STATEMENT OF INTENT

This guideline was developed to be a guide for best clinical practice in the management of Unstable Angina/ Non ST Elevation Myocardial Infarction (UA/NSTEMI). It is based on the best available evidence at the time of development. Adherence to this guideline does not necessarily lead to the best clinical outcome in individual patient care. Thus, every health care provider is responsible for the management of his/her unique patient, based on the clinical presentation and management options available locally.

REVIEW OF THE GUIDELINE

This guideline was issued in 2011 and will be reviewed in 2016 or earlier if important new evidence becomes available.

CPG Secretariat
Health Technology Assessment Unit
Medical Development Division
Level 4, Block E1, Parcel E
Government Offices Complex
62590 Putrajaya, Malaysia

Available on the following websites:

http://www.malaysianheart.org
http://www.moh.gov.my
http://www.acadmed.org.my
SUMMARY

1. Acute coronary syndrome is a spectrum of UA/NSTEMI and STEMI. The clinical presentation will depend on the acuteness and severity of coronary occlusion.

2. The diagnosis of UA/NSTEMI is based on history ± dynamic ECG changes (without persistent ST elevation), ± raised cardiac biomarkers.

3. In UA cardiac biomarkers are normal while in NSTEMI it is elevated.

4. Risk stratification is important for prognosis and to guide management (Flowchart 1, pg 3).

5. Initial management of intermediate/high risk patients includes optimal medical therapy with aspirin IA and clopidogrel IA (or ticagrelor IB), UFH IA or LMWH IA or fondaparinux IA. Prasugrel may be considered as an alternative to clopidogrel in high risk patients after coronary angiography if PCI is planned IB. (Table 1, pg 4)

6. Patients with refractory angina and/or hemodynamically unstable should be considered for urgent coronary angiography and revascularization IC.

7. Intermediate/high risk patients should be considered for early invasive strategy (<72 hours). If admitted to a non-PCI centre, they should be considered for transfer to a PCI centre IA.

8. Low risk patients should be assessed non-invasively for ischemia IA. (Fig 1, pg 5)

9. All patients should receive optimal medical therapy at discharge. This includes aspirin IA, clopidogrel IB (or ticagrelor IB or prasugrel IB if given during PCI), β-blockers IB, ACE-I IA or ARB (if ACE-I intolerant IB) and statins IA. If recurrent or residual ischemia is present, then anti anginal therapy should also be given IC. These include nitrates IC, calcium channel blockers IIIa, C and/or metabolic agents IIIa, C (Table 1, pg 4)

10. These drugs should be uptitrated as outpatient to the recommended tolerated doses IC.

11. Cardiac rehabilitation and secondary prevention programs which includes lifestyle modification is an integral component of management IA.
Flowchart 1: Risk Stratification of UA/NSTEMI

**Low risk**
- no angina in the past
- no ongoing angina
- no prior use of antianginal therapy
- normal ECG
- normal cardiac biomarkers
- normal LV function
- younger age group

**Intermediate/High Risk**
- Patients with recurrent chest pain
- Early post infarction unstable angina
- Dynamic ST-segment changes
- Elevated cardiac biomarkers
- Diabetes
- Hemodynamic instability
- Depressed LV function (LVEF <40%)
- Major arrhythmias (VF, VT)

This includes (see Table 1, pg:4):
- Aspirin
- Clopidogrel or ticagrelor (or prasugrel after coronary angiography)
- Antithrombotics (UFH or LMWH or Fondaparinux)
- β-blockers
- Statins
- ACE-I/ARB
- Nitrates
- + CCB (if β-blockers contraindicated and/or unresponsive to above)

**Medical therapy**
* This includes aspirin + β-blockers + GTN

**Risk stratify as outpatient (Fig1, pg 5)**

**Coronary Angiography and Revascularization**
*If patient is admitted to a non-PCI centre and has ongoing ischaemia despite optimal medical therapy, it is recommended to transfer the patient for coronary angiography with view to revascularization.*

CCB : Calcium channel blockers
UFH : Unfractionated heparin
LMWH : Low Molecular Weight Heparin
GP : Glycoprotein
VF: Ventricular fibrillation
VT: Ventricular tachycardia
<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial and In-hospital medication</th>
<th>Medication at discharge</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>I,A</td>
<td>I,A</td>
<td>Continued long term if tolerating</td>
</tr>
<tr>
<td>+ Clopidogrel</td>
<td>I,A</td>
<td>I,A</td>
<td>Used in addition to aspirin as part of dual antiplatelet therapy. To be continued at least 1 month and ideally for at least a year post UA/NSTEMI and, 6-12months or longer post DES implantation</td>
</tr>
<tr>
<td>or, Ticlopidine</td>
<td>IIa,B</td>
<td>IIa,B</td>
<td>Used in addition to aspirin as part of dual antiplatelet therapy. This is a less preferred alternative to clopidogrel.</td>
</tr>
<tr>
<td>or, prasugrel</td>
<td>I,B</td>
<td>I,B</td>
<td>Used in addition to aspirin as part of dual antiplatelet therapy. Alternative to clopidogrel in high risk patients undergoing PCI.</td>
</tr>
<tr>
<td>or, ticagrelor</td>
<td>I,B</td>
<td>I,B</td>
<td>Used in addition to aspirin as part of dual antiplatelet therapy. Alternative to clopidogrel.</td>
</tr>
<tr>
<td>+ UFH</td>
<td>I,A</td>
<td>-</td>
<td>Given for 2-8 days</td>
</tr>
<tr>
<td>or, LMWH</td>
<td>I,A</td>
<td>-</td>
<td>Given for 2-8 days</td>
</tr>
<tr>
<td>or, fondaprinux</td>
<td>I,A</td>
<td>-</td>
<td>Used in patients treated conservatively. Given for 8 days or duration of hospitalization</td>
</tr>
<tr>
<td>or, Bivalirudin</td>
<td>I,A</td>
<td>Used as an alternative to UFH and GPIIb/IIa inhibitors during PCI</td>
<td></td>
</tr>
<tr>
<td>+ β-blockers</td>
<td>1,B</td>
<td>1,B</td>
<td>Should be administered early if no contraindications and continued indefinitely if ischemia is present. Continued indefinitely in the presence of LV dysfunction (LVEF&lt;40%)</td>
</tr>
<tr>
<td>+ ACE-I</td>
<td>I,A</td>
<td>I,A</td>
<td>Should be administered early in patients with LV dysfunction (LVEF&lt; 40%), heart failure, diabetes, hypertension or CKD. Should be considered long term to prevent recurrent ischemia</td>
</tr>
<tr>
<td>or ARB</td>
<td>IIa, A</td>
<td>I,B</td>
<td>As an alternative to ACE-I in intolerant patients</td>
</tr>
<tr>
<td>+ Statins</td>
<td>I, A</td>
<td>I,A</td>
<td>High potency statins should be used early till target LDL-C levels are achieved and continued indefinitely.</td>
</tr>
<tr>
<td>+/- calcium channel blockers</td>
<td>1,B, IIa,C</td>
<td>I,B, IIa,C</td>
<td>If intolerant to β-blockers indicated for residual/ recurrent ischemia.</td>
</tr>
<tr>
<td>+/- nitrates</td>
<td>I,C</td>
<td>I,C</td>
<td>Indicated for residual/ recurrent ischemia.</td>
</tr>
</tbody>
</table>
Low risk patients have:

- no angina in the past
- no ongoing angina
- no prior use of antianginal therapy
- normal ECG
- normal cardiac biomarkers
- younger age group
- normal LV function

Patients who have undergone revascularization and with residual/recurrent or a change in symptoms should be investigated as above.

All Intermediate/High Risk UA/NSTEMI patients should be considered for coronary angiography and revascularization. (Flowchart 1, pg 3)
MESSAGE FROM THE DIRECTOR GENERAL OF HEALTH

In the last 8 years since the last CPG UA/NSTEMI was published, the management of this most important of prodrome to a full blown STEMI has changed significantly. However, like in 2002, despite the World Health Statistics (2010) reporting a healthy rise in the number of doctors per population, Health Facts 2008 from the Ministry of Health Malaysia still state that the main cause of death in the country is cardiovascular disease.

It is now recognized that early, aggressive management of UA/NSTEMI can improve clinical outcomes both in the short- and long-term. Mounting evidence in the early use of antithrombotic agents, early access to revascularization, and secondary prevention strategies, contribute to the significant reduction of cardiovascular mortality and morbidity.

In the last few years, the establishment of the National Cardiovascular Database, comprising of the Acute Coronary Syndrome (NCVD-ACS), Percutaneous Coronary Intervention (NCVD-PCI), as well as the Malaysian Cardiac Surgery Registry (MyCARE), has now provided us a unified tool to capture important data on cardiovascular disease presentation and management in our country. We now know that the incidence of ACS in Malaysia is approximately 141 per 100,000 population per year, and the inpatient mortality rate is approximately 7%, comparable to many developed countries. We have recorded over 8000 PCI performed in Malaysia over the last 3 years, with a very low rate of serious complications, particularly in elective procedures (<1%).

Further, in the last few years, increasing numbers of Cardiology Units, as well as well-run General Medicine Units, are participating in Phase I to III clinical trials. More Malaysians are now being offered the opportunity to be directly involved in new therapies and are also being provided stringent world-class care in the context of a clinical trial setting.

In this rapidly evolving landscape of UA/STEMI management, and a definite increase in patient load in the face of the rising prevalence of cardiovascular risk factors published in the recent National Health and Morbidity Survey III, it is time now to update this CPG UA/NSTEMI. We believe this will provide healthcare providers with strategies, derived from contemporary evidence, to improve the diagnosis and treatment of this unpredictable condition.

Dato Hasan Abdul Rahman,
Director General of Health,
Ministry of Health, Malaysia
FOREWARD FROM THE AMERICAN COLLEGE OF CARDIOLOGY

On behalf of the American College of Cardiology I want to offer my hearty congratulations to the National Heart Association of Malaysia in their creation of this ACS NSTEMI clinical practice guideline update. Adherence to evidence based medicine has conclusively been shown to improve clinical outcomes. The field of cardiology in particular has been relatively blessed with a plethora of many superb international randomized clinical trials (RCT) that form the backbone of our cardiovascular clinical practice guidelines. The translation and application of the RCT-generated evidence base to the Malaysian “bedside” is the mission of clinical practice guidelines. In particular, NHAM’s Class 1 recommendations for the management of ACS/NSTEMIs represent the “must do’s” in the management of acute coronary syndromes as these care measures directly lead to decrease in mortality and morbidity in cardiovascular disease. In the United States over the past few decades a marked decrease in the cardiovascular mortality and morbidity has been achieved. This admirable accomplishment is directly due to increased adherence in clinical practice guidelines for secondary and primary prevention of coronary disease along with application of evidence based strategies in the management of acute coronary syndromes. NHAM’s clinical practice guideline reflects well the local care environment here in Malaysia creating the potential of saving thousands of lives though your promotion of evidence based ACS care. The participation in a national acute coronary syndrome registry is an important component of the cardiovascular quality cycle. If we don’t measure it, we can’t manage it!! We applaud the leadership of the National Heart Association of Malaysia with its enthusiasm and expertise manifested in NHAM’s updated ACS clinical practice guidelines along with your vigorous promotion of the NCVD Malaysian Acute Coronary Syndrome Registry. The ACC looks forward in future cardiovascular collaborations with the National Heart Association of Malaysia in the areas of cardiovascular science, education and in the promotion of cardiovascular quality.

Congratulations and a personal toast to Malaysian heart health!

Ralph Brindis, MD, MPH, FACC, FSCAI

Immediate Past President,
American College of Cardiology
Members of the Expert Panel

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Dr. Jeyamalar Rajadurai    Consultant Cardiologist,  
Sime Darby Medical Center  
Subang Jaya, Selangor

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Dr. Aris Chandran     Consultant Physician,  
Hospital Sultanah Bainun, Ipoh

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Hospital Besar Pulau Pinang

Dr. Oteh Maskon     Consultant Cardiologist  
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External Reviewers *(in alphabetical order):*

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- Dr. Jeyaindran Sinnadurai: Consultant Physician, Head of Internal Medicine, Ministry Of Health, Hospital Kuala Lumpur
- Dr. Lee Chuey Yan: Consultant Cardiologist, Hospital Sultanah Aminah Johor
- Dr. Lee Fatt Soon: Consultant Geriatrician, Hospital Kuala Lumpur, KL
- Dr. Kim Tan: Consultant Cardiologist, Sunway Medical Center, Sunway, Selangor
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RATIONALE AND PROCESS OF GUIDELINE DEVELOPMENT

Rationale:

Coronary artery disease (CAD) is an important cause of morbidity and mortality in Malaysia. Patients with CAD may present as stable angina or as acute coronary syndromes (ACS). ACS is a spectrum of disease ranging from unstable angina (UA), non ST elevation myocardial infarction (NSTEMI) to ST elevation myocardial infarction depending on the acuteness and severity of the coronary occlusion. The last CPG on UA/NSTEMI was published in 2002. Thus the need for an update.

Objectives:

The objectives of this guideline are to:

- provide guidance on the most effective evidence based therapeutic strategies in patients with UA/NSTEMI to reduce in-hospital morbidity and mortality.
- reduce the risk of recurrent cardiac events in these patients

This Clinical Practice Guideline (CPG) has been drawn up by a committee appointed by the National Heart Association of Malaysia, Ministry of Health and the Academy of Medicine. It comprises cardiologists and general physicians from the government and private sectors as well as from the Universities.

Process:

Evidence was obtained by systematic review of current medical literature on UA/NSTEMI using the usual search engines – PubMed, Medscape and Ovid. The other international guidelines (American and European) on the subject were also studied. After much discussion, the draft was then drawn up by the members of the Expert Panel and submitted to the Technical Advisory Committee for Clinical Practice Guidelines, Ministry of Health Malaysia and key health personnel in the major hospitals of the Ministry Of Health and the Private Sector for review and feedback.

The clinical questions were divided into major subgroups and members of the Expert Panel were assigned individual topics. The group members met several times throughout the development of the guideline. All retrieved literature were appraised by individual members and subsequently presented for discussion during group meetings. All statements and recommendations formulated were agreed collectively by members of the Expert Panel. Where the evidence was insufficient the recommendations were derived by consensus of the Panel. The draft was then sent to local external reviewers for comments. It was also sent to the American College of Cardiology and the European Society of Cardiology for feedback.
The level of recommendation and the grading of evidence used in this guideline was adapted from the American Heart Association and the European Society of Cardiology (ACC/ESC) and outlined on page 13. In the text, this is written in black on the left hand margin. In the Summary and Key Recommendations, it is written as a superscript immediately after the therapeutic agent or at the end of the statement as applicable.

Clinical Questions Addressed:

- What is the current evidence on the best practice strategies to reduce morbidity and mortality in patients with UA/NSTEMI?
- Which of these strategies are applicable to our local setting considering our limited health resources?

Target Group:

This guideline is directed at healthcare providers including general practitioners, medical officers, general and family physicians and cardiologists.

Target Population:

All patients (older than 18 years) presenting with chest pain.

Period of Validity of the Guidelines:

This guideline needs to be revised at least every 5 years to keep abreast with recent developments and knowledge.

Applicability of the Guidelines:

This guideline was developed taking into account our local health resources. The following are available at all state and district government hospitals with physicians.

- ECG machines, measurement of cardiac biomarkers (including troponins), treadmill stress ECG’s and echocardiograms.
- Most of the medications that are recommended in this guideline are already approved for use in Malaysia.
- Intermediate/high risk patients should be identified early and transferred to hospitals with existing catheterization facilities. In accordance with the national health plan, the ministry has already proposed the setting up of catheterization laboratories in most of the state hospitals.

This guideline aims to streamline management of cardiac patients and educate health care professional on strategies to optimize existing resources. We do not anticipate barriers to its implementation.
Implementation of the Guidelines:

The implementation of the recommendations of a CPG is part of good clinical governance. To ensure successful implementation of this CPG we suggest:

- increasing public awareness of CAD and its therapies.
- continuing medical education and training of healthcare providers.
- clinical audit – This is done by monitoring:
  - In-hospital mortality and morbidity in patients admitted with ACS (NCVD registry)
  - Readmission rates for a cardiac related event in patients discharged with a diagnosis of ACS. Elective admissions for cardiac procedure are excluded.
  - Documentation of the following;
    - Risk stratification
    - Discharge medications to include, antiplatelets, statins, ACE-inhibitors and Beta blockers.
    - Discharge plan with regards to cardiac assessment/tertiary care referral.
### GRADES OF RECOMMENDATIONS AND LEVELS OF EVIDENCE

#### GRADES OF RECOMMENDATION

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Conditions for which there is evidence and/or general agreement that a given procedure/therapy is beneficial, useful and/or effective.</td>
</tr>
<tr>
<td>II</td>
<td>Conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a procedure/therapy.</td>
</tr>
<tr>
<td>II-a</td>
<td>Weight of evidence/opinion is in favor of its usefulness/efficacy.</td>
</tr>
<tr>
<td>II-b</td>
<td>Usefulness/efficacy is less well established by evidence/opinion</td>
</tr>
<tr>
<td>III</td>
<td>Conditions for which there is evidence and/or general agreement that a procedure/therapy is not useful/effective and in some cases may be harmful.</td>
</tr>
</tbody>
</table>

#### LEVELS OF EVIDENCE

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Data derived from multiple randomized clinical trials or meta analyses</td>
</tr>
<tr>
<td>B</td>
<td>Data derived from a single randomized clinical trial or large non randomized studies</td>
</tr>
<tr>
<td>C</td>
<td>Only consensus of opinions of experts, case studies or standard of care</td>
</tr>
</tbody>
</table>

Adapted from the American Heart Association/American College of Cardiology (AHA/ACC) and the European Society of Cardiology (ESC)
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1. INTRODUCTION

Cardiovascular Disease (CVD) is one of the main causes of mortality and morbidity in Malaysia. The estimated incidence of Acute Coronary Syndrome (ACS) is 141 per 100,000 population per year, and the in-patient mortality rate is approximately 7%. This data is derived from the National Cardiovascular Disease Database (NCVD) based on the ACS 2006 Annual report. These figures are similar to that of many developed countries. Unstable Angina/Non ST Elevation Myocardial Infarction (UA/NSTEMI) which falls within the spectrum of ACS, is an important cause of cardiac morbidity and mortality.

The last CPG on UA/NSTEMI was published in 2002. Since then, there have been significant advances in the management of this important condition. Thus, it is timely to update this CPG to keep abreast with contemporary evidenced based state of the art management of this condition.

2. DEFINITION OF TERMS

ACS is a clinical spectrum of ischemic heart disease. Depending upon the degree and acuteness of coronary occlusion, it can present as (Figure 2, pg 16):

- Unstable angina (UA)
- Non-ST elevation myocardial infarction (NSTEMI)
- ST elevation myocardial infarction (STEMI)

These changes may be dynamic. A patient presenting with UA may progress to NSTEMI or even STEMI.

The terms Q-wave myocardial infarction (QwMI) and non-Q wave myocardial infarction (NQMI) are no longer preferred.

Unstable angina may be classified as^2^ (Appendix I, pg 51):

I. New onset of severe angina or accelerated angina; no rest pain
II. Angina at rest within past month but not within preceding 48 hours (angina at rest, subacute)
III. Angina at rest within 48 hours (angina at rest, acute)

It may be further classified according to clinical circumstances into either:

A) Secondary – develops in the presence of extracardiac disease
B) Primary – develops in the absence of extracardiac disease
C) Post-infarct – develops within 2 weeks of an acute MI
The diagnosis of NSTEMI is established if a cardiac biomarker is detected. In NSTEMI, ST/T changes may be present in the ECG, whereas in UA they are usually absent and even if they are present, are usually transient.

**FIGURE 2: Pathogenesis of ACS**

ACS occurs due to atherosclerotic plaque rupture, fissure or ulceration with superimposed thrombosis and coronary vasospasm. Depending on the acuteness, degree of occlusion and the presence of collaterals, patients can present as UA, NSTEMI or STEMI.

The aetiology of the plaque fissure or rupture is still unclear. Possible causes include inflammation, infection, uncontrolled blood pressure and smoking. ACS occurring de novo is called Primary UA/NSTEMI.

Occasionally UA/NSTEMI is secondary to a precipitating condition, which is extrinsic to the coronary arterial bed. This is called secondary UA/NSTEMI and can occur due to:

- increased myocardial oxygen demand as occurring in fever, tachycardia and thyrotoxicosis
- reduced coronary blood flow due to hypotension
- reduced myocardial oxygen delivery in anaemia or hypoxemia

Secondary UA/NSTEMI is an important cause of ACS in the elderly.
4. DIAGNOSIS

4.1 History

The symptoms of UA/NSTEMI may be indistinguishable from that of STEMI. These include:

- Chest pain - This is the presenting symptom in most patients. 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.

A significant number of patients, especially women, diabetics and the elderly, present with atypical symptoms. These include:

- Dyspnoea without any history of chest pains.
- Unexplained sweating, nausea and vomiting, syncope and presyncope, fatigue and epigastric discomfort.

In patients with these presentation(s) and with a prior history of coronary artery disease (CAD), a family history of premature CVD, diabetes and other cardiovascular risk factors, the index of suspicion of ACS should be high. Prior history of diabetes and renal disease will influence management.

4.2 Physical Examination

The objective of the physical examination is to identify:

- possible causes,
- precipitating causes and
- consequences of UA/NSTEMI

Uncontrolled hypertension, anaemia, thyrotoxicosis, severe aortic stenosis, hypertrophic cardiomyopathy and other co-morbid conditions such as lung disease should be identified.

Presence of left ventricular failure (hypotension, respiratory crackles or S3 gallop) and arrhythmias carry a poor prognosis. Carotid bruits or peripheral vascular disease indicates extensive atherosclerosis and a higher likelihood of concomitant CAD.
4.3 Electrocardiography

The ECG adds support to the diagnosis and provides prognostic information\(^6-11\). A recording made during an episode of chest pain is particularly valuable.

It should be performed within 10 minutes of the patient’s arrival at the Emergency Department.

Features suggestive of UA/NSTEMI are:

- Dynamic ST/T changes
- ST depression ≥ 0.5 mm in 2 or more contiguous leads
- T-wave inversion – deep symmetrical T-wave inversion

Other ECG changes include new or presumed new onset bundle branch block (BBB)* and cardiac arrhythmias, especially sustained ventricular tachycardia. Evidence of previous infarctions such as Q waves may be present.

However, a completely normal ECG does not exclude the diagnosis of UA/NSTEMI. Serial ECGs should be done as the ST changes may evolve.

* New LBBB should be treated as STEMI

4.4. Cardiac Biomarkers

Cardiac troponins (troponin T or I) are the recommended biomarkers. (Figure 3, pg 19) They are highly specific and sensitive for myocardial injury and/or necrosis (infarction), and also provide important prognostic information, there being a correlation between the level of troponin and cardiac mortality and other adverse cardiac events\(^12-16\). The troponin level may not be elevated if the test is done early (<6 hours). To confidently exclude myocardial necrosis (infarction), a repeat test needs to be done 6–12 hours after admission. Troponin testing can be done in the laboratory (quantitative) or with a hand held rapid semi-quantitative assay. Blood levels may persist for 5–14 days after the acute event.

Non coronary causes for elevated troponins are extremely rare\(^17\). It may occur in acute myocarditis, acute pulmonary embolism, a dissecting aortic aneurysm, acute heart failure and sometimes in septic shock. Severe renal dysfunction may also cause raised troponins in the absence of ACS. A raised level is however associated with an increase in all cause mortality in these patients. (Appendix II, pg 52)
Creatinine kinase (CK) and its MB fraction (CKMB) are also important indicators of myocardial necrosis (infarction). They are however, less sensitive and specific compared to cardiac troponins. CK and CKMB have a shorter half life and hence are more useful than troponins when diagnosing reinfarction.

All patients with NSTEMI have raised troponins, however, the CKMB may be normal in 10-20% of these patients. A raised CKMB in the presence of a normal troponin level has no prognostic significance.

Myoglobin is not cardiac specific. It can be detected as early as 2 hours after the onset of chest pain. A negative test within 4-8 hours of chest pain is useful in ruling out myocardial necrosis (infarction). It should not however be used as the only biomarker to identify patients with NSTEMI.

**FIGURE 3: Time course of elevation of serum cardiac biomarkers in ACS**

(Adopted from "Clinical Implications of the new definition of myocardial infarction". John K French, Harvey D White; Heart 2004;90:99–106)

4.5 Other diagnostic modalities

- Echocardiogram – LV systolic function is an important prognostic indicator in patients with UA/NSTEMI. Transient reversible regional wall motion abnormalities may be detected during ischemia.

**Key message:**

- The diagnosis of UA/NSTEMI is based on history ± dynamic ECG changes (without persistent ST elevation), ± raised cardiac biomarkers.
- In UA cardiac biomarkers are normal while in NSTEMI it is elevated.
- A raised troponin level has diagnostic and prognostic significance 1A.
5. RISK STRATIFICATION

5.1 Assessment of Risk

The initial evaluation should be used to provide information about the diagnosis and prognosis. An attempt should be made to simultaneously answer 2 questions:

- What is the likelihood that the signs and symptoms represent ACS? (Appendix III, pg 53)
- What is the likelihood of an adverse clinical outcome – death, MI (or recurrent MI), stroke, HF, recurrent symptomatic ischemia, and serious arrhythmia?

In making a diagnosis of ACS one should consider the symptoms, ECG abnormalities and cardiac biomarkers. The absence of risk factors does not exclude a diagnosis of ACS.

5.2 Rationale for Risk Stratification

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

Early assessment would help in determining the:

- prognosis of the patient
- management strategies
  - selection of the site of care (coronary care unit, monitored step-down ward or outpatient setting)
  - selection of appropriate therapy and the need for coronary angiogram and revascularization

5.3 Risk Scores for prognosis of UA/NSTEMI

Several risk stratification scores have been developed and validated in large patient populations. In clinical practice, 2 risk scores that are commonly used are:

- TIMI Risk Score\textsuperscript{20,21} - it is less accurate in predicting events, but is simple and widely accepted. (Appendix IV, pg 54)

- GRACE risk scores\textsuperscript{22} (Appendix V, pg 55)
Both risk scores confer additional important prognostic value beyond global risk assessment by physicians. These validated risk scores may refine risk stratification, thereby improving patient care in routine clinical practice. We have proposed a simplified risk stratification model as outlined in Flowchart 1, pg 3.

5.4 Risk Assessment for Bleeding

Hemorrhagic complications are an independent risk factor for subsequent mortality in ACS patients and in those undergoing PCI. These patients can be identified by:

- ACUITY HORIZONS-AMI Bleeding Risk Score
- CRUSADE Bleeding Risk Score

These scores are calculated based on age, clinical status and hemodynamics at presentation, serum creatinine and hematocrit level and the use and combinations of antiplatelets and anticoagulants.

6. TRIAGE

Triage helps in identifying patients who need urgent care. Rapid assessment and aggressive management of high risk patients may result in an improvement in outcome and a reduction in mortality.

Rapid assessment includes:

- evaluation of patient’s clinical status:
  - mental status
  - comfort status
  - respiration
  - peripheral perfusion

- vital signs:
  - blood pressure
  - rate and volume of pulse
  - respiratory rate

- history:
  - presence and severity of chest pains

Key messages

- Risk stratification is important for prognosis and to guide management.
past history of coronary and vascular events, interventions and surgery
- risk factors
  ▪ hypertension
  ▪ diabetes mellitus
  ▪ dyslipidaemia
  ▪ previous medications – eg anti-anginals, antiplatelets
  ▪ family history of premature CAD

- ECG
- cardiac biomarkers
  - troponins
  - CK-MB

Based on the above clinical assessment, patients can be risk stratified to (Flowchart 1, pg 3):

I. Intermediate/high risk
II. Low risk

The TIMI Risk Score and the Grace Risk Score (see 5.3) are also used to provide additional prognostic information.

The appropriate management, which includes the rapidity and the degree of invasiveness, is generally guided by the risk status of the patient. There is evidence that high risk patients have increasing benefit from therapies (like low molecular weight heparin (LMWH), glycoprotein (GP) IIb/IIIa inhibitors) and an invasive strategy.

The recommended therapy based on risk-stratification is as in Flowchart 1, pg 3.

**Key messages**
- Intermediate/high risk patients benefit from early angiography and revascularization.²

7. Management of UA/NSTEMI

The goals of management are:

- Immediate relief of ongoing ischemia and angina
- Prevention of recurrent ischemia and angina
- Prevention of serious adverse cardiac events
7.1 Pre-hospital Management

Based on the triage:

- **If the history is suggestive of ACS:**
  - Give soluble aspirin 300 mg crushed stat
  - Give sublingual GTN
  - Do 12 lead ECG and cardiac biomarkers

- **If the ECG and cardiac biomarkers are suggestive of ACS**
  - Give clopidogrel 300 mg stat if available.
  - Send the patient to the nearest healthcare facility where definitive treatment can be given.

- **If the ECG and cardiac biomarkers are inconclusive for ACS**
  - **Low risk patients** can be referred as outpatient for cardiac assessment. (Fig 1, pg 5)
  - **Intermediate / High Risk patients** should be admitted

7.2 In-Hospital Management  (Table1, pg 4)

7.2.1 Initial management – General Measures

Following risk stratification:

- low risk patients may be treated as outpatient.

- High risk patients preferably should be admitted to CCU/HDU with continuous ECG monitoring.

- supplemental oxygen should be given to maintain SpO₂ >90%, in patients with left ventricular failure, respiratory distress or having high risk features for hypoxemia.

- for pain relief, morphine (intravenous 2 mg to 5 mg) together with concomitant intravenous anti-emetic may be given.

7.2.2. Medications - Antiplatelet agents

7.2.2.1 Oral antiplatelet agents

7.2.2.1.1 Acetylsalicylic acid (ASA)

- Recommended loading dose: 300 mg of soluble/chewable aspirin. Enteric coated aspirin is not recommended for initial loading dose because of its slow onset of action.
Maintenance dose: 75-150 mg daily of soluble or enteric coated aspirin \(^{26,27}\)

Aspirin in excess of 300-325 mg per day is associated with increased risk of minor bleeding without greater efficacy \(^{27}\).

### 7.2.2.1.2 Adenosine Diphosphate (ADP) Receptor Antagonists

These include:

- **Clopidogrel** – loading dose: 300 to 600 mg, maintenance dose: 75 mg/day \(^{28,29}\)

- **Ticlopidine** – dose: 250 mg b.i.d. It is associated with neutropenia in 1% of patients \(^{30}\). Due to this safety reason, it is not preferred. Patients on ticlopidine should have their total white cell count monitored regularly for the initial 3 months.

- **Prasugrel** – loading dose 60 mg, maintenance dose: 10 mg/day
  - To date, outcome data is only available in ACS patients undergoing PCI \(^{31}\). It is recommended to be given after coronary angiography in patients planned for PCI.
  - Its use in other subsets of patients is still being evaluated.
  - It is not recommended for patients >75 years old, <60 kg weight, past history of transient ischemic attack or stroke due to a higher risk of major bleeding.

- **Ticagrelor** – loading dose: 180 mg, maintenance dose: 90 mg bid.
  - Ticagrelor was shown to significantly reduce cardiovascular endpoints when compared to clopidogrel in patients with ACS \(^{32}\).
  - This agent is short acting and thus can be used in patients who may need surgery without increasing the risk of bleeding.
  - Potential drawback is dyspnoea and transient ventricular pauses during the first week. This was rarely associated with symptoms or need for a pacemaker. There was also a small increase in non CABG related major bleeding \(^{32}\).
7.2.2.2 Intravenous Antiplatelet Therapy – Glycoprotein (GP) IIb/IIIa Inhibitors

These include:
- Abciximab
- Tirofiban
- Eptifibatide

These agents may be used in high risk patients awaiting transfer to a PCI facility for an early invasive strategy. Its routine use as “upstream therapy” prior to PCI is now no longer practiced. 33,34.

7.2.3. Anticoagulant Therapy

These include: (Table 2, pg 27)
- Unfractionated heparin (UFH)
- Low Molecular Weight Heparin (LMWH)-Enoxaparin 35,36,37
- Anti Xa inhibitor-Fondaparinux

1, A
- It is best used in UA/NSTEMI patients treated conservatively 38,39.
- It is associated with an increase in catheter-related thrombus and coronary angiographic complications. It is not recommended as the sole anticoagulant during PCI 38,39.
- If used in UA/NSTEMI and the patient requires an invasive strategy, UFH should be given during the procedure. When used in PCI, it is associated with lower bleeding rates than LMWH 38,39,40.

Presently newer oral anti Xa inhibitors are undergoing evaluation for ACS.

- Anti IIa inhibitors – Bivalirudin

1, B
- It may be used as a substitute for heparin in patients with heparin-induced thrombocytopenia (HIT) 41.
- It is reasonable to use bivalirudin as an alternative to UFH and GP IIb/IIIa inhibitors in patients undergoing PCI 42-45.

1, A
- It is associated with less bleeding.
- To date it is not yet available in Malaysia.
Key messages

- High risk patients preferably should be continuously monitored in CCU/HDU\textsuperscript{1,3}.

- Intermediate/high risk patients should be given ASA\textsuperscript{1A}, clopidogrel\textsuperscript{1A} (or prasugrel\textsuperscript{1B} or ticagrelor\textsuperscript{1B}) and UFH\textsuperscript{1A} or LMWH\textsuperscript{1A} or fondaparinux\textsuperscript{1A}. Prasugel may be given after coronary angiography in high risk patients undergoing PCI\textsuperscript{1B}. (Table 1, pg 4)

- Low risk patients should be given aspirin\textsuperscript{1A} and risk stratified as outpatient with non invasive tests for reversible ischemia. (Fig 1, pg 5)
**TABLE 2: Doses of Anticoagulant Agents in UA/NSTEMI and during PCI**

<table>
<thead>
<tr>
<th>AGENT</th>
<th>DOSSING REGIMEN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UFH</strong></td>
<td>**Initial IV bolus: 60 IU/kg (max 4000 IU) followed by infusion of 12 IU/kg/hour (max 1000 IU/hour) adjusted to maintain aPTT 1.5-2.0x normal. <strong>Duration of therapy</strong>: 2-8 days <strong>35-37</strong>&lt;br&gt;<strong>Loading Dose:</strong>&lt;br&gt;• Empirical loading dose: 5000-10000 IU, or&lt;br&gt;• Weight adjusted loading dose:&lt;br&gt;  - Not receiving GP IIb/IIIa inhibitors: 70-100 IU/kg&lt;br&gt;  - Receiving GP IIb/IIIa inhibitors: 50-70 IU/kg&lt;br&gt;<strong>Further doses if procedure is &gt; 1 hour may be by:</strong>&lt;br&gt;• Empirical weight adjusted doses:&lt;br&gt;  - Not receiving GP IIb/IIIa inhibitors: 60 IU/kg&lt;br&gt;  - Receiving GPIIb/IIIa inhibitors: 50 IU/kg&lt;br&gt;• Guided by ACT monitoring&lt;br&gt;  - Not receiving GP IIb/IIa inhibitors maintain ACT: 250-300 secs&lt;br&gt;  - Receiving GP IIb/IIIa inhibitors maintain ACT: 200 secs</td>
</tr>
<tr>
<td><strong>Enoxaparin</strong></td>
<td><strong>Initial 30 mg IV bolus and then 15 minutes later by:</strong>&lt;br&gt;sc 1.0 mg/kg every 12 hours if age less than 75 years&lt;br&gt;sc 0.75 mg/kg every 12 hours if age 75 years and above&lt;br&gt;<strong>Duration of therapy</strong>: 2-8 days <strong>35,37</strong>&lt;br&gt;Depends on prior enoxaparin use:&lt;br&gt;• No prior use: 0.5-0.75 mg/kg IV bolus&lt;br&gt;• Prior use within 8 hours of PCI: no additional dose&lt;br&gt;• Prior use between 8-12 hours of PCI: 0.3 mg/kg IV. Supplemental UFH may also be given during PCI</td>
</tr>
<tr>
<td><strong>Bivalirudin</strong></td>
<td><strong>0.1 mg/kg bolus and 0.25 mg/kg/hour infusion</strong>&lt;br&gt;Depends on prior bivalirudin/UFH use:&lt;br&gt;• Prior treatment with bivalirudin: additional 0.5 mg/kg bolus and increase infusion rate to 1.75 mg/kg/hour&lt;br&gt;• Prior treatment with UFH: wait 30 mins then 0.75 mg/kg bolus and infusion of 1.75 mg/kg/hour&lt;br&gt;• No prior treatment: 0.75 mg/kg bolus and infusion of 1.75 mg/kg/hour</td>
</tr>
<tr>
<td><strong>Fondaparinux</strong></td>
<td><strong>2.5 mg sc daily for 8 days or duration of hospitalization</strong> <strong>38,39</strong>&lt;br&gt;<strong>If used during PCI, additional 50-60 IU/kg UFH is recommended.</strong>*</td>
</tr>
</tbody>
</table>

*For doses in renal impairment see section 9.3, Table 6, pg 35*
7.2.4 Anti-Ischemic Drug Therapy

These agents may be given either for relief of ischemia (symptoms) or for prognosis.

7.2.4.1 Nitrates (Table 3, pg 29)

Sublingual glyceryl trinitrate (GTN 0.5 mg) – Patients with UA/NSTEMI with ongoing chest pain should receive sublingual GTN 0.5 mg every 5 minutes for a total of 3 doses. If symptoms still persist, intravenous GTN should be considered.

Intravenous nitrates – may be administered in the following situations:

- No symptom relief after 3 doses of sublingual GTN
- Presence of dynamic ECG changes
- Presence of left ventricular failure
- Concomitant high blood pressure.

Oral nitrates may be given after 12 to 24 hours of pain free period. Rebound angina may occur with abrupt cessation of nitrates.

Contraindications to nitrate therapy:

- Hypotension (SBP< 90 mmHg)
- RV infarction
- History of phospho-diesterase 5 inhibitors ingestion (depending upon the half-life of the agent)

7.2.4.2 β-blockers (Table 4, pg 29)

In the absence of contraindications, β-blockers should be administered early.

Contraindications for β-blockers in UA/NSTEMI:

- Patients with marked first-degree AV block (PR interval greater than 0.24s).
- Second- or third-degree AV block.
- History of bronchial asthma
- Severe peripheral arterial disease
- Acute decompensated LV dysfunction
- Cardiogenic shock.
Table 3: Recommended dosages of Nitrates in UA/NSTEMI*

<table>
<thead>
<tr>
<th>Compound</th>
<th>Route</th>
<th>Dosage</th>
<th>Time of Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroglycerine, Glyceryl trinitrate</td>
<td>Sublingual</td>
<td>0.3 - 0.6 mg, can repeat up to 3 times at 5 minute intervals</td>
<td>2 minute</td>
</tr>
<tr>
<td></td>
<td>Intravenous</td>
<td>5 – 200 µg/min*</td>
<td>1 minute</td>
</tr>
<tr>
<td></td>
<td>GTN Spray</td>
<td>0.4 – 0.8 mg per metered dose, no more than 3 sprays at 5 minute intervals</td>
<td>2 minute</td>
</tr>
<tr>
<td></td>
<td>Transdermal patch</td>
<td>2.5 – 20 mg over 12 hours on, then 12 hours off</td>
<td>1 – 2 hours</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>Intravenous</td>
<td>2 – 12 mg / hour</td>
<td>1 minute</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>10 – 20 mg, 2 – 3 times daily</td>
<td>30 – 60 minutes</td>
</tr>
<tr>
<td>Isosorbide mononitrate</td>
<td>Oral (LA)</td>
<td>30-60 mg daily, ( max 120 mg )</td>
<td></td>
</tr>
</tbody>
</table>

*The dose of IV nitrates should be titrated every 5 – 10 minutes until symptoms and/or ischaemia is relieved and the desired haemodynamic response is obtained

*As stated in MIMS Malaysia

Table 4: Recommended dosages of β -blockers in UA/NSTEMI*

<table>
<thead>
<tr>
<th>Type</th>
<th>Initiation dose</th>
<th>Target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol</td>
<td>25 mg bd</td>
<td>100 mg bd</td>
</tr>
<tr>
<td>Atenolol</td>
<td>25 mg od</td>
<td>100 mg od</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg od</td>
<td>10 mg od</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg bd</td>
<td>25 mg bd</td>
</tr>
</tbody>
</table>

*As stated in MIMS Malaysia
7.2.4.3 Calcium Channel Blockers (Table 5, pg 30)

Calcium channel blockers (CCB) may be used in UA/NSTEMI in the following situations:

- Verapamil or diltiazem as an alternative to patients who are not able to tolerate or who have contraindication to β-blockers.48
- Continuing or recurring angina despite adequate doses of nitrates and β-blockers – verapamil, diltiazem, slow release nifedipine and amlodipine.
- Prinzmetal’s angina (variant angina)

Short-acting dihydropyridine CCB should be avoided

Table 5: Recommended dosages of Calcium Channel Blockers in UA/NSTEMI*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diltiazem</td>
<td>Immediate release 30-90 mg tds</td>
</tr>
<tr>
<td></td>
<td>Slow release 100-200 mg od</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Immediate release 40-80 mg tds</td>
</tr>
<tr>
<td></td>
<td>Slow release 120-240 mg od</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>2.5-10 mg od</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Slow release 30-90 mg od</td>
</tr>
</tbody>
</table>

*As stated in MIMS Malaysia

7.2.5 Lipid Modifying Drugs

Current data indicate that early initiation of high dose statin therapy soon after admission for UA/NSTEMI can reduce major adverse cardiac events due to its pleotropic effects49-54. Patients with ACS undergoing PCI, have also been found to benefit with the administration of high dose statins before and within 10 days of the procedure55-57.

The statins that have been studied in UA/NSTEMI to date are:

- Atorvastatin – 80 mg od
- Simvastatin – 40 mg od
7.2.6 Angiotensin Converting Enzyme Inhibitor (ACE-I)/ARB (Table 7, pg 39)

I, A

These should be considered early for patients with LV dysfunction and diabetes 55.

Key messages

- Patients should be treated with optimal medical therapy. (Table 1, pg 4)
- Nitrates I,C, β-blockers I,B + CCBs I,C are given for relief of ischemia.
- Statins I,A and ACE-I (for LV dysfunction, LVEF < 40%) I,A are given for prognosis.

8. Revascularization Strategies

There is a strong rationale for early revascularization in intermediate/high risk patients with UA/NSTEMI 56,57. (Flowchart 1, pg 3, Appendix IV, pg 54) Contemporary antiplatelet and anticoagulant therapies have reduced the early hazard of PCI.

With increasing procedure experience, technological improvements in PCI and the development of new antiplatelet and anticoagulant regimens there is a general trend for early revascularization in these patients following optimal medical therapy.

8.1. Routine early invasive management 58-61

I, B

- Urgent (as soon as possible after hospital presentation) 62 – coronary angiography/revascularization for patients with refractory or recurrent angina associated with dynamic ST deviation, heart failure, life threatening arrhythmias and/ or hemodynamic instability

I, A

- Early (<72 hours) coronary angiography/revascularization- in patients with high-risk features as predicted by a positive biomarker assay, ST segment changes or a high risk score according to the TIMI scale or equivalent 58-61.

I1b, B

Routine invasive evaluation is not recommended in low risk patients 58-61.

However these patients are recommended to have non-invasive assessment for inducible or silent ischemia.
8.2 Routine early conservative management (selective invasive therapy)\textsuperscript{63,64,65}

The use of aggressive anticoagulant and antiplatelet agents has also reduced the incidence of adverse outcomes in patients managed conservatively\textsuperscript{63,64,65}. Selective coronary angiography/revascularization is indicated for those who cannot be stabilized medically or in whom objective evidence of significant ischemia is provoked in the sub acute phase.

A conservative strategy is recommended for women who are stabilized and remain biomarker negative\textsuperscript{66}.

An early invasive or conservative therapy is a reasonable option for men who are stabilized and remain biomarker negative\textsuperscript{66}.

Patients with UA/NSTEMI treated conservatively are at risk of developing recurrent adverse cardiac events. Thus these patients need to be evaluated periodically for reversible ischemia using non invasive tests. If ischemia is present, they should be considered for coronary angiography and revascularization.

**Key messages**

- Patients with refractory angina and/or hemodynamically unstable should be considered for urgent coronary angiography and revascularization\textsuperscript{1,C}.

- Intermediate/high risk patients should be considered for early invasive strategy (<72 hours)\textsuperscript{1,A}. If admitted to a non-PCI centre, they should be considered for transfer to a PCI centre\textsuperscript{1,B}. (Flowchart 1, pg 3)

- Low risk patients should be assessed non-invasively for ischemia\textsuperscript{1,C}. (Fig 1, pg 5)

- All patients should receive optimal medical therapy. (Table 1, pg 4)

9.1 UA/NSTEMI in the Elderly

Cardiovascular morbidity and mortality increases by 70% for every 10 year increase in age\textsuperscript{18,67–68}.
9.1.1 Clinical presentation:

A high index of suspicion is necessary to make a diagnosis of UA/NSTEMI in elderly patients. Atypical presentations occur more frequently. These include:

- dyspnoea
- diaphoresis
- nausea and vomiting
- neurological symptoms such as acute confusional states and syncope

ACS frequently develops as a “secondary” coronary event in the setting of another acute illness e.g. pneumonia. The elderly often are in heart failure at the time of presentation \(^{69}\). The ECG’s may be non diagnostic.

9.1.2 Management

There is limited trial data to guide management in the elderly especially in the setting of advanced age (more than 75 years) or significant co-morbidity (e.g. prior stroke, renal impairment). One should consider the biological age rather than the chronological age of the patient when making management decisions. The elderly are a heterogenous group and the risk benefit ratio of each intervention should be individualized. Creatinine clearance should be calculated to enable appropriate drug dosing. (Appendix VI, pg 56)

I, A • Both aspirin and clopidogrel (especially in those undergoing PCI) confer greater absolute and relative benefits in the elderly \(^{70,71}\).

I, B • Prasugrel should be avoided in patients older than 75 years in view of the bleeding risk \(^{31}\).

I, A • In a meta-analysis, both UFH and LMWH were equally effective in the elderly \(^{72}\). However bleeding risk is higher with both agents.

I, B • Elderly patients have more bleeding complications with the use of GPIIb/IIIa inhibitors \(^{73,74}\). If required, the dose should be adjusted according to the renal function.

I, A • The elderly have greater in-hospital and long term benefits with an early invasive strategy \(^{75-79}\). In some trials, all the benefits of an early invasive strategy were in the elderly rather than in younger patients \(^{75}\). However there is an increased risk of major bleeding \(^{80}\).
When selecting patients for an early invasive strategy, the risk benefit ratio must be considered. For patients with multi vessel disease and not suitable for CABG, partial revascularization of the culprit lesion may be a consideration.

- Long term management post discharge should include medications that have been proven beneficial in secondary prevention.

9.2 UA/NSTEMI in Women

Women develop CAD about a decade later than men at a time when they are older and have more co-morbidity such as obesity, diabetes, hypertension and osteoarthritis \(^{81}\). However gender is not an independent predictor of 1 year survival.

9.2.1 Clinical Presentation

Women presenting with ACS often have atypical symptoms such as neck and shoulder ache and dyspnœa. Often, women have non specific ECG changes such as T wave changes even in the absence of heart disease, thus making the diagnosis of CAD difficult.

9.2.2 Management

In general, there are no gender specific differences in the efficacy of the commonly used drugs in ACS. The following are some important differences:

- Prasugrel is associated with more bleeding in individuals who are less than 60kg in weight \(^{31}\).
- A meta-analysis indicates a lack of benefit of GPIIb/IIIa inhibitors in women \(^{82}\). The bleeding risk is also higher.
- There is conflicting data regarding the benefits of an early invasive strategy in women with UA/NSTEMI \(^{66,84-86}\). Until this issue is resolved in randomized controlled trials, an invasive strategy is best reserved for women with ongoing ischemia and raised troponins.

9.3 UA/NSTEMI in Chronic Kidney Disease (CKD)

In patients with ACS, the presence of CKD is an additional high-risk feature associated with increased mortality, the more severe the CKD, the higher the mortality \(^{87-90}\).
The creatinine clearance can be calculated using the Cockcroft-Gault formula (Appendix VI, pg 56). Drug doses should be adjusted according to renal function.

Patients with renal impairment were excluded from most clinical trials. In general, the management of patients with CKD is similar to those with normal renal function except for the following differences:

- Patients with CKD have more co-morbidity.
- ACE-I and ARB may cause worsening renal function and hyperkalemia.
- They are at increased bleeding risks. The doses of antiplatelet agents need to be adjusted accordingly to avoid excessive bleeding (Table 6, pg 35). Bivalirudin and fondaparinux seem to be associated with less bleeding than heparin or enoxaparin

A recent meta-analysis showed that patients with CKD presenting as UA/NSTEMI and treated with an early invasive strategy had better outcomes, particularly in patients with mild to moderate renal insufficiency.

PCI in patients with CKD is associated with increased risks of:

- bleeding
- worsening renal function and acute on chronic renal failure due to contrast nephropathy and/or cholesterol embolisation. Strategies should be taken to reduce this risk. (Appendix VII, pg 56 and VIII, pg 57)

Table 6: Dosages of Anti-thrombotics in CKD*

<table>
<thead>
<tr>
<th>Anti-Thrombotic</th>
<th>Loading Dose</th>
<th>Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Enoxaprin</td>
<td>30 mg IV</td>
<td>1 mg/kg sc every 24 hours if CrCl &lt; 30 ml/min</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Avoid if Cr Cl &lt; 30 ml/min</td>
<td>Avoid if Cr Cl &lt; 30 ml/min</td>
</tr>
<tr>
<td>Eptifibatide</td>
<td>180 mcg/kg</td>
<td>IV Infusion 1.0 mcg/kg/min if Cr Cl &lt; 50 ml/min</td>
</tr>
<tr>
<td>Tirofiban</td>
<td>IV infusion 0.4 mcg/kg/min for 30 mins</td>
<td>IV infusion 0.05 mcg/kg/min if Cr Cl &lt;30 ml/min</td>
</tr>
</tbody>
</table>

9.4 UA/NSTEMI in Diabetes

Diabetics have an increased mortality following an ACS. The glucose level at admission has been shown to be a significant predictor of 1 year mortality with a predictive value equivalent to LV systolic dysfunction. Diabetics should be treated aggressively with:

- Antiplatelet agent – aspirin and clopidogrel or prasugrel.
- Prasugrel has been found to be more effective in diabetics.
- GP IIb/IIIa inhibitors – a contemporary trial indicated only a modest reduction in adverse events.
- Early invasive approach – diabetics are however at higher risk of contrast nephropathy than non diabetics.

There is still a lack of consensus on the optimal management of blood sugars during the acute event. Intensive insulin therapy to achieve normoglycemia in the acute setting has not been shown to reduce mortality and is associated with an increase in the episodes of hypoglycemia. A general consensus is to keep blood sugars less than 8 mmol/l in the acute setting and then aim for optimal control following discharge.

10. Post Hospital Discharge

- The acute phase of UA/NSTEMI is usually 1 to 3 months. The risk of recurrence of ischaemic events, STEMI or death is highest during this period. Following this, most patients assume a clinical course similar to that of patients with chronic stable angina.

- Several lifestyle modification measures and drug therapies have been shown to be effective in improving long-term outcome. However they are underutilized. Therefore health care providers should ensure that patients with UA/NSTEMI receive appropriate treatment post hospital discharge and ensure that patients remain compliant to treatment.

Important discharge instructions should include:

- education on medication
- Patients given sublingual nitrates should be instructed in its proper and safe use.
- lifestyle change and CV risk factors modification
- scheduling of timely follow-up appointment and dates for further investigations
- referral to a cardiac rehabilitation program where appropriate
However they are underutilized. Therefore health care providers should ensure that patients with UA/NSTEMI receive appropriate treatment post hospital discharge and ensure that patients remain compliant to treatment.

Important discharge instructions should include:
- Education on medication
  - Patients given sublingual nitrates should be instructed in its proper and safe use.
- Lifestyle change and CV risk factors modification
- Scheduling of timely follow-up appointment and dates for further investigations
- Referral to a cardiac rehabilitation program where appropriate

### 10.1 Medications post-discharge (Table1, pg 4)

#### 10.1.1 Antiplatelet agents

- ASA should be prescribed at 75-150 mg daily unless contraindicated.\(^{26,27}\)
- In patients who cannot tolerate ASA, clopidogrel is an alternative. It has better risk reduction.\(^{101}\) When clopidogrel is not available, ticlopidine can be given.
- The combination of ASA and clopidogrel 75 mg daily should be continued for at least one month and ideally up to 9 to 12 months after UA/NSTEMI treated medically.\(^{71,102}\) and in patients who have undergone PCI with bare metal stents.
- If patients received drug eluting stents during PCI then dual antiplatelet treatment is recommended.\(^{71,102,103}\)
  - The duration of dual antiplatelet therapy following DES implantation is for 6 to 12 months or longer.\(^{103}\)
- There are no recent clinical trial data on the use of triflusal in ACS.

#### 10.1.2 β-blockers (see section 7.2.4.2)

- β-blockers should be continued for patients with ischemia unless contraindicated.
  - Long term treatment following UA/NSTEMI may lead to significant mortality reduction.\(^{104}\)
- β-blockers should be continued indefinitely in patients with reduced LV function, with or without symptoms of heart failure.\(^{105,106}\)
10.1.3 Lipid Modifying Therapy

- There is a large body of evidence that early initiation of statin therapy improves outcome regardless of baseline LDL-C levels in patient with ACS\(^ {49-51,07-109}\).

- More aggressive lipid lowering further lowers cardiovascular event rates\(^ {110}\).

Lipid management includes:

- Assessment of a fasting lipid profile for all patients, within 24 hours of hospitalization.

- Statins, in the absence of contra-indications, regardless of baseline LDL-C and diet modifications, should be initiated soon after admission and continue indefinitely to provide lifelong benefits\(^ {111,112}\). This also applies to patients post PCI.

- LDL-C level should be targeted <2.0 mmol/L for most patients\(^ {111,112}\).

- Patients with low HDL-C may benefit from fibrates or nicotinic acid\(^ {113,114}\).

10.1.4 Angiotensin-converting enzymes inhibitors (ACE-Is) (Table 7, pg 39)

- ACE-Is have shown long term benefit in all patients with evidence of LV dysfunction (LVEF ≤40%)\(^ {115-117}\) and in patients with diabetes, hypertension or CKD unless contraindicated\(^ {1018-120}\).

- For all other patients ACE-Is should be considered to prevent recurrence of ischaemic events\(^ {121-124}\).

- For patients with reduced LV systolic function, ACE-I should be initiated early, during the course of hospitalization. Agents and doses of proven efficacy are recommended.
Table 7: Recommended dosages of ACE-I in UA/NSTEMI

<table>
<thead>
<tr>
<th>Type</th>
<th>Initiation dose</th>
<th>Target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>6.25 mg bd-tds</td>
<td>25-50 mg tds</td>
</tr>
<tr>
<td>Ramipril</td>
<td>2.5 mg bd</td>
<td>10 mg od</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5-5 mg od</td>
<td>20 mg bd</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>5 mg od</td>
<td>40 mg od</td>
</tr>
<tr>
<td>Perindopril</td>
<td>2-2.5 mg od</td>
<td>8-10 mg od</td>
</tr>
</tbody>
</table>

10.1.5 Angiotensin-Receptor Blockers (ARBs) (Table 8, pg 39)

ARBs should be substituted for patients with ACE-I intolerance.  

Table 8: Recommended dosages of ARB in UA/NSTEMI

<table>
<thead>
<tr>
<th>Type</th>
<th>Initiation dose</th>
<th>Target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valsartan</td>
<td>40-80 mg od</td>
<td>160 mg od</td>
</tr>
</tbody>
</table>

10.1.6 Aldosterone receptor antagonist

Long-term aldosterone receptor blockade should be considered in patients who are in heart failure and already treated with ACE-I and β-blockers. These agents include spironolactone and epleronone.

Care should be taken in patients with renal dysfunction and hyperkalaemia.

10.1.7 Anti Anginal Therapy

Anti anginals are not required for patients with successful revascularization and no residual ischaemia.

10.2 Follow-up investigations (Fig 1, pg 5)

In the outpatient evaluation of low risk UA/NSTEMI patients, the following investigations maybe considered:

- Echocardiogram to assess LV function
- Treadmill stress test
- Stress echocardiogram – treadmill or pharmacological stress
- Nuclear perfusion study
- MRI – stress MRI for ischaemia and perfusion MRI for viability
Low risk patients with significant demonstrable ischaemia and all intermediate/high risk patients should be considered for revascularization.

Key messages

- Patients should be on optimal medical therapy at discharge. This includes ASA $^{I,A}$, clopidogrel (for at least a month and ideally for at least a year) $^{I,B}$, β-blockers $^{I,B}$ + CCBs $^{I,C}$, ACE-I $^{I,A}$ or ARB $^{I,B}$ and statins $^{I,A}$. (Table 1, pg 4)
- These drugs should be uptitrated during outpatient visits to the recommended tolerated doses $^{I,C}$.
- Low risk patients should be assessed non-invasively for ischaemia $^{I,C}$. (Fig 1, pg 5)

11. Cardiac Rehabilitation/Secondary prevention

Cardiac rehabilitation is aimed at improving the physical and psychological well being of the patient. It has been shown to reduce mortality by approximately 20%-25% $^{130-132}$. There was also a trend towards reduction in non-fatal recurrent MI over a median follow-up of 12 months $^{133}$.

11.1 Cardiac rehabilitation programs include:

- Counselling and educating the patient and family members on CAD
- Beginning an exercise program
- Helping the patient modify risk factors such as high blood pressure, smoking, high blood cholesterol, physical inactivity, obesity and diabetes
- Providing vocational guidance to enable the patient to return to work
- Supplying information on physical limitations
- Educating and ensuring compliance to medications
- Providing emotional support

Cardiac rehabilitation/secondary prevention programs are generally divided into 3 main phases:

- Phase 1: Inpatient CR (also known as Phase 1 CR): a program that delivers preventive and rehabilitative services to hospitalized patients following ACS
- Phase 2: Early outpatient CR (also known as Phase 2 CR): generally within the first 3 to 6 months but continuing up to 1 year
- Phase 3: Long-term outpatient CR (also known as Phase 3 or Phase 4 CR): beyond 1 year
11.2 Return to physical activity

Physical activity can be resumed at 50% of maximal exercise capacity in a patient with preserved LV function without inducible ischemia within 1 week post-discharge. This should be gradually increased over time preferably guided by treadmill stress test.

11.3 Risk factor modification:

- Smoking cessation – Patients who quit smoking can reduce the rate of reinfarction and death as early as 1 year.
- Weight – Achieve or maintain optimal body weight.
- Exercise – Encourage a minimum of 30–60 minutes of moderate activity 3-4 times weekly (walking, cycling, swimming or other equivalent aerobic activities).
- Diet – To consume low cholesterol or low saturated fat diet.
- Lipids – Aim for an LDL-C < 2.0 mmol/l.
- Hypertension – Aim for a blood pressure of <140/85 mmHg. In diabetics the target is <130/80 mmHg. In elderly patients, a higher BP target may be acceptable.
- Diabetes Mellitus – Optimal glycemic control in diabetes. (Refer CPG on Diabetes)

11.4 Discharge Instructions

- Therapeutic lifestyle changes should be initiated in all patients and reemphasized during follow up.

- Patients should be on optimal medical therapy. (Table 1, pg 4). They should be educated on the importance of adherence to drug therapy to ensure optimal outcomes. Patients with DES should be warned of the consequences of non compliance to anti platelet drug therapy.

- The doses of ACE-I/ARB and β-blockers should be uptitrated to the maximal tolerated doses.

- Patients should be instructed on how to use GTN. If the chest pain does not subside after 2 GTN’s or if there is a change in the usual pattern of angina, they should go to the nearest health facility.
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## APPENDIX I: Braunwald’s Classification of Unstable Angina*

<table>
<thead>
<tr>
<th>Severity</th>
<th>CLINICAL CIRCUMSTANCES</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>I—New onset of severe angina or accelerated angina; no rest pain</td>
<td>Develops in Presence of Extracardiac Condition That Intensifies Myocardial Ischemia (Secondary UA)</td>
<td>I A</td>
<td>IB</td>
<td>IC</td>
</tr>
<tr>
<td>II—Angina at rest within past month but not within preceding 48 hours (angina at rest, subacute)</td>
<td></td>
<td>IIA</td>
<td>IIB</td>
<td>IIC</td>
</tr>
<tr>
<td>III—Angina at rest within 48 hours (angina at rest, acute)</td>
<td></td>
<td>IIIA</td>
<td>IIIB-$T_{neg}$ IIIB-$T_{pos}$</td>
<td>IIIC</td>
</tr>
</tbody>
</table>

UA : Unstable angina; T : Troponins

### Appendix II: Elevations of cardiac troponin in the absence of overt ischaemic heart disease*

<table>
<thead>
<tr>
<th>Damage related to secondary myocardial ischaemia (MI type 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachy- or bradyarrhythmias</td>
</tr>
<tr>
<td>Aortic dissection and severe aortic valve disease</td>
</tr>
<tr>
<td>Hypo- or hypertension, e.g. haemorrhagic shock, hypertensive emergency</td>
</tr>
<tr>
<td>Acute and chronic heart failure without significant concomitant coronary artery disease (CAD)</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>Coronary vasculitis, e.g. systemic lupus erythematosus, Kawasaki syndrome</td>
</tr>
<tr>
<td>Coronary endothelial dysfunction without significant CAD, e.g. cocaine abuse</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Damage not related to myocardial ischaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac contusion</td>
</tr>
<tr>
<td>Cardiac incisions with surgery</td>
</tr>
<tr>
<td>Radiofrequency or cryoablation therapy</td>
</tr>
<tr>
<td>Rhabdomyolysis with cardiac involvement</td>
</tr>
<tr>
<td>Myocarditis</td>
</tr>
<tr>
<td>Cardiotoxic agents, e.g. anthracyclines, herceptin, carbon monoxide poisoning</td>
</tr>
<tr>
<td>Severe burns affecting &gt;30% of body surface</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indeterminant or multifactorial group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apical ballooning syndrome</td>
</tr>
<tr>
<td>Severe pulmonary embolism or pulmonary hypertension</td>
</tr>
<tr>
<td>Peripartum cardiomyopathy</td>
</tr>
<tr>
<td>Renal failure</td>
</tr>
<tr>
<td>Severe acute neurological diseases, e.g. stroke, trauma</td>
</tr>
<tr>
<td>Infiltrative diseases, e.g. amyloidosis, sarcoidosis</td>
</tr>
<tr>
<td>Extreme exertion</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Acute respiratory failure</td>
</tr>
<tr>
<td>Frequent defibrillator shocks</td>
</tr>
</tbody>
</table>

## Appendix III: Likelihood That Signs and Symptoms Represent an ACS secondary to CAD

<table>
<thead>
<tr>
<th>Greater Likelihood</th>
<th>Lower Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History</strong></td>
<td></td>
</tr>
<tr>
<td>Chest or left arm pain or discomfort as chief symptom reproducing prior documented angina</td>
<td>Chest pains in the absence of any of the greater likelihood characteristics</td>
</tr>
<tr>
<td>Known history of CAD, including MI</td>
<td>Recent cocaine use</td>
</tr>
<tr>
<td>New chest or left arm pain or discomfort as chief symptom</td>
<td></td>
</tr>
<tr>
<td>Age greater than 70 years</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td><strong>Examination</strong></td>
<td></td>
</tr>
<tr>
<td>Transient MR murmur, hypotension, diaphoresis, pulmonary edema, or rales</td>
<td>Chest discomfort reproduced by palpation</td>
</tr>
<tr>
<td>Extracardiac vascular disease</td>
<td></td>
</tr>
<tr>
<td><strong>ECG</strong></td>
<td></td>
</tr>
<tr>
<td>New, or presumably new, transient ST-segment deviation (1 mm or greater) or T-wave inversion in multiple pre-cordial leads</td>
<td>T-wave flattening or inversion less than 1 mm in leads with dominant R waves</td>
</tr>
<tr>
<td></td>
<td>Normal ECG</td>
</tr>
<tr>
<td><strong>Cardiac Biomarkers</strong></td>
<td></td>
</tr>
<tr>
<td>Elevated cardiac TnI, TnT, or CK-MB markers</td>
<td>Normal</td>
</tr>
</tbody>
</table>

### APPENDIX IV: TIMI RISK SCORE FOR UA/NSTEMI

<table>
<thead>
<tr>
<th>TIMI Risk Score</th>
<th>All-Cause Mortality, New or Recurrent MI, or Severe Recurrent Ischemia Requiring Urgent Revascularization Through 14 d After Randomization, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>4.7</td>
</tr>
<tr>
<td>2</td>
<td>8.3</td>
</tr>
<tr>
<td>3</td>
<td>13.2</td>
</tr>
<tr>
<td>4</td>
<td>19.9</td>
</tr>
<tr>
<td>5</td>
<td>26.2</td>
</tr>
<tr>
<td>6-7</td>
<td>40.9</td>
</tr>
</tbody>
</table>

The TIMI risk score is determined by the sum of the presence of 7 variables at admission:

1 point is given for each of the following variables:

- Age 65 y or older
- At least 3 risk factors for CAD (family history of premature CAD, hypertension, elevated cholesterol, active smoker, diabetes)
- Known CAD (coronary stenosis of $\geq 50\%$)
- Use of aspirin in prior 7 days
- ST-segment deviation ($\geq 0.5$ mm) on ECG
- At least 2 anginal episodes in prior 24 h
- Elevated serum cardiac biomarkers

**Total Score = 7 points**

- **Low Risk**: $\leq 2$ points
- **Moderate Risk**: 3-4 points
- **High Risk**: $\geq 5$ points

Adapted from:

APPENDIX V: **GRACE PREDICTION SCORE CARD AND NOMOGRAM FOR ALL CAUSE MORTALITY FROM DISCHARGE TO 6 MONTHS**

APPENDIX VI: Calculation Of Creatinine Clearance

Estimated GFR (ml/min) = \[
\frac{(140-\text{age}) \times \text{weight}}{(0.814 \times \text{SCr} \, [\mu\text{mol/L}])}
\]
or
\[
1.2 \frac{(140-\text{age})}{\text{SCr} \, [\mu\text{mol/L}]}
\]

\(\text{SCr} \): serum creatinine

For women multiply by 0.85

Severity Of CKD*

<table>
<thead>
<tr>
<th>SEVERITY OF CKD</th>
<th>CREATININE CLEARANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal to mild</td>
<td>&gt;60 ml/min</td>
</tr>
<tr>
<td>Moderate</td>
<td>30-59 ml/min</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;30 ml/min</td>
</tr>
</tbody>
</table>


APPENDIX VII: Prevention of Contrast Induced Nephropathy

<table>
<thead>
<tr>
<th>Contrast Agent</th>
<th>ACC/ESC Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Isomolar agent</td>
<td>I, A</td>
</tr>
<tr>
<td>- Low osmolar agents</td>
<td>IIa, B</td>
</tr>
<tr>
<td>- use minimal volume</td>
<td>I, C</td>
</tr>
<tr>
<td>Avoid nephrotoxic agents eg NSAIDS, metformin</td>
<td>I, C</td>
</tr>
<tr>
<td>Saline Infusion</td>
<td>I, C</td>
</tr>
<tr>
<td>Sodium Bicarbonate</td>
<td>IIa, B</td>
</tr>
<tr>
<td>Acetylcysteine</td>
<td>IIb, B</td>
</tr>
</tbody>
</table>
## APPENDIX VIII: Prevention of Contrast Induced Nephropathy

<table>
<thead>
<tr>
<th>AGENT</th>
<th>CONCENTRATION</th>
<th>DOSE / FLOW RATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Chloride*</td>
<td>0.9% solution</td>
<td>Rate of 1.0-1.5 ml/kg/hr for 3h-12h before and 6h-24h after the procedure ensuring a urine flow rate of 150 ml/hour Reduce rate to 0.5 ml/kg/hr if LVEF&lt;40%</td>
</tr>
<tr>
<td>Sodium Bicarbonate**</td>
<td>154 mEq/L in 5% dextrose in water (154 ml of 1000 mEq/l of sodium bicarbonate + 850 ml of 5% Dextrose)</td>
<td>3 ml/kg/hr for 1 hour before the contrast followed by an infusion of 1 ml/kg/hr for 6 hours after the procedure</td>
</tr>
<tr>
<td>N-acetylcysteine***</td>
<td>1200 mg twice daily, one day before and one day after the contrast</td>
<td></td>
</tr>
</tbody>
</table>


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- Panel of external reviewers who reviewed the draft

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