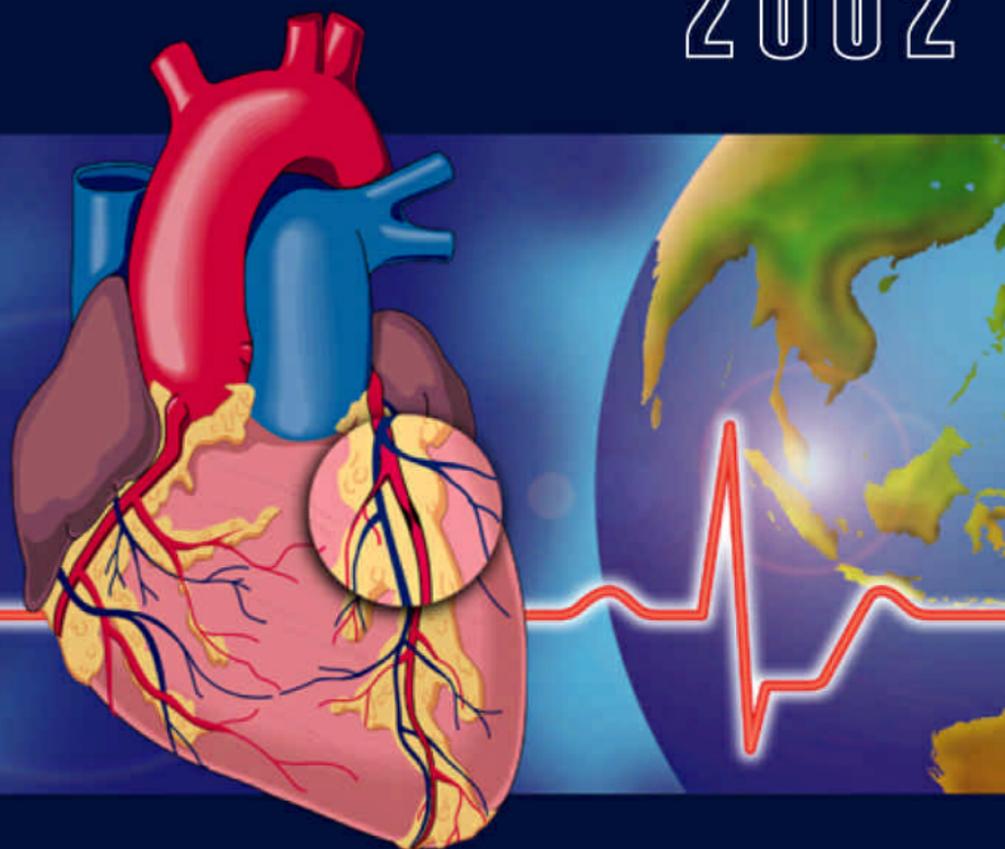


Clinical Practice Guidelines on

# UA / NSTEMI

2002



Ministry of Health  
Malaysia



National Heart  
Association of Malaysia



Academy of Medicine  
Malaysia



## PREFACE

**C**oronary artery disease (CAD) is a major health problem and the leading cause of death in Malaysia. Unstable Angina (UA) and Non ST Elevation Myocardial Infarction (NSTEMI) are the common manifestations of this disease.

Over the last few years, there has been an exponential growth in understanding the diagnosis, treatment and prevention of UA and NSTEMI. The committee first met in August 2001 and after reviewing the currently available evidence, these guidelines were drawn up and the evidence is graded accordingly. These guidelines are intended to assist medical and health personnel in the proper evaluation and management of UA / NSTEMI patients.

I would like to thank the panel of experts who put together these guidelines and to those who attended the final draft presentation for their contribution.

Finally, I would like to thank Sanofi-Synthelabo and Bristol Myers Squibb for their grant and the secretariat services by Sanofi-Synthelabo to make these guidelines a reality.



**Dr David Quek Kwang Leng**  
(Chairperson)

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## 1. INTRODUCTION

Cardiovascular disease is the most common cause of death in Malaysia. Acute Coronary Syndromes (ACS) represent a large number of hospitalisations (33,623 patient admissions, Year 2000) in government hospitals and are a major health problem.<sup>1</sup> These are part of the spectrum of clinical presentations that result from a common underlying pathophysiological mechanism.<sup>2</sup>

These guidelines address the diagnosis and management of patients with ACS (which includes Unstable Angina [UA] and Non ST Elevation Myocardial Infarction [NSTEMI]). They will serve as a reference guide for healthcare providers to appropriately manage the sequelae of these life threatening disorders such as recurrent angina with hospital readmission (40-50%),<sup>3</sup> reinfarctions (9.8% in six months)<sup>4</sup> and mortality of 11.1% in one year.<sup>4</sup>

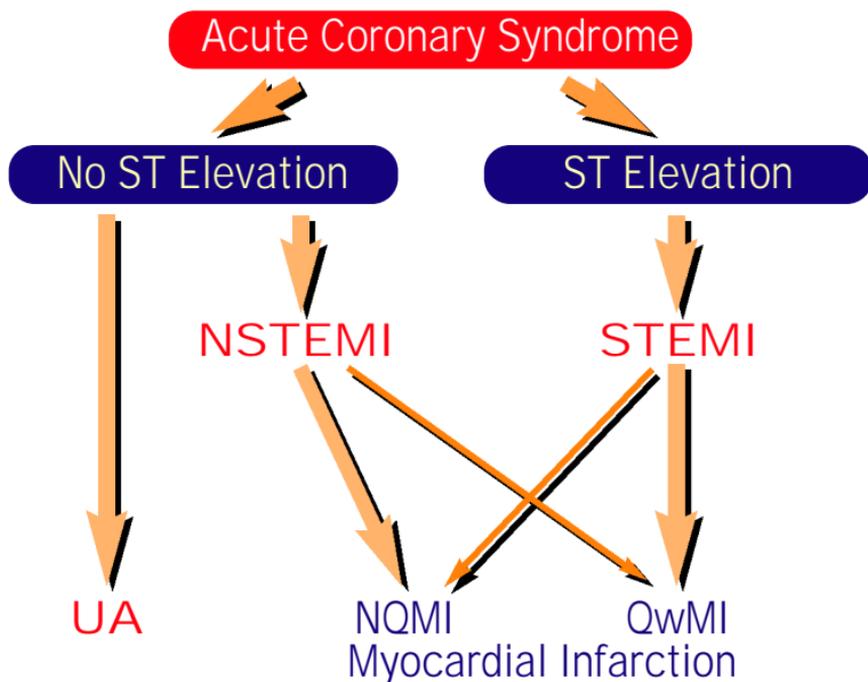
The mortality of ST Elevation Myocardial Infarction (STEMI) has decreased with newer diagnostic and therapeutic strategies over the last 20 years while the mortality of NSTEMI remained very much unchanged. However, with recent advances in the diagnostic and therapeutic strategies for UA / NSTEMI, there are opportunities for all of us to contribute and perhaps modify the natural history of these syndromes.

Treatment strategies for the guidelines in the management of UA / NSTEMI, like the recent guidelines by National Heart Association of Malaysia / Academy of Medicine / Ministry of Health Malaysia<sup>5,6,7</sup> have been graded based on levels of evidence using the system outlined below:

<b>GRADE A</b>	Based on evidence from one or more randomised clinical trials
<b>GRADE B</b>	Based on evidence from high quality clinical trials but with no randomised clinical trial data available
<b>GRADE C</b>	Based on expert committee reports and/or clinical experience of respected authorities but lacking in directly applicable studies of good quality

## 2. DEFINITION OF TERMS

ACS has evolved as a useful operational term to refer to any constellation of clinical symptoms that are compatible with acute myocardial ischaemia. This new terminology more accurately describes ACS at the time of presentation as AMI [ST elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI), rather than Q-wave myocardial infarction (QwMI) and non-Q wave myocardial infarction (NQMI)] as well as UA (Fig. 1). These guidelines focus on 2 components of this syndrome: UA / NSTEMI.



**Figure 1.** Nomenclature of ACS. Patients with ischaemic discomfort may present with or without ST segment elevation on the ECG. The majority of patients with STEMI ultimately develop a QwMI, whereas a minority develop a NQMI. Patients who present without ST segment elevation are experiencing either UA or an NSTEMI. The distinction between these 2 diagnoses is ultimately made based on the presence or absence of a cardiac marker detected in the blood. Most patients with NSTEMI ultimately develop a NQMI, whereas a minority develop a QwMI. Not shown is Prinzmetal's angina, which presents with transient chest pain and ST segment elevation but rarely MI.

*Modified from Antman EM, Braunwald E. Acute myocardial infarction. In: Braunwald EB, ed. Heart disease: a textbook of cardiovascular medicine. Philadelphia, PA: WB Saunders, 1997.*



In these guidelines, UA / NSTEMI are considered to be closely related conditions whose pathogenesis and clinical presentations are similar but of differing severity; that is, they differ primarily in whether the ischaemia is severe enough to cause sufficient myocardial damage to release detectable quantities of a marker of myocardial injury, most commonly troponin I (TnI), troponin T (TnT), or creatine kinase-MB (CK-MB).

Once it has been established that no biochemical marker of myocardial necrosis has been released (with a reference limit of the 99th percentile of the normal population),<sup>8</sup> the patient with ACS may be considered to have experienced UA. The diagnosis of NSTEMI is established if a marker has been released. In the latter condition, ECG ST segment or T-wave changes may be persistent, whereas they may or may not occur in patients with UA, and if they do, they are usually transient. Markers of myocardial injury may be detected in the bloodstream hours after the onset of ischaemic chest pain, which allows the differentiation between UA and NSTEMI. Thus, at the time of presentation, patients with UA and NSTEMI may be indistinguishable and therefore are considered together in these guidelines.

### 3. PATHOGENESIS OF UA / NSTEMI

These conditions are characterised by an imbalance between myocardial oxygen supply and demand. Five nonexclusive causes are recognised (Table 1).<sup>9</sup>

**Table 1: Causes of UA\***

1.	Nonocclusive thrombus on pre-existing plaque
2.	Dynamic obstruction (coronary spasm or vasoconstriction)
3.	Progressive mechanical obstruction
4.	Inflammation and/or infection
5.	UA secondary to precipitating conditions

\* These causes are not mutually exclusive; some patients have 2 causes.



With the first 4 causes, the imbalance is caused primarily by a reduction in oxygen supply to the myocardium, whereas with the fifth cause, the imbalance is due principally to increased myocardial oxygen requirement, usually in the presence of a fixed restricted oxygen supply.

- 3.1 The most common cause of UA / NSTEMI is reduced myocardial perfusion that results from coronary artery narrowing caused by a thrombus that developed on a disrupted atherosclerotic plaque and is usually nonocclusive. Microembolisation of platelet aggregates and components of the disrupted plaque causing distal microinfarction is believed to be responsible for the release of myocardial markers in many of these patients.
- 3.2 A less common cause is dynamic obstruction, which may be caused by intense focal spasm of a segment of an epicardial coronary artery (Prinzmetal's angina). This spasm is caused by hypercontractility of vascular smooth muscle and/or by endothelial dysfunction. Dynamic coronary obstruction can also be caused by the abnormal constriction of smaller vessels.
- 3.3 A third cause of UA is severe narrowing without spasm or thrombus. This occurs in some patients with progressive atherosclerosis or with restenosis after a percutaneous coronary intervention (PCI).
- 3.4 The fourth cause is arterial inflammation, caused by or related to infection, which may be responsible for arterial narrowing, plaque destabilisation, rupture and thrombogenesis. Activated macrophages and T-lymphocytes located at the shoulder of a plaque increase the expression of enzymes such as metalloproteinases that may cause thinning and disruption of the plaque, which in turn may lead to UA / NSTEMI.



3.5 The fifth cause is UA secondary to a precipitating condition, which is extrinsic to the coronary arterial bed. These patients have underlying coronary atherosclerotic narrowing that limits myocardial perfusion, and they often have chronic stable angina.

UA secondary to precipitating conditions includes:

- Increased myocardial oxygen requirements, such as fever, tachycardia and thyrotoxicosis;
- Reduced coronary blood flow, such as hypotension; or
- Reduced myocardial oxygen delivery, such as anaemia or hypoxaemia.

These 5 causes of UA / NSTEMI are not mutually exclusive.

## 4. DIAGNOSIS OF UA / NSTEMI

### History

Chest pain is the presenting symptom in most patients with UA / NSTEMI. Chest pain or discomfort is usually retrosternal, central or in the left chest and may radiate to the jaw or down the upper limb. It may be crushing, pressing or burning in nature. The severity of the pain is variable. It is difficult to differentiate between symptoms of STEMI and UA / NSTEMI.

Some patients may present in acute left ventricular failure. Atypical presentation such as unexplained fatigue, shortness of breath, epigastric discomfort or nausea and vomiting may be seen, especially in women, diabetics and the elderly. In patients with multiple cardiovascular risk factors, one must have a high index of suspicion in order not to miss the diagnosis.

The three common presentations are:<sup>10</sup>

Rest angina	Angina occurring at rest and prolonged, usually > 20 minutes
New-onset angina	New-onset angina of at least CCS Class III* severity
Increasing angina	Previously diagnosed angina that has become more frequent, longer in duration or more easily provoked

<sup>10</sup>Grading of Angina Pectoris by CCS Classification (see appendix 1, page 37)



## Physical Examination

The objective of the physical examination is to identify precipitating factors as well as the consequences of UA / NSTEMI. Uncontrolled hypertension, anaemia, thyrotoxicosis, severe aortic stenosis, hypertrophic cardiomyopathy and other comorbid conditions such as lung disease should be sought.

Evidence of left ventricular dysfunction (hypotension, respiratory crackles or S3 gallop) carries a poor prognosis. The presence of carotid bruit or peripheral vascular disease identifies patients with a higher likelihood of significant CAD.

## Electrocardiography

The ECG adds support to the diagnosis and provides prognostic information.<sup>11-19</sup> A recording made during an episode of chest pain is particularly valuable.

Features to diagnose UA / NSTEMI are:

- 1) ST segment depression  $> 0.05$  mV
- 2) T-wave inversion - marked  $> 0.2$  mV symmetrical T-wave inversion in the precordial leads

Other ECG changes include bundle branch block (BBB)\* and cardiac arrhythmias, especially sustained ventricular tachycardia. Serial ECGs should be done as the ST changes may evolve. However, a completely normal ECG does not exclude the diagnosis of UA / NSTEMI.

*\*New LBBB should be treated as STEMI*

## 5. BIOCHEMICAL CARDIAC MARKERS

Serum levels of creatine kinase (CK) and its MB fraction are important indicators of myocardial necrosis. A major limitation of both assays is their relatively low specificity and sensitivity early ( $< 6$  hours) after the onset of symptoms.<sup>26,27</sup> The risk of adverse outcomes in patients without persistent ST segment elevation was greater in patients with CK-MB elevation. However, other biochemical markers, such as troponin I (TnI) and troponin T (TnT), appear to have a greater prognostic value.

Troponin C, TnI and TnT are involved in the contraction of myocardial cells. The amino acid sequence of troponin C is the same in myocardial and skeletal muscle cells, while myocardial and skeletal forms of TnI and TnT differ.<sup>28</sup>

**Grade A** Assays with high specificity and sensitivity for myocardial TnI and TnT are available, and several studies have demonstrated their ability to detect myocardial injury and their potential usefulness as a risk stratification tool.<sup>28-33</sup>

The prognostic value of TnI or TnT to predict the risk for death, MI and the need for revascularisation at 30 days, is equal. The properties and values of the various biochemical cardiac markers are shown in **Table 1**.<sup>34,35</sup>

Although myoglobin is not cardiac specific, it has high sensitivity. It is detected as early as 2 hours after the onset of pain. A negative test for myoglobin within the first 4 to 8 hours is useful in ruling out myocardial necrosis. However, it should not be used as the only cardiac marker to identify patients with NSTEMI (**Figure 2**).<sup>27,37</sup>

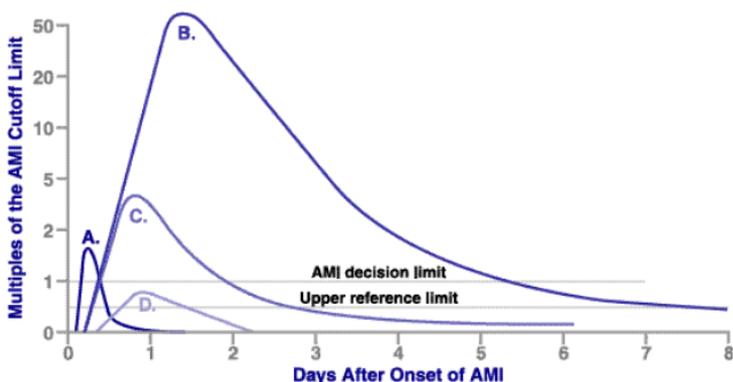


Figure 2. Plot of the appearance of cardiac markers in blood vs. time after onset of symptoms.

Peak A, early release of myoglobin. Peak B, cardiac troponin after AMI. Peak C, CK-MB after AMI. Peak D, cardiac troponin after UA. Data are plotted on a relative scale, where 1.0 is set at the AMI cutoff concentration.

**Table 1. Biochemical Cardiac Markers for the Evaluation and Management of Patients Suspected of Having an ACS but Without ST segment Elevation on 12-Lead ECG**

Marker	Advantages	Disadvantages	Clinical Recommendation
Cardiac troponins	<ol style="list-style-type: none"> <li>1. Powerful tool for risk stratification</li> <li>2. Greater sensitivity and specificity than CK-MB</li> <li>3. Detection of recent MI up to 2 weeks after onset</li> <li>4. Useful for selection of therapy</li> <li>5. Detection of reperfusion</li> </ol>	<ol style="list-style-type: none"> <li>1. Low sensitivity in very early phase of MI (&lt;6 h after symptom onset) and requires repeat measurements at 6 - 12 h, if negative</li> <li>2. Limited ability to detect late minor reinfarction</li> </ol>	Useful test to diagnose myocardial damage, clinicians should familiarise themselves with diagnostic “cutoffs” used in their local hospital laboratory
CK-MB	<ol style="list-style-type: none"> <li>1. Rapid, cost-efficient, accurate assays</li> <li>2. Ability to detect early reinfarction</li> </ol>	<ol style="list-style-type: none"> <li>1. Loss of specificity in setting of skeletal muscle disease or injury including surgery</li> <li>2. Low sensitivity during very early MI (&lt;6 h after symptom onset) or later after symptom onset (&gt;36 h) and for minor myocardial damage (detectable by troponins)</li> </ol>	Prior standard and still acceptable diagnostic test in most clinical circumstances
Myoglobin	<ol style="list-style-type: none"> <li>1. High sensitivity</li> <li>2. Useful in early detection of MI</li> <li>3. Detection of reperfusion</li> <li>4. Most useful in ruling out MI</li> </ol>	<ol style="list-style-type: none"> <li>1. Very low specificity in setting of skeletal muscle injury or disease</li> <li>2. Rapid return to normal range limits sensitivity for later presentations (normalised within 6 hours)</li> </ol>	Should not be used as the only diagnostic marker because of lack of cardiac specificity



Elevation of CK-MB level is strongly related to mortality in patients with ACS without ST segment elevation, and that the increased risk begins with CK-MB levels just above normal.<sup>36,37</sup> A normal level of CK-MB however does not exclude minor myocardial damage and its attendant risk of adverse outcome.<sup>27</sup>

Cardiac specific troponins are the primary biochemical marker for ACS. It is emphasised that cardiac troponin levels may not rise for 6 hours after onset of symptoms. A negative troponin level at < 6 hours should prompt a repeat 6 to 12 hours after the onset of pain.<sup>29,33</sup> Cardiac troponin can be measured in the chemistry laboratory or with a hand-held rapid qualitative assay. If performed in the laboratory, results should be available within 60 mins.

## 6. RISK STRATIFICATION

### Assessment of Risk

The assessment of risk should begin with the assessment of the likelihood of CAD. The 5 most important factors derived from the clinical history that relates to the likelihood of CAD, ranked in the order of importance, are:<sup>20,21,22</sup>

- 1) The nature of the angina symptoms
- 2) Prior history of CAD
- 3) Sex
- 4) Age
- 5) Diabetes, other traditional risk factors

Once UA / NSTEMI is established, the likelihood of an adverse clinical outcome is estimated. Apart from age and a past history of CAD, clinical examination, electrocardiogram and biochemical cardiac marker measurement make up the key elements of risk assessment.

### Rationale of Risk Stratification

Patients with UA / NSTEMI have an increased risk of death, recurrent MI, recurrent symptomatic ischaemia, serious arrhythmias, heart failure and stroke.



However, UA and NSTEMI share ill-defined borders with severe chronic stable angina pectoris, a condition with much lower risk; and STEMI, a condition that has a higher risk of death and nonfatal ischaemic events.<sup>23,24</sup> An assessment of prognosis would not only help instil the need for urgency of the initial evaluation and treatment, but would also help direct the use of valuable resources such as:

- 1) Selection of the site of care (coronary care unit, monitored step-down ward or outpatient setting) and
- 2) Selection of appropriate therapy, such as platelet Glycoprotein IIb/IIIa antagonists and coronary interventions.

### **Recommendations**

- 1) A determination of the likelihood of acute ischaemia caused by CAD should be made in all patients with chest discomfort.
- 2) Patients with UA / NSTEMI should undergo early risk stratification that focuses on angina symptoms, physical examination findings, ECG findings and biochemical markers of cardiac injury.
- 3) A 12-lead ECG should be obtained immediately (within 10 minutes) in patients with ongoing chest discomfort and as soon as possible in patients who have a history consistent with acute ischaemic pain but whose discomfort has resolved by the time of evaluation.
- 4) Biochemical markers of cardiac injury should be measured in all patients who present with chest discomfort consistent with UA / NSTEMI. A cardiac-specific troponin is the preferred biomarker and, if available, should be measured in all patients. CK-MB by mass assay is also acceptable. In patients with negative cardiac markers within 6 hours of the onset of chest pain, another sample should be taken in the 6 to 12 hour timeframe.



## Criteria for High and Low Risk for Death or MI<sup>23,24</sup>

### High Risk

- Patients with severe symptoms
  - recurrent ischaemia [either with accelerating tempo of ischaemic symptoms in preceding 48 hours or prolonged ongoing (> 20 minutes) rest pain]
  - patients with rest angina which is not relieved with nitrates
  - patients with early post-infarction UA
  - patients with previous or prior revascularisation (PCI, CABG)
  - patients with prior ASA treatment of less than 7 days
- Patients with haemodynamic instability within the observation period
  - pulmonary oedema
  - new or worsening mitral regurgitation (MR)
  - hypotension, bradycardia or tachycardia
- Patients with ECG abnormalities
  - dynamic ST segment changes > 0.05mV, particularly ST segment depression
  - transient ST segment elevation
  - T-wave inversion > 0.2 mV
  - pathological Q-waves
  - bundle-branch block, new or presumed new
  - sustained ventricular tachycardia
- Patients with elevated troponin levels
- Patients with left ventricular (LV) dysfunction and LV ejection fraction (by echocardiogram) < 40%

### Low Risk\*

- Patients who have no recurrence of chest pain within the observational period
- Patients without ST segment depression or elevation but rather negative T-waves, flat T-waves or normal ECG
- Patients without elevation of troponin or other biomarkers of cardiac injury

\* The assessment of risk should be made continuously as an estimation of risk is subject to change over time.

The TIMI risk score for UA / NSTEMI is another useful tool for risk stratification and management strategies. (see appendix 2, page 38)



## 7. TRIAGE

Chest pain is a common presentation at most health care facilities. As there is a wide variety of causes of chest pain, which ranges from life threatening ACS to musculo-skeletal pain, the healthcare provider must accurately triage patients with chest pain so that those with suspected ACS can be evaluated rapidly and definitive treatment started.

In most patients without any prior history of CAD, the chest pain is not an emergency. However, effective triaging can be achieved by taking a targeted history to elicit symptoms suggestive of ACS.

This can be done by asking the following questions;

- Are you a known case of CAD?
- Elicit any co-morbid risk factors, such as smoking, diabetes, hypertension, dyslipidemia or a family history of CAD?
- Is the pain constricting or pressing in nature (suggestive of angina)?
- Does the pain (with reference to angina) radiate to any part?
- Is there pain at rest and has the pain been prolonged (> 20 minutes)?
- In CAD patients, is there any relief of pain with sublingual nitrates?

Based on the answers to these questions, if a diagnosis of ACS is suspected, the patient should have a 12-lead ECG done within 10 minutes. If no such facility is available, the patient should be sent immediately to the nearest place where it is available.

The 12-lead ECG is central in triaging patients by stratifying them into one of the following groups:

- **ST segment elevation or new onset LBBB**  
High specificity of evolving STEMI
- **ST segment depression**  
Strongly suggestive of ischaemia
- **Non-diagnostic or normal ECG**  
In patients with positive risk factors, a repeat ECG and cardiac biomarkers are indicated.



Cardiac biomarkers are now considered of critical importance in the evaluation and stratification of patients with UA / NSTEMI. The choice of biomarkers will depend on the time of onset and duration of chest pain.

Healthcare providers must send any patient who is suspected of ACS with chest discomfort and positive cardiac biomarkers to a healthcare facility where definitive treatment can be started immediately.

### **Prehospital Management**

The level of prehospital management given will depend on the accuracy of the diagnosis, the level of facilities available both at the healthcare facility and in the ambulance transporting the patient to the centre for definitive care.

Based on the triage of patients with suspected ACS,

- **If the targeted history is suggestive of ACS**
  - Give acetylsalicylic acid (ASA) 300 mg crushed stat.
  - Give sublingual nitrates.
  - Do a 12-lead ECG or send to a place where it can be done.
  - If available do cardiac biomarkers.
- **If the ECG and biomarkers are suggestive of ACS**
  - Send the patient to the nearest healthcare facility where definitive care can be provided.
- **If the ECG and biomarkers are inconclusive of ACS**
  - **Low risk patients:** they can be referred to as out-patients for cardiac assessment.
  - **High risk patients:** patients must be admitted.

All patients with a suspected or confirmed diagnosis of ACS should be transported in an ambulance equipped with adequate facilities for monitoring their vital signs. They should be given adequate pain relief, nitrates and nasal oxygen.

## Emergency Department Management.

All patients presenting with chest pain to the Emergency Department (ED) should be triaged<sup>†</sup> Yellow. A rapid, targeted history must be taken and if suggestive of ACS, a 12-lead ECG must be done within 10 minutes of arrival at the department. Based on the history and ECG findings, they should be triaged and stratified into the appropriate category as follow:

- **EMERGENCY = RED : Acute STEMI**
- **URGENCY = YELLOW : UA / NSTEMI**
- **NON-URGENT = GREEN : Low risk / non cardiac chest pain**

<sup>†</sup> Based on the triage code used at the Emergency Department of all Government Hospitals.

If available, patients should have point-of-care biomarkers done to increase the accuracy of the diagnosis and optimise risk stratification of the patients.

If the patient has had an ECG done prior to arrival at the Emergency Department, a repeat ECG should be done and the patient re-triaged.

## 8. ANTITHROMBOTIC THERAPY

Antithrombotic therapy is essential to improve the disease outcomes and to lower the risk of death, MI or recurrent MI. Currently, a combination of ASA, clopidogrel, unfractionated heparin (UFH) or low molecular weight heparin (LMWH) and a platelet GP IIb/IIIa receptor antagonist represent the most effective therapy. The intensity of the treatment is tailored to individual risk as summarised in the table below:

Low Risk UA / NSTEMI patient	High Risk UA / NSTEMI patient
ASA + Clopidogrel* + SC LMWH or IV UFH	ASA + Clopidogrel* + SC LMWH or IV UFH + IV platelet GP IIb/IIIa antagonist

*\*If clopidogrel is not available, ticlopidine 250mg bid is recommended.*



## 8.1 ORAL ANTIPLATELET AGENT

Antiplatelet therapy is an essential therapy to modify the disease process and progression.

### 8.1.1 Cyclo-oxygenase inhibitors

#### **Grade A** *Acetylsalicylic acid (ASA)*

ASA acts by irreversibly inhibiting cyclooxygenase-1 within platelets, hence preventing the formation of thromboxane A<sub>2</sub>. This inhibits platelet aggregation promoted by this pathway but not by others. Part of the benefit of ASA could be due to its anti-inflammatory properties, which could reduce plaque rupture and its sequelae.<sup>46</sup>

From the ISIS-2 trial,<sup>47</sup> 160mg/day of ASA was used which definitively established the efficacy of ASA in suspected MI. Hence a minimum initial ASA dosage of 160 mg is recommended for UA / NSTEMI patients.

In the collaborative overview of randomised trials of antiplatelet therapy, there is significant reduction of death, MI and stroke by prolonged antiplatelet therapy in various categories of patients.<sup>40</sup>

An overview of trials with different doses of ASA in long-term treatment of patients with CAD suggests similar efficacy for daily doses ranging from 75 to 325 mg.

In patients who present with suspected ACS and are not already receiving ASA, the first dose may be crushed ASA to rapidly achieve a high blood level. Subsequent doses may be swallowed.

Contraindications to ASA include intolerance and allergy (primarily manifested as asthma), gastrointestinal or genitourinary bleeding as well as some haematological disorders.



### 8.1.2 Adenosine Diphosphate Receptor Antagonists

Two thienopyridines - ticlopidine and clopidogrel - are currently approved for antiplatelet therapy. They act differently from ASA-thromboxane A2 pathway by blocking adenosine diphosphate (ADP), resulting in inhibition of platelet aggregation.

#### **Grade A** | ***Clopidogrel (Plavix)***

In the CAPRIE trial,<sup>42</sup> patients were randomised to receive 325 mg/day ASA or 75 mg/day clopidogrel. There was a relative risk reduction in incidence of ischaemia, MI or vascular death by 8.7% in favour of clopidogrel.

In the recently published CURE trial,<sup>45</sup> patients who presented within 24 hours after the onset of ACS were randomised to receive clopidogrel (300 mg immediately, followed by 75 mg once daily) or placebo in addition to ASA for 3 to 12 months. The results showed a significant reduction in incidence of death from cardiovascular causes, nonfatal MI or stroke in the treatment group (9.3 % compared to 11.4 % in placebo).

#### **Grade A** | ***Ticlopidine (Ticlid)***

In an open-label trial,<sup>41</sup> patients with UA were randomised to ticlopidine 250mg twice a day versus standard therapy. At 6-month follow-up, ticlopidine was shown to reduce the rate of fatal and nonfatal MI by 46%. Therefore, ticlopidine can be considered an alternative for long-term therapy in patients who do not tolerate ASA.

The use of ticlopidine is associated with neutropenia in 2.4% of patients.<sup>48</sup> It is advisable to use this drug with caution. Monitoring of the full blood counts with differential leucocyte and platelet counts should be carried out at the beginning of treatment, every 2 weeks for the first 3 months of treatment and within 15 days of stopping treatment if this occurs during the first 3 months of therapy. If neutropenia



(<1500 neutrophils/mm<sup>3</sup>) or thrombocytopenia (<100,000 platelets/mm<sup>3</sup>) occurs, ticlopidine should be withdrawn and blood counts monitored until they return to normal. Patients should be advised to report immediately any fever, sore throat or mouth ulcers (which may be associated with neutropenia).

Recommended Dosage	
Initial dose	ASA 300 mg Clopidogrel 300mg*
Maintenance dose	ASA 75-150 mg for life Clopidogrel 75 mg for 1 year*

*\*For those with ASA intolerance and where clopidogrel is not available, ticlopidine 250mg bid is recommended.*

### 8.1.3 Other Antiplatelet Agents

Sulfapyrazone, dipyridamole, prostacyclin, prostacyclin analogues and oral glycoprotein IIb/IIIa antagonist<sup>43,44,74</sup> have not been associated with benefits in UA / NSTEMI. Hence they are not recommended.

## 8.2 ANTICOAGULANTS

Heparin, either Unfractionated Heparin (UFH) or Low Molecular Weight Heparin (LMWH), is a key component in the antithrombotic management of UA / NSTEMI.

### 8.2.1 Unfractionated Heparin (UFH)

Heparin is a mixture of sulphated mucopolysaccharides, which binds to antithrombin III. Activated antithrombin III inactivates factor IIa (thrombin), factor IXa and factor Xa, thereby inhibiting coagulation. Heparin and activated antithrombin III inhibit thrombin-induced platelet aggregation.

Several randomised trials suggest that UFH can improve clinical outcome compared with ASA alone. The greatest benefit was observed during the period of intravenous therapy, with “rebound” in recurrent



events after stopping UFH observed in one study. A meta-analysis showed a 33% reduction in death or MI at 2 to 12 weeks follow-up when comparing UFH plus ASA versus ASA alone, although this reduction was of borderline significance.<sup>49</sup>

**Grade A** | **8.2.2 Low Molecular Weight Heparin (LMWH)**

A major advance in the use of heparin has been in the development of LMWH, which inhibits factor IIa and factor Xa.

LMWHs are obtained by depolymerisation of standard UFH to provide chains with different molecular weights. The pharmacodynamics and pharmacokinetic profiles of different commercial preparations of LMWHs vary, with their mean molecular weights ranging from 4,200 to 6,000.

**The advantages of LMWH are:**

1	Decreased binding to heparin-binding proteins
2	More predictable effects
3	Measurement of aPTT not required
4	Administered subcutaneously, avoiding difficulty with continuous IV administration
5	Associated with more frequent minor, but not major bleeding <sup>50,51,52</sup>
6	Stimulate platelets less than UFH and are less frequently associated with heparin-induced thrombocytopenia <sup>53,54</sup>
7	An economic analysis of the ESSENCE trial suggested cost savings with enoxaparin <sup>55</sup>

There is convincing evidence in ASA treated patients that LMWH is better than placebo. Two trials have provided data in favour of LMWH (enoxaparin) over UFH when administered as an acute regimen.<sup>50,51</sup> The other LMWHs have produced similar benefits in the acute phase

treatment. Thus it can be concluded that the acute LMWH treatment is at least as effective as UFH in UA / NSTEMI. The duration of treatment should be between 2 - 7 days.

**Complications of UFH / LMWH Treatment** – Minor bleeding is usually treated by simply stopping the treatment. Major bleeding such as haematemesis, melaena or intracranial haemorrhage may require the use of heparin antagonist with the attendant risk of reducing a rebound thrombotic phenomenon. The anticoagulant and haemorrhagic effects of UFH are reversed by an equimolar concentration of protamine sulphate, which neutralises the anti-factor IIa activity, but results in only partial neutralisation of the anti-factor Xa of LMWH.

Recommended Dosage		
UFH	IV Bolus	- 60 - 70 U/kg (maximum of 5,000U) - Infusion of 12 U/kg/hour (maximum of 1,000U/hour)
	Target aPTT	- 1.5 - 2.0 times or approximately 60 - 80 seconds - It should be monitored and measured
LMWH	Enoxaparin (Clexane)	- 1mg / kg, SC, bid
	Nadroparin (Fraxiparine)	- 0.1ml / 10kg, SC, bid

### 8.2.3 Direct Thrombin Inhibitors

The prototype agent is hirudin, a naturally-occurring anticoagulant from the medicinal leech. The GUSTO-IIb and OASIS studies<sup>56,57</sup> showed that hirudin was superior to UFH in the reduction of death and MI in UA / NSTEMI. Hirudin has been approved for patients with heparin-induced thrombocytopenia. However, none of the hirudins are currently licensed for acute coronary syndrome.

### 8.2.4 Oral Anticoagulants

Currently there is no evidence to support the use of oral anticoagulants in UA / NSTEMI



### 8.3 PLATELET GLYCOPROTEIN IIb/IIIa RECEPTOR ANTAGONISTS

The glycoprotein (GP) IIb/IIIa receptor is the principal receptor involved in the final step in platelet aggregation - namely, the binding of plasma fibrinogen or von Willebrand factor to this activated membrane protein. This results in the formation of cross-bridges between adjacent platelets, linking them together to form a scaffold for the advancing haemostatic plug. Thrombosis can be effectively kept in check by blockade of this receptor. It is by interruption of this “final common pathway” that the new platelet GP IIb/IIIa receptor antagonists prevent platelet aggregation, resulting in a reduction in the clinical morbidity and mortality in patients who present with UA / NSTEMI.

Three intravenous GP IIb/IIIa receptor antagonists have now been approved for clinical use. Abciximab (Reopro) is a Fab fragment of a humanised murine monoclonal antibody that recognises the fibrinogen receptor. On the other hand, the cyclic heptapeptide eptifibatid (Integrilin) and the nonpeptide mimetic tirofiban (Aggrastat) are competitive inhibitors of fibrinogen binding.

Numerous trials have documented the efficacy of GP IIb/IIIa receptor antagonists in the prevention of complications associated with percutaneous coronary interventions (PCI).<sup>58-64</sup> In this regard, all the three clinically approved GP IIb/IIIa receptor antagonists have shown similar efficacy. However, differing efficacy of these compounds has also been demonstrated in large prospective placebo-controlled randomised trials of patients enrolled with UA / NSTEMI. In particular, two trials with tirofiban and one trial with eptifibatid have documented their efficacy in enhancing infarct-free survival at 1 and 6 months when started several days prior to angiography and subsequent triage to medical therapy, PCI, or Coronary artery bypass graft surgery (CABG) as anatomically and clinically appropriate.<sup>66-68</sup> On the other hand, the GUSTO IV ACS trial has shown that 24-48 hours of abciximab is not superior to placebo in patients with UA / NSTEMI.<sup>69</sup> This indicates that abciximab is not beneficial as first line medical therapy in UA / NSTEMI unless it is part of an early revascularisation strategy, as suggested from the CAPTURE trial.<sup>61</sup>



Randomised trials have also shown that GP IIb/IIIa receptor antagonists used during the initial phase of pharmacological therapy preceding PCI (“upstream” use) result in a risk reduction in death or MI.<sup>70</sup> Furthermore, the reduction in event rates was magnified at the time of PCI. It appears that the salutary benefits of GP IIb/IIIa receptor antagonists are most marked in patients undergoing early PCI while these drugs are still infusing, during which potent platelet inhibition is maintained. The benefit of GP IIb/IIIa receptor antagonists was mainly present in patients with on-going ischaemia or with other high-risk features such as an elevated TnT or Tnl at baseline.<sup>61,66,67,71,72</sup>

Prolonged treatment with oral GP IIb/IIIa receptor antagonists in patients with UA / NSTEMI or after PCI did not show any evidence of benefit.<sup>73,74</sup>

## Recommendations

- Grade A** | 1. Based on current clinical data, tirofiban and eptifibatide should be considered, in addition to ASA, clopidogrel and UFH / LMWH, for upstream use in UA / NSTEMI patients with continuing ischaemia or with other high risk features.
- Grade A** | 2. Although upstream use of abciximab for plaque stabilisation in UA / NSTEMI patients not emergently undergoing coronary angiography is not recommended, it can be used for 18-24 hours in those patients in whom a PCI is planned within the next 24 hours.
- Grade A** | 3. For patients with UA / NSTEMI undergoing angioplasty or stenting not pretreated with a GP IIb/IIIa receptor antagonist, abciximab and eptifibatide remain the agents of first and second choices.



Recommended Dosage		The dosing regimen for the initial phase of pharmacological therapy preceding PCI (upstream use) and during PCI are as follows:
1. Abciximab (Reopro)	Upstream use and planned PCI  PCI	<ul style="list-style-type: none"> <li>- IV Bolus - 0.25mg/kg for 18-24 hours before the procedure</li> <li>- Followed by continuous infusion of 0.125µg/kg per minute (to a maximum of 10µg/minute) for 12 hours</li> <li>- IV Bolus - 0.25mg/kg for 10-60 minutes before the start of PCI</li> <li>- Followed by continuous infusion of 0.125µg/kg per minute (to a maximum of 10µg/minute) for 12 hours</li> </ul>
2. Eptifibatid (Integrilin)	Upstream use  PCI	<ul style="list-style-type: none"> <li>- IV Bolus - 180 µg/kg</li> <li>- Followed by an infusion of 2 µg/kg per minute for 72 hours or until hospital discharge</li> <li>- In the case of PCI, the infusion should be continued for 96 hours</li> <li>- IV Bolus - 180 µg/kg</li> <li>- Immediately followed by a 2 µg/kg/minute infusion</li> <li>- Then a second 180 µg/kg bolus 10 minutes later</li> <li>- The infusion should be continued until hospital discharge, up to 18-24 hours</li> </ul>
3. Tirofiban (Aggrastat)	Upstream use  PCI	<ul style="list-style-type: none"> <li>- IV Bolus - 0.4 µg/kg per minute for 30 minutes</li> <li>- Followed by an infusion of 0.1 µg/kg/minute for 48 - 108 hours</li> <li>- In the case of PCI, the infusion should be continued 12 - 24 hours after PCI</li> <li>- IV Bolus - 10 µg/kg over 3 minutes</li> <li>- Followed by an infusion of 0.15 µg/kg/minute for 36 hours</li> </ul>



## 9. ANTI-ISCHAEMIC AGENTS

The goals of therapy are to relieve ischaemia and to prevent serious adverse outcomes such as AMI or death. In these patients, anti-ischaemic agents are initiated together with planning for a definitive treatment strategy. Anti-ischaemic therapy includes:

**Grade C** Admission for bed rest with continuous ECG monitoring for continuing ischaemia and detection of arrhythmias for high risk patients. Supplemental oxygen should be given to all patients to maintain  $SpO_2 > 90\%$ .

### **Grade C** 9.1 NITRATES

Nitrates reduce myocardial oxygen demand and increase myocardial oxygen supply.

IV nitrates should be instituted in patients who:

- Do not get symptomatic relief with three 0.5mg sublingual nitrate tablets (in the absence of contraindications such as use of sildenafil within 24 hours)
- Have ECG evidence of myocardial ischaemia
- Have concomitant heart failure.

In normotensive patients, SBP should not fall below 110mmHg, while in hypertensive patients, the mean arterial pressure should not drop  $> 25\%$ .

Oral nitrates may be given after 12 to 24 hours of pain free period. Rebound angina may recur with abrupt cessation of nitrates.<sup>75</sup>



<b>Recommended Dosage</b>			
<b>Compound</b>	<b>Route</b>	<b>Dosage</b>	<b>Onset time</b>
<b>Nitroglycerine, Glyceryl Trinitrate</b>	<b>Intravenous</b>	<b>5 - 200µg / minute</b>	<b>1 minute</b>
	<b>Sublingual</b>	<b>0.3 - 0.6mg, can repeat up to 5 times after 5 minutes</b>	<b>2 minutes</b>
	<b>Transdermal Patch</b>	<b>5 - 10mg over 24 hours</b>	<b>1-2 hours</b>
<b>Isosorbide dinitrate</b>	<b>Intravenous</b>	<b>1.25 - 5.0mg / hour</b>	<b>1 minute</b>
	<b>Sublingual</b>	<b>2.5 - 10mg</b>	<b>3-4 minutes</b>
<b>Isosorbide mononitrate</b>	<b>Oral</b>	<b>20 - 30mg, 2 - 3 times daily up to 120mg in divided doses</b>	<b>30-60 minutes</b>

## **Grade C | 9.2 MORPHINE**

Morphine is a potent analgesic and anxiolytic agent with haemodynamic effects. Careful blood pressure monitoring is required.

It is recommended for patients who have persistent or recurrent symptoms despite anti-ischaemic therapy.

<b>Recommended Dosage</b>	
<b>IV Bolus</b>	<b>2 - 5 mg</b>
<b>Repeated dose</b>	<ul style="list-style-type: none"><li>- May be given</li><li>- Doses above 10 mg IV should be used with caution</li><li>- IV anti-emetic should be given together</li></ul>



Adverse effects include hypotension especially in fluid depleted patients, nausea, vomiting and respiratory depression occasionally occurs. Naloxone (0.4 to 2.0 mg IV) may be given to reverse or overcome morphine overdose with respiratory and/or circulatory depression.

### **Grade B | 9.3 BETA-BLOCKERS**

Beta-blockers competitively block the effects of catecholamines on beta-receptors. Beta-blockers reduce myocardial oxygen consumption through reduction in myocardial contractility, sinus rate, AV node conduction and systolic blood pressure. In the absence of contraindications, oral beta-blockers should be started early.

Beta-blockers without intrinsic sympathomimetic activity are preferred; these include metoprolol, propranolol, atenolol or esmolol. Contraindications to early beta-blocker use are second- or third-degree AV block, asthma, decompensated heart failure and severe peripheral arterial disease.<sup>76</sup>

<b>Recommended Dosage</b>	Target resting heart rate is 50 - 60 bpm
Metoprolol	25 - 100 mg PO bid
Propranolol	20 - 80 mg PO tds
Atenolol	25 - 100 mg PO daily

### **Grade B | 9.4 CALCIUM ANTAGONISTS**

Calcium antagonists reduce inward calcium flux across cell membranes. They inhibit myocardial and vascular smooth muscle contraction, slow AV node conduction and depress the sinus node. The effect on vasodilation, inotropism, AV block and sinus node slowing varies with different calcium antagonists.<sup>77,78</sup>

The use of rapid-release, short-acting dihydropyridines (eg. nifedipine) are associated with increased risk in patients without adequate beta-blockade,<sup>79,80</sup> and should be discouraged.



### Indications:

- Continuing or recurring angina in patients who are already on adequate doses of nitrates and beta-blockers or those unable to tolerate adequate doses of nitrates and/or beta-blockers
- Prinzmetal's angina (variant angina)

Recommended Dosage		
Drug	Usual Dose	Duration of Action
Diltiazem	Immediate release : 30 - 120 mg, 3 times daily	Short
	Slow release: 100 - 360 mg once daily	Long
Verapamil	Immediate release : 40 - 160 mg, 3 times daily	Short
	Slow release : 120 - 480 mg once daily	Long

Other calcium antagonists have not been studied in the context of UA / NSTEMI.

## **Grade A** | 10. STATINS

Statins have been shown to be beneficial in patients with UA / NSTEMI irrespective of their serum lipid levels.<sup>81,82,83</sup> They should be started early after the onset of UA / NSTEMI.<sup>84</sup>



## 11. REVASCULARISATION

### Early Conservative versus Early Invasive Strategies

Broadly speaking, there are two different management approaches to patients presenting with UA / NSTEMI, i.e. 'early conservative' (EC) and 'early invasive' (EI). In the EC strategy, coronary angiogram is reserved for patients with evidence of ischaemia despite optimal medical therapy. In the EI approach, all patients without contraindications for coronary revascularisation are subjected to coronary angiogram and revascularisation (if clinically indicated).

#### Rationale for EC

The 2 main trials to support this are TIMI IIIb<sup>36</sup> and VANQWISH.<sup>86</sup> The limitations of these trials are that they were done before the widespread use of GP IIb/IIIa receptor antagonists and stents which make EI safer with better long term results.

#### Rationale for EI

The 3 main trials that support this strategy are FRISC II,<sup>3</sup> TACTICS-TIMI18<sup>85</sup> and DANAMI-3.<sup>87</sup> TACTICS-TIMI 18 also demonstrated the benefits of pre-treatment with GP IIb/IIIa antagonists (upstream use).

#### Recommendations

##### **Grade A**

1. An EI strategy is recommended in patients with UA / NSTEMI and any of the high risk indicators mentioned earlier in the Risk Stratification chapter (refer to page 11).

##### **Grade A**

2. An EI strategy is not recommended in patients with:
  - a) extensive comorbidities (eg, liver or pulmonary failure, cancer), in whom risks of revascularisation are not likely to outweigh the benefits
  - b) Low risk UA / NSTEMI patients (refer to page 11)



**Grade B** | In the situation where facilities for EI strategy are not available, patients with high risk UA / NSTEMI as outlined should be considered for upstream treatment with GP IIb/IIIa antagonists, provided that patients can be adequately monitored.

The final decision on which strategy to use should be individualised to each patient based on a multitude of factors including the patient profile, facilities and expertise available.

## 12. POST HOSPITAL DISCHARGE

The acute phase of UA / NSTEMI is usually over within 2 months. The risk of progression to MI or the development of recurrent MI or death is highest during this period. Most patients then resume a clinical course similar to that of patient with chronic stable CAD

**Grade C** | Patients who do not undergo coronary revascularisation, patients who have failed revascularisation or patients with recurrent symptoms following revascularisation should continue optimum medical treatment and lifestyle changes after hospital discharge.

**Grade C** | Post discharge antiangina therapy is not required for patients with successful revascularisation and no recurrent ischaemia.

**Grade C** | Patients given sublingual nitrates should be instructed in its proper and safe use.

### **Antiplatelet**

**Grade A** | ASA should be prescribed at 75-150mg daily indefinitely unless contraindicated.<sup>40</sup> In high risk UA / NSTEMI patients, clopidogrel should be added and continued for at least one year.

Patients who cannot tolerate ASA, clopidogrel is an alternative. When clopidogrel is not available, ticlopidine can be given.



## **B-blockers**

**Grade A** B-blockers should be prescribed in patients with prior MI in the absence of contraindication.

**Grade A** B-blockers should be continued indefinitely in those with residual LV dysfunction and who are at risk for residual ischaemia.

## **Lipid-lowering therapy**

There is a wealth of evidence that cholesterol-lowering therapy for patients with average<sup>88,89</sup> or high cholesterol<sup>90</sup> after MI or UA reduces vascular events and death.

**Grade A** Statins should be started early prior to hospital discharge in all patients. Patients with normal LDL cholesterol levels but low HDL cholesterol may benefit from fibrate therapy.<sup>91</sup> Statins should be continued indefinitely to provide life long benefits.<sup>106</sup>

## **Angiotensin-converting enzyme inhibitors (ACEIs)**

**Grade A** ACEIs should be considered in patients with evidence of LV dysfunction (EF < 40%).<sup>92,93,94</sup>

A reduction in the rates of mortality and vascular events was reported in the Heart Outcomes Prevention Evaluation (HOPE) study with the long term use of ACEIs in moderate-risk patients with CAD, many of whom had preserved LV function.<sup>95</sup>

**Grade B** In patients with LV dysfunction who cannot tolerate ACEIs, angiotensin receptor blockers may be considered.<sup>96</sup>

The above recommendations are made for their potential prognostic benefits. For control of ischaemic symptoms, nitrates, B-blockers and calcium antagonists may be used.



## Use of medications

**Grade C** Prior to hospital discharge patients should be instructed on their medications and their proper use.

**Grade C** Angina lasting more than 2 - 3 minutes should prompt the patient to take one dose of sublingual nitrates. This may be repeated at 5-minute intervals for a total of 3 doses. If symptoms persist after 15 minutes, the patient should seek prompt medical attention at the nearest hospital.

## Post discharge follow up

**Grade C** All should be followed up in 2 - 6 weeks.

**Grade B** Patients managed initially with a conservative strategy who experience recurrent unstable angina or severe (Canadian class III) chronic stable angina should be considered for revascularisation.

**Grade B** Patients who are asymptomatic or have tolerable stable angina at follow up visits may be managed with long term medical therapy.

## Grade A Stress Test

Exercise testing should be considered in the outpatient evaluation of low risk UA / NSTEMI patients. The findings of ischaemic ST segment changes or limiting chest pain are associated with significantly increased risk of subsequent cardiac events. Such patients should be considered for revascularisation. The absence of these findings identifies a low risk patient subset who can be managed medically.



## 13. REHABILITATION

Cardiac rehabilitation is aimed at optimizing the physical, psychological and social well-being of patients following the acute event.

The objectives are:

- 1) To facilitate adjustment to the acute event and reduce psychological stress to the patients and their families
- 2) To advocate and maintain a healthy lifestyle and to encourage risk factor modification
- 3) To gradually return patients to their prior level of activities
- 4) To ensure compliance to medications
- 5) To educate patients and their families on CAD

### Risk factor modification

**Grade B** Smoking cessation.<sup>97</sup>

Patients who quit smoking can reduce the rate of deaths and infarction within the first year.

**Grade B** Weight. To achieve or maintain optimum weight.

**Grade B** Exercise.<sup>98</sup>

Encourage a minimum of 30 - 60 minutes of moderate activity 3 - 4 times per week (walking, cycling, swimming or other equivalent aerobic activities).

**Grade A** Diet. To consume low cholesterol or low saturated fat diet.

**Grade A** Cholesterol.<sup>88,89,90,104</sup> To take cholesterol lowering medications.

**Grade A** Hypertension.<sup>99,100,101</sup> Aim for a blood pressure < 130 / 80 mmHg.

**Grade A** Diabetes.<sup>102,103</sup> Optimal control of hyperglycaemia in diabetes.



## Life style issues

**Grade C** | Safety and timing of resumption of sexual activity e.g 1-2 weeks for low risk patients and 4 weeks for post CABG patients.

**Grade C** | Specific mention should be made about when they can resume driving, commercial air travel and return to work.

## 14. QUALITY ASSURANCE / AUDIT POINTS

### Cost Effectiveness Issues

These guidelines have made recommendations based mainly on published research evidence. Neither the cost (i.e. the budgetary implications) nor the cost effectiveness of these various treatment modalities has been taken into consideration. In order to establish the cost effectiveness of a specific treatment, one has to take into account the direct treatment cost (including consultation cost, medication cost, procedure cost, traveling cost etc), the indirect treatment cost (e.g. opportunity cost) and the efficacy of such therapy in achieving the desired outcome.<sup>105,106</sup> To date, no local studies are available to assess the cost effectiveness of various treatment modalities recommended by these guidelines. This area may be the subject of future research, and the output of such research will be very useful to assist practitioners, patients and other stake-holders in making appropriate decisions in the management of UA / NSTEMI.

### Quality Assurance / Audit Points

The following indicators / audit points have been suggested for individual institutions to assess the standard of care rendered. The initial audit provides an indication of baseline local standard, and a follow-up audit several months later allows an assessment of changes in standard. This exercise should also enable identification of reasons for any failure to meet the guideline standard, and methods to improve awareness of the guidelines.



Some quality assurance / audit points to consider:

#### Diagnosis of UA / NSTEMI

- Percentage of patients presenting with chest pain who have 12-lead ECG done at ED
- Percentage of patients presenting with chest pain who have biomarkers done at ED
- Percentage of patients with 2 sequential biomarkers done (ED, CCU, wards)

#### Recognition and documentation of high risk indicators

- Recognition and documentation of high risk indicators in patients diagnosed to have UA / NSTEMI (CCU, wards):
  1. New or presumed new ST segment depression at presentation
  2. Elevated Troponin levels
  3. Recurrent angina / ischaemia at rest or with low level activities despite intensive anti-ischaemic therapy
  4. Recurrent angina / ischaemia with CHF symptoms, an S3 gallop, pulmonary oedema, worsening crackles or new / worsening MR
  5. High risk findings on non-invasive stress testing
  6. Depressed LV systolic function (e.g. EF < 0.40 on non-invasive testing)
  7. Haemodynamic instability or angina at rest accompanied by hypotension
  8. Sustained VT, VF (major arrhythmias)
  9. Patients with early post-infarction unstable angina
  10. Within 6 months of PCI
  11. Prior CABG

#### Appropriate and timely referral to tertiary care

- Early / timely referral to cardiologist: patients with above high risk indicators for EI (CCU, wards)



### Use of antiplatelet agents

- Percentage of patients with UA / NSTEMI prescribed and given ASA 300 mg stat upon diagnosis
- Percentage of patients prescribed ASA 75 – 150 mg on discharge
- Patients not given ASA, contraindications to ASA documented
- Percentage of patients with UA / NSTEMI prescribed and given clopidogrel 300 mg stat upon diagnosis
- Percentage of patients prescribed clopidogrel 75 mg daily on discharge
- Percentage of patients on ticlopidine at appropriate dose of 250 mg bd
- Percentage of patients on ticlopidine appropriately monitored on follow-up

### Use of anticoagulants

- Percentage of UA / NSTEMI patients given UFH / LMWH
- Percentage of UA / NSTEMI patients on UFH appropriately monitored
- Time from provisional diagnosis to the initiation of UFH / LMWH
- aPTT monitoring 4-6 hours after initiating UFH and thereafter daily
- Daily aPTT ratio within the therapeutic range
- Documentation of cessation of UFH < 2 days
- Percentage of patients given optimal duration of UFH / LMWH (2-7 days)

### Use of GP IIb/IIIa receptor antagonist

- Use of GP IIb/IIIa receptor antagonist in UA / NSTEMI patients with continuing ischaemia despite ASA and anticoagulant therapy (CCU)
- Use of GP IIb/IIIa receptor antagonist when EI is not available (CCU)
- Appropriate monitoring of patients on GP IIb/IIIa receptor antagonist

### Control of risk factors

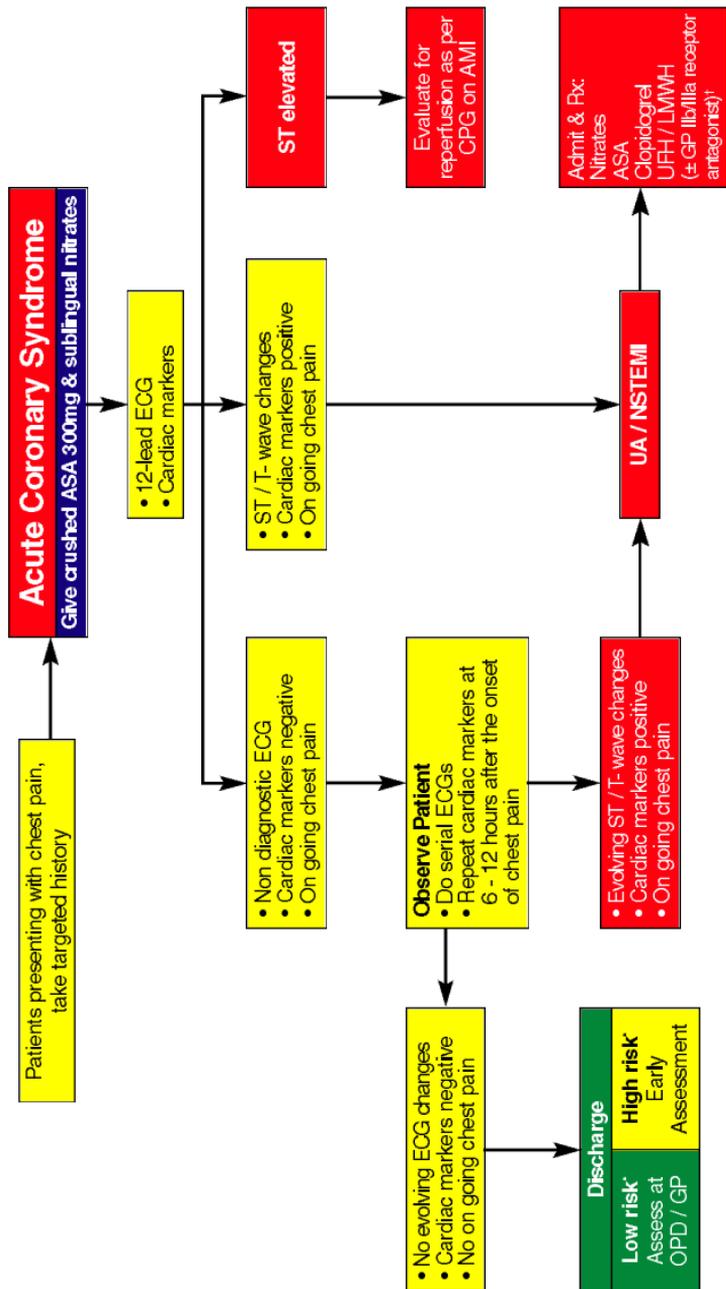
- UA / NSTEMI patients given statin
- Patient and family advised on smoking cessation
- BMI documented, obese patients informed of optimal weight, and advised on weight reduction
- Patient and family advised on exercise frequency and intensity unless contraindicated
- Patient and family advised on low saturated fat, low cholesterol diet
- Optimal hypertension control
- Tight control of hyperglycaemia



## 15. SUMMARY

- Acute Coronary Syndromes (ACS) pose a major health problem in Malaysia and are a major cause of hospitalisations and premature deaths.
- These guidelines focus on recently accepted medical terms, i.e.: UA / NSTEMI / STEMI, which describe ACS more accurately.
- These guidelines also detail the current understanding of the pathophysiological mechanisms of UA / NSTEMI which include:
  - Non-occlusive thrombus on pre-existing plaque
  - Progressive mechanical obstruction
- The diagnosis of UA / NSTEMI depends on the presence of the following criteria:
  - Chest pains of ischaemic nature
  - ECG changes
  - Rise and fall of cardiac biomarkers
- Risk stratification of patients is crucial as this may direct the use of valuable resources such as admission into CCU, use of GP IIb/IIIa antagonist or early recourse to Percutaneous Coronary Intervention.
- Appropriate use of antithrombotic therapy such as ASA, clopidogrel, LMWH and GP IIb/IIIa antagonist is essential to improve the outcome of UA / NSTEMI.
- The intensity of such antithrombotic treatment is tailored to the individual risk profile of the UA / NSTEMI patient.
- Adjunctive pharmacotherapy includes nitrates, morphine, beta-blockers, calcium antagonists and statins.
- High-risk patients should be stratified for early invasive (EI) treatment strategies.
- In situations where facilities for EI strategies are not available, they should be considered for upstream treatment with GP IIb/IIIa antagonists, provided that patients can be monitored adequately.
- Optimum rehabilitation and secondary prevention are also mandatory. This includes the use of ASA, clopidogrel, beta-blockers, lipid lowering agents, ACEIs; as well as modifying other risk factors.
- Finally, in view of the implied increased costs of such new medical strategies, some quality assurance or medical audit should be implemented to ensure rational and cost effective decision-making and healthcare planning.

# Algorithm for the triage and management of Acute Coronary Syndrome



\*Please refer to pages 20 - 22 of this CPG

Colours used reflect the Triage category of the patients.



## APPENDIX 1

Grading of Angina Pectoris according to the Canadian Cardiovascular Society (CCS)<sup>107</sup>

CLASS	DESCRIPTION
I	<i>Ordinary physical activity does not cause angina</i> such as walking or climbing stairs. Angina occurs with strenuous, rapid or prolonged exertion at work or recreation.
II	<i>Slight limitation of ordinary activity.</i> Angina occurs on walking or climbing stairs rapidly; walking uphill; walking or climbing stairs after meals; in cold, in wind, or under emotional stress; or only during the few hours after awakening. Angina occurs on walking > 2 blocks on the level and climbing > 1 flight of ordinary stairs at a normal pace and under normal conditions.
III	<i>Marked limitation of ordinary physical activity.</i> Angina occurs on walking 1 to 2 blocks on the level and climbing 1 flight of stairs under normal conditions and at a normal pace.
IV	<i>Inability to carry on any physical activity without discomfort - angina symptoms may be present at rest.</i>

## APPENDIX 2

### TIMI RISK SCORE for UA / NSTEMI

HISTORICAL	POINTS	RISK OF CARDIAC EVENTS (%) BY 14 DAYS IN TIMI 11B*		
		Risk Score	Death or MI	Death, MI or Urgent Revasc
Age 65	1			
3 CAD risk factors (FHx, HTN, chol, DM, active smoker)	1			
Known CAD (stenosis 50%)	1			
ASA use in past 7 days	1			
<b>PRESENTATION</b>				
Recent ( 24H) severe angina	1			
cardiac markers	1			
ST deviation 0.5mm	1			

**RISK SCORE=Total Points (0-7)**

\*Entry criteria: UA or NSTEMI defined as ischemic pain at rest within past 24H, with evidence of CAD (ST segment deviation or +marker)

For more info go to [www.timi.org](http://www.timi.org)

Antman et al *JAMA* 2000;284:835-842



## APPENDIX 3. ABBREVIATIONS

<b>ACC</b>	= American College of Cardiology	<b>DAVIT</b>	= Danish Study Group on Verapamil in Myocardial Infarction
<b>ACEI</b>	= angiotensin-converting enzyme inhibitor	<b>EC</b>	= early conservative
<b>ACS</b>	= acute coronary syndrome	<b>ECG</b>	= electrocardiogram
<b>ADP</b>	= adenosine diphosphate	<b>ED</b>	= emergency department
<b>AHA</b>	= American Heart Association	<b>EF</b>	= ejection fraction (left ventricle)
<b>AMI</b>	= acute myocardial infarction	<b>EI</b>	= early invasive
<b>aPTT</b>	= activated partial thromboplastin time	<b>EPIC</b>	= Evaluation of c7E3 for the Pre-vention of Ischaemic Complications
<b>ASA</b>	= acetylsalicylic acid	<b>EPILOG</b>	= Evaluation of PTCA to Improve Long-term Outcome by c7E3 GP IIb/IIIa receptor blockade
<b>CABG</b>	= coronary artery bypass graft surgery	<b>EPISTENT</b>	= Evaluation of Platelet IIb/IIIa Inhibitor for STENTing
<b>CAD</b>	= coronary artery disease	<b>ESSENCE</b>	= Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q wave Coronary Events
<b>CAPRIE</b>	= Clopidogrel versus ASA in Patients at Risk of Ischaemic Events	<b>FRAXIS</b>	= FRAXiparine in Ischaemic Syndrome
<b>CAPTURE</b>	= c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina	<b>FRIC</b>	= FRagmin In unstable Coronary artery disease study
<b>CCS</b>	= Canadian Cardiovascular Society	<b>FRISC</b>	= Fragmin during Instability in Coronary Artery Disease
<b>CCU</b>	= Coronary Care Unit	<b>FRISC II</b>	= Fast Revascularisation During Instability in Coronary Artery Disease
<b>CHF</b>	= congestive heart failure	<b>GP</b>	= glycoprotein
<b>CK</b>	= creatine kinase	<b>GUSTO-II</b>	= Global Use of Strategies to Open Occluded Coronary Arteries-II
<b>CURE</b>	= Clopidogrel in Unstable angina to Prevent ischaemic Events		
<b>DANAMI</b>	= DANish trial in Acute Myocardial Infarction		

<b>GUSTO-III</b>	= Global Use of Strategies to Open Occluded Coronary Arteries-III	<b>PRISM</b>	= Platelet Receptor Inhibition in Ischaemic Syndrome Management
<b>HDL</b>	= high-density lipoprotein	<b>PRISM-PLUS</b>	= Platelet Receptor Inhibition in Ischaemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms
<b>HINT</b>	= Holland Interuniversity Nifedipine/metoprolol Trial	<b>PTCA</b>	= percutaneous transluminal coronary angioplasty
<b>HOPE</b>	= Heart Outcomes Prevention Evaluation	<b>PURSUIT</b>	= Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy
<b>IMPACT</b>	= Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis	<b>RESTORE</b>	= Randomised Efficacy Study of Tirofiban for Outcomes and REstenosis
<b>IV</b>	= intravenous	<b>RR</b>	= relative risk
<b>ISIS</b>	= International Study of Infarct Survival	<b>SC</b>	= Subcutaneous
<b>LBBC</b>	= left bundle-branch block	<b>STEMI</b>	= ST segment elevation myocardial infarction
<b>L-CAD</b>	= Lipid Coronary Artery Disease Study	<b>TIMI</b>	= Thrombolysis In Myocardial Infarction
<b>LDL</b>	= low-density lipoprotein	<b>TnI</b>	= troponin I
<b>LMWH</b>	= low-molecular-weight heparin	<b>TnT</b>	= troponin T
<b>LV</b>	= left ventricular, left ventricle	<b>TTP</b>	= thrombotic thrombocytopenia purpura
<b>MI</b>	= myocardial infarction	<b>UA</b>	= unstable angina
<b>MIRACL</b>	= Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering	<b>UFH</b>	= unfractionated heparin
<b>MR</b>	= Mitral Regurgitation	<b>VANQWISH</b>	= Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital
<b>NSTEMI</b>	= non-ST segment elevation myocardial infarction		
<b>PCI</b>	= percutaneous coronary intervention		
<b>PO</b>	= per oral		



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