CHAPTER

201

Management Strategies in Non-ST Elevation Acute Coronary Syndrome (NSTE-ACS) in India

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INTRODUCTION

The clinical spectrum of non-ST elevation acute coronary syndrome (NSTE-ACS) may range from unstable angina to non-ST segment myocardial infarction (NSTEMI). The clinical presentation depends on the severity of coronary stenosis and the degree of thrombus. Unstable angina is defined as myocardial ischemia at rest or on minimal exertion in the absence of cardiomocyte necrosis. These patients have substantially lower risk of death and derive less benefit from intensified antiplatelet therapy as well as early coronary angiography. Those patients who have an acute chest pain and cardiomyocyte necrosis as evidenced by troponin elevation are labelled as NSTEMI. These individuals may present with ongoing ischemia, electrical or hemodynamic instability and require angiography and appropriate revascularization at the earliest.

CHALLENGES IN ACS MANAGEMENT IN INDIA

The management strategies often depend on risk assessment, available facilities and financial constraints. An analysis of data from Indian ACS registries highlight the problems related to accessibility of health care, literacy and economic status on management outcomes. NSTEMI patients are older, have more risk factors and present late. The utilization of evidence based medication is less. The mortality rate was high in regions that faced inadequate access to health care and was 5% and 6% in Himachal Pradesh and North East registry. Inadequate access to health care, difficulty in transportation and poor socioeconomic background are impediments to the care of patients in rural areas. In urban centres, out of pocket expenses remain challenging for patients.

All patients presenting to a health care provider with symptoms suggestive of ACS should be considered as high priority. An arbitrary division is made to categorize the health care facilities available in India for care of ACS patients (Table 1). In big cities, centres 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. Telemedicine is advancing rapidly in India and networking between the centres can be helpful.

The risk stratification at presentation is useful, however it is important to understand that patients who are stable initially, may become a high risk subsequently or vice versa. TIMI risk score is easy to use in day to day clinical practise and can be accessed at www.timi.org. A low TIMI score <3 usually indicates a low risk and a TIMI score >3 indicates intermediate or high risk.

Data from western countries suggest that patients with acute chest pain might be better served by transportation to an advanced centre (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 majority of patients. These patients should preferably be admitted to category A hospitals or promptly transferred to such a facility.

MANAGEMENT STRATEGIES

Patients who are awaiting hospitalization should receive non enteric coated aspirin (162-325 mg), 300mg of clopidogrel and 40mg atorvastatin. Nitrates should be used for pain relief. Table 2 summarise recommendations and duration for rhythm monitoring.

Fibrinolytic (thrombolytic) therapy and upstream use of

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

Category	Facilities
A	Advanced care with ICCU, catheterization laboratory, IABP, PCI and CABG surgery
B	ICCU with trained staff for thrombolysis, CPR, defibrillation, pacing, etc.
C	ICU with no special cardiac care
D	No ICCU or ICU

Abbreviations: ICCU- Intensive coronary care unit, IABP- Intra-aortic balloon pump, ICU- Intensive care unit, CPR- Cardio-pulmonary resuscitation. Others as in text.

Table 2: Recommended hospital category and duration of cardiac rhythm monitoring in patients after NSTE-ACS diagnosis

Clinical presentation	Hospital category	Rhythm monitoring
NSTEMI at low risk for cardiac arrhythmias	A, B	≤ 24hours
NSTEMI at intermediate or high risk for cardiac arrhythmias	A	> 24 hours
Unstable angina	A, B, C	Variable

Abbreviations as in text.

glycoprotein IIb/IIIa agents should not be used as these agents can prove harmful. The management will be discussed as follows:

1. Anti-ischemic and analgesic therapy: The goal of the anti-ischemic therapy is to decrease myocardial oxygen demand. Oxygen should be administered when oxygen saturation is < 90% or if the patient is in respiratory distress. Opiate administration is reasonable if symptoms persist.

   Nitrates: Nitrates are recommended for pain relief. Intravenous nitroglycerin (NTG) is particularly helpful in patients who are unresponsive to sublingual NTG. Nitrates should be used with caution if systolic blood pressure is below 100mm of Hg.

   Beta-blockers: Beta blockers are useful for pain relief and reduce myocardial oxygen consumption by multiple mechanisms. Early administration of beta blockers particularly intravenous can precipitate shock and their use should be avoided in unstable patients.

2. Platelet inhibition: Platelet activation plays a key role in NSTE-ACS and antiplatelet therapy should be administered once the diagnosis is entertained. Aspirin should be administered to all patients unless contraindicated.

   P2Y12 inhibitors: The dual antiplatelet regimen includes one of the P2Y12 inhibitors along with aspirin and is used for 1 year following NSTE-ACS.

   Clopidogrel (300-600 mg loading and 75 mg maintenance dose) along with aspirin has been shown to reduce recurrent ischemic events as compared to aspirin alone. In patients considered for percutaneous coronary intervention (PCI), a loading dose of 600 mg is advised. In India, clopidogrel remains the most popular P2Y12 inhibitor for use in NSTE ACS treated by conservative or invasive treatment. The drug is cost effective, safe, efficacious and widely available in our country.

   Prasugrel (60 mg loading and 10 mg/ day maintenance dose) is a prodrug that irreversibly blocks platelet P2Y12 receptors with a faster onset and a more profound inhibition effect than clopidogrel. The drug is recommended in patients who are proceeding to PCI and loading dose is administered after the coronary anatomy is known.

   Ticagrelor (180 mg loading followed by 90 mg twice a day) is an oral, reversibly binding P2Y12 inhibitor with a plasma half life of 6-12 hours. It has a rapid and consistent onset of action as well as faster offset of action with rapid recovery of platelet function.

   It is recommended for conservative or interventional treatment. The drug is expensive, needs to be taken twice a day and has side effects including dyspnea. Cangrelor is an intravenous agent and is currently not available in India.

   Glycoprotein IIb/IIIa inhibitors: Intravenous GP IIb/IIIa inhibitors block platelet aggregation and the indications for their use have undergone a major change. In patients treated with newer antiplatelets, GP IIb/IIIa inhibitors should be limited to bail out situations or thrombotic complications during PCI.

3. Anticoagulation: Anticoagulants are used to inhibit thrombin generation and activity, thereby reducing thrombus related events. There is evidence that anticoagulation is effective in reducing ischemic events in NSTE ACS and that the combination with platelet inhibitors is more effective than either treatment alone.

   Unfractionated Heparin (UFH) remains a widely used anticoagulant. In the PCI setting, UFH is given as an intravenous bolus, either under activated clotting time (ACT) guidance or in a weight adjusted manner.

   Low molecular weight heparin: Enoxaparin (1mg/ kg twice daily) is a preferred anticoagulant and is a good option in patients treated conservatively or by invasive strategy. It should be administered up to hospital discharge in conservative strategy.

   Fondaparinux is a selective factor X a inhibitor that binds reversibly and prevents thrombin formation. It has favourable efficacy-safety profile and is recommended regardless of the management strategy, unless the patient is scheduled for immediate coronary angiography.

   Bivalirudin is recomended as an alternative anticoagulant for urgent and elective PCI in moderate or high risk NSTE ACS. It reduces the risk of bleeding as compared with UFH/ LMWH plus GP IIb/IIIa inhibitor.

4. Other medications: Lipid lowering treatment

   It is recommended to initiate high intensity statin therapy as early as possible after admission in all patients.

   ACE inhibition: ACE inhibitors are recommended in patients with systolic left ventricular (LV) dysfunction or heart failure. ARBs are indicated in patients who are intolerant of ACE inhibitors.

5. Invasive coronary angiography and revascularization: Invasive coronary angiography, followed by coronary revascularization is performed in the majority of patients hospitalised with NSTE-ACS. Angiography identifies the culprit lesion and assesses suitability for PCI and coronary artery bypass graft (CABG) surgery.

   Routine invasive versus selective invasive approach

   A large number of studies and several meta-analysis have shown that a routine invasive

Table 3: Risk criteria mandating invasive strategy in NSTE-ACS
Very-high-risk criteria
• Haemodynamic instability or cardiogenic shock
• Recurrent or ongoing chest pain refractory to medical treatment
• Life-threatening arrhythmias or cardiac arrest
• Mechanical complications of MI
• Acute heart failure
• Recurrent dynamic ST-T wave changes, particularly with intermittent ST-elevation
High-Risk criteria
• Rise or fall in cardiac troponin compatible with MI
• Dynamic ST-or T-wave changes (symptomatic or silent)
• GRACE score >140
Intermediate-risk criteria
• Diabetes mellitus
• Renal insufficiency (eGFR <60 mL/min/1.73 m^2)
• LVEF <40% or congestive heart failure
• Early post-infarction angina
• Prior PCI
• Prior CABG
• GRACE risk score >109 and <140
Low-risk criteria
• Any characteristics not mentioned above

Abbreviations: eGFR- estimated glomerular filteration rate, GRACE- Global Registry of Acute Coronary Events, LVEF- left ventricular ejection fraction. Other abbreviations as in text. Adapted from Reference 4.

strategy is better to a selective invasive strategy and improves clinical outcomes and reduces recurrent ACS episodes, subsequent rehospitalisation and revascularization.

Table 3 shows the risk criteria for determining the timing of invasive strategy

A. Immediate invasive strategy (<2 hours): Very high NSTE-ACS patients (i.e with at least one criteria according to Table 3) carry a poor prognosis. As mentioned earlier, these patients should be immediately transferred to centres with PCI capabilities.

B. Early invasive strategy (<24 hours): Early invasive strategy is defined as coronary angiography performed within 24 hours of hospital admission (table 3). This implies timely transfer for patients admitted to hospital without onsite catheterization facilities.

C. Invasive strategy (<72 hours): This is the recommended maximal delay for angiography in patients with at least one intermediate risk criterion, recurrent symptoms or known ischemia on non-invasive testing. Even if hospital transfer is required, the 72 hour window for coronary angiography should be compiled with.

D. Selective invasive strategy: Patients with no recurrence of symptoms and none of the criteria listed in table 3 are considered at low risk of ischemic events. In these patients, a non-invasive stress test (preferably with imaging) for inducible ischemia is recommended before deciding on an invasive strategy.

Percutaneous coronary revascularization or CABG.

The main difference between management of patients with stable ischemic heart disease and NSTE-ACS is a stronger impetus for early revascularization in those with NSTE-ACS. The PCI of culprit vessel is performed immediately. The non-culprit vessels are treated in same sitting or in a staged fashion. New generation drug eluting stents (DES) are recommended over bare metal stent.

In patients with left main coronary artery (LMCA), complex coronary artery disease (CAD), a heart team approach to revascularization decisions is recommended.

Conservative treatment: Conservative management is continued in low risk patients who have stabilized on medical management and have negative stress test. It is also recommended in patients with non-obstructive CAD or CAD not amenable to revascularization due to severe or diffuse disease.

6. Long tem therapy: The goals for continued medical therapy after discharge relate to potential prognostic benefits (primarily shown for antiplatelet agents, betablockers, statins and ACEI/ARB). Lifestyle changes such as diet, exercise and smoking cessation, are of paramount importance.

CONCLUSION

NSTE-ACS is a leading cause of cardiovascular mortality and morbidity. Management of NSTE-ACS has evolved considerably during the recent years. Pharmacotherapy includes potent antiplatelet agents, a variety of anticoagulants, statins, and other drugs. The major shift is a general acceptance of an early invasive strategy for those patients who display very high, high or intermediate risk criteria. These patients benefit from an early revascularization.

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