peri-procedural MI because of its short half-life.

Many other biochemical markers like CRP, NT- Pro BNP, myoglobin are commercially available. At the present time, there use is not recommended for the diagnosis.

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

2.4 Risk Stratification at presentation:

Many patients with NSTE- ACS require observation/hospitalization in an environment with continuous electrocardiographic monitoring and defibrillation capability. The risk stratification at presentation is useful, however, it is important to understand that patients who are stable initially, may become high risk subsequently or vice versa.

NSTE ACS includes a heterogeneous group of patients with a highly variable prognosis. The risk stratification is necessary for prognosis assessment and treatment. A simple TIMI risk score[10] which takes into consideration clinical variable can be used (Table 2). The TIMI risk score is available at www.timi.org. A low TIMI score <3 usually indicates a low risk and a TIMI score > 3 indicates intermediate or 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) indicate a high risk. Elevation of troponin or CK-MB indicates myocyte necrosis and a high risk. It is important to note that the TIMI risk score is just a guide and may not be reliable in young patients. There are other risk models based on PURSUIT trial [11] and GRACE registry[12].

Data from western countries suggest that patients with acute chest pain might be better served by transport to an adequately equipped facility (category A) than by sending them to a less equipped facility (category B, C or D). It is well documented that early invasive therapy (early coronary angiography followed by appropriate revascularization) is preferable in high risk patients. These patients should preferably be admitted to category A hospitals or promptly transferred to such a facility. If a high risk patient is initially admitted in Category B, C or D hospital, a decision for transportation should be taken. The decision is to be individualized depending on the clinical, social and economic considerations.

2.5 Differential diagnosis:

A number of patients evaluated for suspected NSTE ACS are found not to have acute ischemia. This includes patients with non cardiac pain (e.g. pulmonary embolism, musculoskeletal or esophageal discomfort) or cardiac pain not caused by myocardial ischemia (e.g. pericarditis). These patients should be evaluated as dictated by the individual presentation.

3.0 MANAGEMENT OF NSTE-ACS:

Patients who are awaiting hospitalization are advised to chew non enteric coated aspirin (162 to 325 mg). They may receive sublingual nitrate or GTN spray for pain relief.

Patients with definite or probable NSTE-ACS who are stable should be admitted to an impatient 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 without any major complications.

3.1 What not to do ?

A. 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.

B. Glycoprotein IIb/IIIa agents like abciximab, tirofiban and eptifibatide are mostly useful in patients undergoing percutaneous coronary interventions (PCI). The routine “upstream” use of the agents is not recommended.

3.2 Anti- ischemic and analgesic therapy:

All patients must receive medication for relief of pain. 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 heart failure. Nitrates should be used with caution if systolic blood pressure is below 100 mm of Hg.

Morphine sulfate (1 to 5 mg intravenously), if available, is a good option for pain relief in patients whose symptoms are not relieved despite NTG or other anti ischemic therapy. The non steroidal anti inflammatory drugs (NSAIDs) and COX-2 inhibitors should not be administered for pain relief due to increased risk of cardiovascular events [13].

Oral beta blockers are useful for pain relief. The use of intravenous beta blockers should be avoided particularly in haemodynamically 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 limited role to play.

3.3 Antiplatelet agents:

Platelet activation plays a key role in NSTE- ACS and antiplatelet therapy should be administered once the diagnosis is entertained. Aspirin (cyclo oxygenese inhibitor) should be administered to all patients unless contraindicated.

Initial dose of chewed non-enteric aspirin from 162 to 325 mg is recommended. The subsequent dose of aspirin can be 75 to 150mg 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 12 months unless there is an excessive risk of bleeding.

A new antiplatelet agent, belonging to thienopyridine group of ADP receptor inhibitors has recently been investigated in TRITON TIMI- 38 trial[14]. Prasugrel reduces the platelet aggregation by irreversibly binding to P2Y12 receptors on the platelets. Prasugrel is a prodrug and has rapid onset of action (1 hour). It is converted to active and inactive metabolites. The active metabolite has half life of about 7 hours. In patients undergoing PCI for ACS, the agent showed lower incidence of ischaemic events when compared to clopidogrel. It was particularly effective in diabetics (4.2%

absolute risk reduction for ACS). Bleeding incidence was similar (2.2% vs 2.3%). The agent is correctly recommended for the following patients (1) Patient presenting with STEMI (2) NSTEMI patient with diabetes mellitus or young male patients undergoing PCI (3) Patient with history of stent thrombosis (4) non responders to clopidogrel. This agent is contraindicated in patients with >75 years of age or in patient having history of TIA or any stroke. The loading dose is 60 mg orally. The maintenance dose is 10 mg daily. In patient weighing <60 kg, the maintenance dose has to be reduced to 5 mg daily.

Another new drug, ticagrelor has been found to be superior as compared to clopidogrel in ACS[15]. Ticagrelor is an oral, reversible, non thinopyridine P2Y12 antagonist. This is not a prodrug. This has a more rapid onset of action (30 min) and rapid off sent of action (4-72 hours). In ACS, Ticagrelor was associated with mortality reduction compared to clopidogrel (9.8% vs 11.7%, P=<0.001). However nonfatal bleeding was higher (16.1% vs 14.6%, P=0.0084). The loading dose is 180 mg. Maintenance dose is 90 mg twice daily thereafter.

All patients presenting with ACS/NSTEMI should receive aspiring plus any one of these three (Clopidogrel/Prasugrel/Ticagrelor) agents.

The use of GP IIb / IIIa inhibitors has undergone a major change in the current era of high dose clopidogrel and newer anticoagulants. These agents are used either upstream beginning prior to angiography or administered after angiography during the PCI. The upstream use of GP IIb/IIIa inhibitors have considerably reduced. Eptifibatide have not shown efficacy in reducing ischemic events in high risk NSTE-ACS patients when used upstream and maintained during the PCI procedure. In routine practice, these days patients are often taken to catheterization laboratory without prior use of GP IIb / IIIa agent[16]. Any of the three agents is used depending on the clinical and angiographic characteristics.

3.4 Anticoagulants:

Anticoagulation is recommended for all patients in addition to antiplatelet agents[3,4]. An increasing number of anticoagulants (previously referred to as antithrombins) 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 where as 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[17]. 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 NSTE ACS[18]. Bivalirudin reduces the risk of bleeding as compared with UFH/LMWH plus GP IIb/IIIa inhibitor.

3.5 Statins & other drugs:

Statins are recommended for all NSTE ACS patients, irrespective of cholesterol levels. Statin should be initiated early after admission, with the aim of achieving LDLC levels <70 mg/dL. Atorvastatin is usually the preferred agent. High dose (40-80 mg) is used for the initial period (1-2 months). Subsequent dosing is bsed on the target LDL (<70 mg/dL) level.

ACE inhibitors are indicated in patients with reduced LV systolic function in diabetes and all other patient of proven CAD. ARB are indicated in those patients who are intolerant to ACE inhibition.

4. CORONARY REVASCULARIZATION :

Revascularization for NSTE 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[19].

4.1 Coronary angiography :

An invasive strategy always starts with angiography. The indications for urgent and routine early angiography are shown in table 3 and 4.

Those patients who have no recurrence of chest pain, normal serial ECGs, no elevation of troponins and no heart failure are considered as low risk. In these patients, a stress test is advised prior to discharge. Coronary angiography is contemplated, if the stress test is positive.

4.2 Conservative and Invasive strategy :

There is a controversy which remains as to the optimal timing between hospital admissions, initiation of medical therapy and invasive evaluation. There are large numbers of randomized controlled trials (RCT) which have addressed this issue. The term invasive strategy refers to coronary angiography and subsequent revascularization within 2 to 24 hours of hospitalization. Conservative strategy (selective invasive) refers to initial medical stabilization followed by angiography and appropriate revascularization, usually within 72 hours or prior to hospital discharge. RCTS 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[20]. This strategy reduces cardiovascular death and MI at up to 5 years of follow-up[21]. From the available data, following conclusions can be drawn.

1. High risk/unstable patients benefit most from the early revascularization therapy & these patients should be promptly treated in advanced centers.

2. A systematic approach of immediate angiography is not necessary in patients who are stabilized with a contemporary pharmacological approach. Likewise, immediate transfer of stabilized patients admitted in hospitals without onsite cardiac catheterization facilities is not mandatory, but should be organized within 72 h. Figure 1 provides a flow chart for management of NSTE-ACS patients.

4.3 Percutaneous Coronary Intervention (PCI) and Coronary Artery Bypass Grafting (CABG) :

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 same sitting or in 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.

5. LONG TERM MANAGEMENT:

Patients with NSTE 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 is very important. This is termed as therapeutic life style changes (TLC). Smoking cessation, weight reduction, blood pressure control, management of diabetes, lipid intervention, antiplatelet agents, beta blockers, ACE inhibitors (or ARB) remain extremely important interventions. Isotonic exercise like brisk walk, swimming, cycling, jogging for 30-45 minutes daily or at least 150 minutes weekly should be advised to all these patients. The exercise prescription (type, duration and intensity) should be individualized based on the clinical status of the patient. Lastly psychological factors like anxiety and depression are to be identified and treated[(22)].

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Table 1 : Type of hospitals / centers treating ACS patients in India.

Category	Facilities
• A	Advanced care with ICCU, catheterization laboratory, PCI and Coronary artery bypass graft (CABG) Surgery.
• B	ICCU with trained staff for thrombolysis, CPR, defibrillation, pacing etc.
• C	ICU with no specialized cardiac care
• D	No ICCU or ICU
Abbreviations: ICCU = Intensive coronary care unit, ICU = Intensive care unit, CPR = Cardio-pulmonary resuscitation. Other as in text.	

Table 2 : The TIMI risk score for NSTE-ACS.

Characteristics	Points
Historical	
Age ≥ 65	1
≥ 3 risk factors for CAD	1
Known CAD (Stenosis ≥ 50 %)	1
Aspirin use in past 7 days	1
Presentation	
Recent (≤ 24 H) severe angina	1
ST – segment deviation ≥ 0.5 mm	1
↑ Cardiac markers	1
Risk Score = Total Points	(0-7)

Abbreviations : As in text

Table 3 : Indications for urgent coronary angiography and invasive strategy.

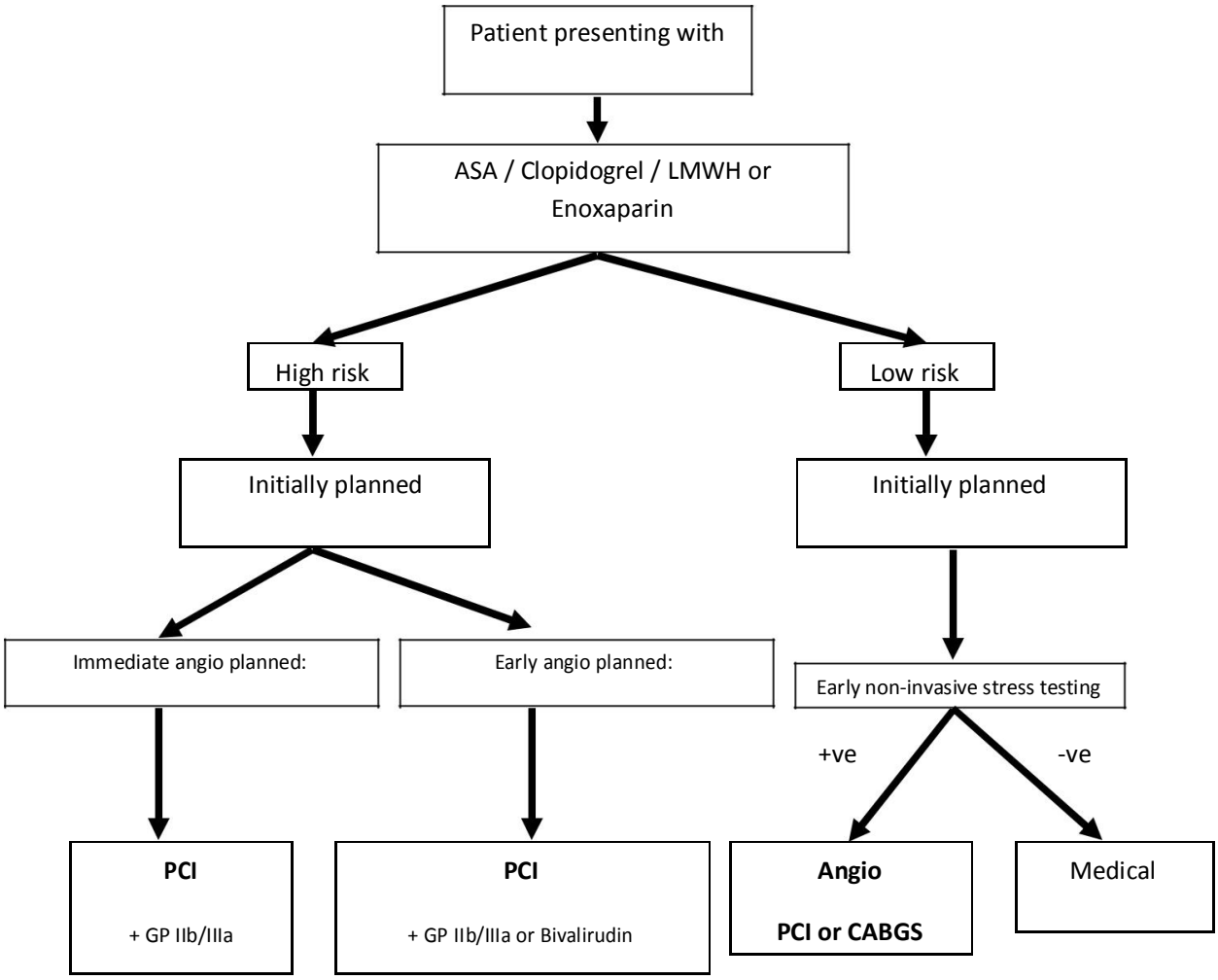
- Refractory angina (e.g. evolving MI).
- Recurrent angina despite intense antianginal treatment (associated with ST depression ($\leq$ 2 mm) or deep negative T waves.
- Clinical symptoms of heart failure or haemodynamic instability ('Shock').
- Life threatening arrhythmias (ventricular fibrillation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

Table 4 : Indications for early coronary angiography :

- Elevated troponin levels.
- Dynamic ST or T wave changes.
- Diabetes mellitus, reduced renal function.
- Depressed LVEF < 40%.
- Early post MI angina.
- PCI within 6 months.
- Previous CABG.
- Intermediate to high risk according to risk score.

Abbreviations : as in text.

Figure 1 : Flow – chart for management of NSTE-ACS.



Abbreviation : as in text

CONSENSUS DOCUMENT FOR THE DIAGNOSIS AND TREATMENT OF ST ELEVATION ACUTE CORONARY SYNDROME

1.0 AIM AND SCOPE OF THESE RECOMMENDATIONS

Recent documents have described the evidence-based diagnosis and management of acute ST segment elevation myocardial infarction (STEMI)[1-4]. While these are erudite and exhaustive, they are tailored to the situation in developed countries. Because of the substantially different ground reality in India, there is a need for modifications in the interpretation of the evidence and application of treatments to the Indian context.

This statement attempts to provide guidance to Indian physicians and healthcare providers at the grass-root level in making decisions for the optimal management of patients with STEMI.

2.0 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). It must be recognized that pain may be atypical in character or location. A 12-lead ECG must be performed as soon as possible. ECG should be interpreted within ten (10) minutes of arrival in health care centre. If the initial ECG is not suggestive of STEMI but the patient continues to have symptoms, repeat ECGs must be obtained (every 15 minutes, not after 12 hours or next day) and compared to the first ECG. 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.

Equipment, personnel and training

Every primary health center should have a functioning ECG machine available 24 hours a day. Health workers at these centers should be trained to recognize the cardinal features of STEMI so that treatment can be initiated without delay. It may not be necessary for all health centers to have access to facilities for cardiac biomarker testing. Use of qualitative test-strips in these centers may be expensive and may lead to diagnostic confusion, and their use should be discouraged..

3.0 MANAGEMENT OF STEMI

3.1 Risk stratification

The initial assessment should include the rapid identification of patients who may be at high risk of cardiogenic shock or death. The following characteristics have been most consistently associated with adverse outcomes in patients with STEMI[5-7]:

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.

3.2 Initial treatment

The first treatment that should be given is 325 mg of (preferably) non enteric-coated aspirin to be chewed[8]. All patients should receive aspirin. Clopidogrel should be administered at a loading dose of 300 to 600 mg to all patients[9-10]. Patients undergoing primary PCI should receive a 600 mg loading dose[11].

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[12]

3.3 Choice of reperfusion therapy

3.3.1 Fibrinolytic therapy vs. primary PCI

Reperfusion therapy is the cornerstone of STEMI management and should be instituted in all patients presenting within 12 hours of onset of symptoms[8-13]. The most efficacious reperfusion therapy available is timely primary PCI, but it may not be the most effective in the Indian context, given the relative paucity of PCI-capable centers[14]. 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[15]. 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 [15] were from rural areas), a third of patients did not receive any form of reperfusion therapy.

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 90 minutes from the time of arrival at the hospital[4]. 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.

Table 1

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†21
2. Failed fibrinolytic therapy
3. High-risk pa□ents‡*22

3.3.2 Choice of fibrinolytic agent

Traditionally, streptokinase has been the most commonly used fibrinolytic agent in India. However, streptokinase is not fibrin-specific, requires to be given as an infusion over one hour and may be associated with hypersensitivity reactions. Recently, there is some favorable evidence for the use of tenecteplase in Indian settings[16-17]. Tenecteplase has theadvantage 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[18].

Personnel and training

Given that nearly a third of patients in urban India do not receive any reperfusion therapy, it may be worthwhile for the government to consider making tenecteplase available at primary health centers as a policy decision. This would also entail adequate training of medical and paramedical personnel at these centers so that they can administer tenecteplase without delay. Studies conducted around the world have found that administration of bolus-dose fibrinolytic agents by paramedical personnel is safe. The government should commission studies to confirm the safety of such a practice in the Indian context before its widespread implementation.

3.3.3 The case for pre-hospital fibrinolysis

Due to lack of awareness, lack of ambulance services and the distances involved, most patients with STEMI living in urban/semi-urban India reach hospital after a delay of 5 hours[15]. This delay 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[19].

3.4 Transport of patients to centers with CCUs and/or PCI capability

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. 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[15].

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 2 below.

Table 2

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†21
2. Failed fibrinolytic therapy
3. High-risk pa□ents‡*22

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

ÿ *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 IIor III, ST-segment depression of ≥2 mm inthe anterior leads, or ST-

22 segment elevation of≥1 mm in right-sided lead V4 (V4R).

** PCI may then be performed as and when needed or as part of a pharmacoinvasive strategy*

3.5 Adjunctive therapies

3.5.1 Antiplatelet treatment

Aspirin and clopidogrel should be administered as discussed in section 3.2. Glycoprotein IIb/IIIa antagonists may be used in patients undergoing primary PCI although their role in patients pre-loaded with clopidogrel is unclear. These agents may be administered in the catheterization laboratory, at the time of the procedure. There is no role of administering these agents within the context of a strategy to bridge the time delay before primary PCI (facilitated PCI)[25]. Abciximab, eptifibatide and tirofiban appear to be similarly effective and may be used depending upon local preferences and availability[3].

3.5.2 Antithrombotic therapy

Patients receiving fibrinolytic 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[13,24]. Recent studies suggest that low molecular weight heparins (LMWH) may be better than unfractionated heparin (UFH) for this purpose[24-26]. 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[27]. There is no role for bivalirudin among patients receiving fibrinolytic therapy.

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

Patients not receiving any reperfusion therapy Fondaparinux may be the preferred agent among patients who have not received any reperfusion therapy[29].

3.5.3 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 (see footnote in table 2), or do not have other contraindications to beta-blocker therapy[21]. Intravenous beta-blockers may be administered in the first 24 hours in the presence of hypertension or tachyarrhythmia, in the absence of the above contraindications[2].

3.5.4 ACE inhibitors and ARBs

ACE inhibitors improve survival in patients who have reduced left ventricular ejection fraction (LVEF $\leq$ 40%) and those who are in heart failure following STEMI[4]. 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. ARBs may be used in patients who do not tolerate ACE inhibitors[30-31].

3.5.5 Other agents

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[4]. 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 $\leq$70mg/dL may be a useful target.

3.6 Management post-fibrinolytic therapy

Several studies have suggested that routine angiography and PCI of the infarct related artery may reduce the rates of re-occlusion or re-infarction [32-35]. However, none of these studies have shown a reduction in mortality with this strategy. Because of the resource intensiveness of this strategy and the absence of an effect on survival, this panel favors 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 is the key to maintaining adherence to therapy in the long run.

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