



## GUIDELINE

## MANAGEMENT OF ACUTE CORONARY SYNDROMES CLINICAL GUIDELINE

SAMA/Acute Coronary Syndrome Working Group

### PART 1: UNSTABLE ANGINA AND NON-ST ELEVATION MYOCARDIAL INFARCTION

This guideline describes the recognition and management of unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI). These are two of the three components of the acute coronary syndrome (ACS). These forms of ACS most often arise from erosion or rupture of coronary atherosclerotic plaque and subsequent thrombus formation causing incomplete coronary occlusion. The term ACS, as used in this guideline, refers to these two components only. The third component, not discussed here, is ST-segment elevation myocardial infarction (STEMI), which is most frequently associated with complete coronary occlusion.

ACS is a clinical emergency requiring urgent assessment. It is characterised by chest pain, ST-segment changes in the electrocardiogram (ECG) and a rise in the serum markers of myocardial injury/infarction.

ACS encompasses a variety of clinical presentations. Risk stratification is essential to enable triage of patients to the optimal level of care and specific therapy. Careful clinical assessment is the cornerstone of this risk stratification.

The pharmaceutical treatment of ACS is directed primarily at the dissolution of the developing intracoronary thrombus by antiplatelet (aspirin and clopidogrel) and anticoagulant therapy (heparin), and secondarily to the relief of symptoms by anti-anginal and analgesic medications. Low-molecular-weight heparin (LMWH) is at least as effective and safe as standard intravenous unfractionated heparin (UH). Coronary angiography is advised for all high-risk patients and those in whom reversible ischaemia or left ventricular dysfunction is discovered. The need for coronary revascularisation is dictated by the findings at angiography. In high-risk patients, appropriate, early revascularisation is recommended in preference to standard medical therapy and 'ischaemia-

driven' revascularisation. The glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors should be used in association with percutaneous coronary intervention (PCI) in high-risk patients.

All patients with ACS should receive secondary preventive treatment. It is imperative that they stop smoking. Dietary modification, physical rehabilitation, long-term low-dose aspirin use,  $\beta$ -blockade for those diagnosed with myocardial infarction, tight control of blood pressure, cholesterol lowering with a statin, and treatment with an angiotensin-converting enzyme (ACE) inhibitor should be prescribed.

### 1. ABBREVIATIONS

ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome(s); ADP = adenosine diphosphate; bd = twice daily; BP = blood pressure; CAD = coronary artery disease; CCU = coronary care unit; CK = creatine kinase; CK-MB = creatine kinase MB iso-enzyme; CNS = central nervous system; CRP = C-reactive protein; ECG = electrocardiogram; GI = gastrointestinal; GPIIb/IIIa = glycoprotein IIb/IIIa; HIT = heparin-induced thrombocytopenia; hrly = hourly; IV = intravenous; LDL = low-density lipoprotein; LMWH = low-molecular-weight heparin; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; p.o. = by mouth; PTT = partial thromboplastin time; s = seconds; STEMI = ST-segment elevation myocardial infarction; subcut = subcutaneously; TIMI = thrombolysis in myocardial infarction; UA = unstable angina; UH = unfractionated heparin.

### 2. INTRODUCTION

Erosion or rupture of a coronary atheromatous plaque and ensuing intraluminal thrombus formation are the pathological events that precipitate ACS.

Acute coronary syndrome (ACS) describes the variety of clinical events that may arise from an acute exacerbation of chronic atheromatous coronary artery disease. Typically, these syndromes are accompanied by cardiac ischaemic chest pain with ST-segment changes in the electrocardiogram (ECG) and/or a rise in the serum markers of myocardial injury. Plaque erosion or rupture and ensuing intraluminal thrombus formation are the basic pathological events that precipitate the syndrome. The thrombus generated by the process may cause partial or total occlusion of a coronary vessel.<sup>1</sup> Myocardial injury/necrosis may arise either from obstruction of coronary flow at the ruptured plaque or from embolisation of the intraluminal thrombus into smaller distal vessels and the microcirculation. Less frequently ACS may arise from coronary

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vasospasm or from myocardial oxygen demand outstripping supply and causing myocardial ischaemia. The term ACS includes unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation MI (STEMI). These manifestations of acute myocardial ischaemia in time may revert to the pre-symptomatic state, or evolve into a non-Q-wave (or so-called non-transmural) MI or a Q-wave (or transmural) MI. Patients with UA or NSTEMI ACS are at a significant risk of death and myocardial infarction (or re-infarction) within the first week (around 4% despite treatment).<sup>2</sup> Thereafter the combined risk of these events continues to be 1 - 2 % per month at least for the first year.

Acute coronary syndrome includes unstable angina, non-ST-segment elevation myocardial infarction and ST-segment elevation myocardial infarction.

This guideline deals with the management of the first two components of the syndrome.

The boundaries between UA, NSTEMI and STEMI are not always well defined. The three entities are portions of the continuum of the clinical manifestations that arise from a single pathogenetic mechanism and may overlap one another (Fig. 1).

**Unstable angina** is the clinical state in which there is a change in the pattern of anginal pain. This may be the new onset of symptoms, more frequent or more severe angina, or chest pain at rest. Myocardial injury is unlikely and very limited in extent when it occurs. The resting ECG may show ST-segment depression and/or T-wave inversion or transient ST-segment elevation, or may remain normal. The serum markers may remain within their normal biological ranges or fall between the normal range and the level diagnostic of myocardial infarction.

**Non-ST-segment elevation myocardial infarction** may have symptoms indistinguishable from unstable angina. The resting

ECG more frequently shows ST-segment depression or T-wave inversion. Although ST-segment elevation may be observed it is, by definition, never sustained. There will always be a clear-cut rise in the serum markers to levels that are diagnostic of myocardial infarction.

**ST-segment elevation myocardial infarction** most frequently arises from the abrupt, total occlusion of an epicardial coronary artery by thrombus causing transmural myocardial ischaemia that may progress to infarction over time (usually between 3 and 6 hours). There will be ST-segment elevation in the ECG or new-onset left bundle-branch block and an incremental release of the markers of myocardial necrosis into the serum. Q waves commonly develop. The management of STEMI differs radically from that of unstable angina and NSTEMI. The primary medical treatment of STEMI is early reperfusion either by fibrinolysis or by PCI. While the fibrinolytic drugs, e.g. streptokinase (Kabikinase, Streptase) and alteplase (Actilyse), effectively disrupt fibrin clot, they concurrently cause intense platelet activation. The fibrinolytic drugs increase mortality in UA and NSTEMI<sup>3</sup> and should not be used in ACS other than STEMI.

This guideline deals only with the management of the UA and the NSTEMI components of ACS (Fig. 2). The term ACS is therefore used henceforth in reference only to UA and NSTEMI. The management of STEMI, the third component of ACS, will be the subject of another guideline that is yet to be developed.

**ACS is among the commonest clinical presentations of coronary artery disease.** It requires the prompt co-operation of the patient and the collaboration of emergency medical

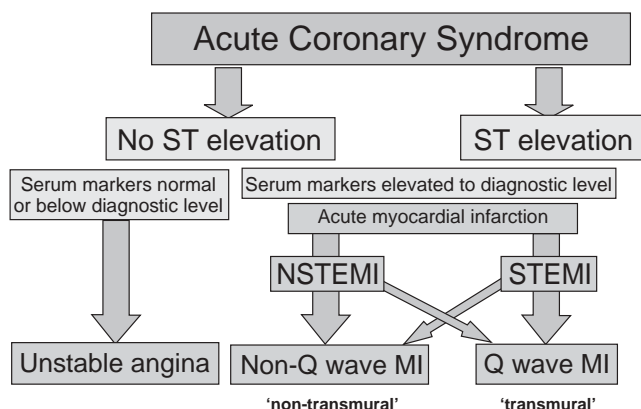


Fig. 1. The interrelationship of the components of acute coronary syndrome on presentation, during evolution and at final outcome (adapted from Braunwald E, et al., J Am Coll Cardiol 2000; 36: 970-1062).

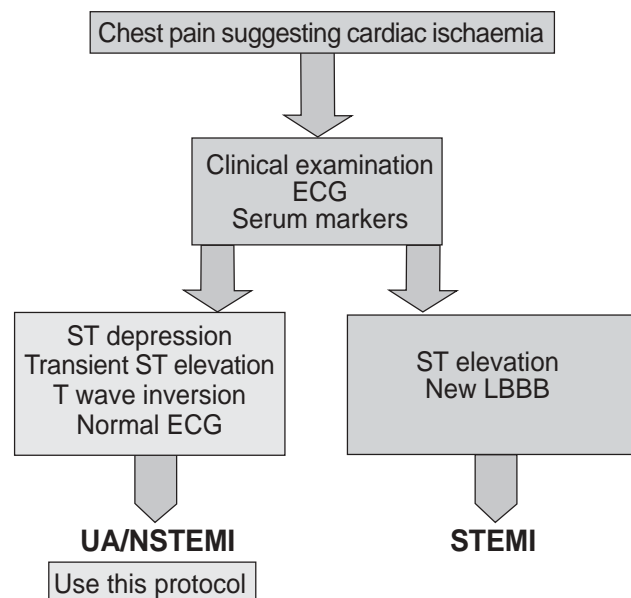


Fig. 2. The differentiation of unstable angina/non-ST-segment elevation myocardial infarction from ST-segment elevation myocardial infarction.



services, family practitioners, specialist physicians, cardiologists and specialised cardiac care units to achieve an optimal clinical outcome. The general public must be educated to recognise that chest discomfort may herald impending cardiac infarction and requires immediate medical attention either by the family practitioner or the local casualty department. This syndrome has started to emerge within the South African black community. Medical personnel need to be made aware that it is no longer rare to encounter ACS in blacks. Access to emergency medical services within peri-urban and rural areas should be improved and the qualifications of their personnel upgraded. Emergency medical service personnel and family practitioners must be brought to appreciate the urgency implicit in ACS and the need for a rapid therapeutic response.

This guideline has been developed at a time when there is intensive, ongoing research into the management of ACS. Certain issues within this therapeutic arena have yet to be clearly defined. In particular, the interrelationship of various therapies (clopidogrel, LMWH, GPIIb/IIIa inhibitors and PCI) and the efficacy and safety of using them in combination requires to be clarified. The editor and the contributors therefore offer this guideline as the most reasonable course of action to be taken at present, based upon the available evidence.

### 3. THE DIAGNOSIS OF UNSTABLE ANGINA AND NSTEMI

ACS constitutes a clinical emergency. Early initiation of treatment is mandatory. In particular, acute STEMI requires immediate differentiation from other forms of ACS and emergent reperfusion therapy. Every patient with chest pain should be comprehensively evaluated including history taking and clinical examination of the cardiovascular system, the immediate recording of a resting ECG and urgent evaluation of the serum markers of myocardial injury.

The diagnosis of ACS is based on clinical evaluation of the patient, the resting ECG and the serum markers of cardiac injury/infarction.

Particular attention must be paid to the factors that influence the risk stratification of the patient. These are found among the clinical features, deviations of the ST segment in the ECG, and elevation of the serum markers of cardiac injury/infarction.

Failure to recognise and manage ACS correctly may arise from incorrect interpretation of the ECG, preconceptions that obscure the recognition of the syndrome in (especially younger) women and blacks, failure to recognise ACS in patients presenting with symptoms other than chest pain, and insufficient attention to a history of recent changes in the patient's anginal symptoms.<sup>4</sup>

### 3.1 Clinical presentation

**Symptoms.** The features of cardiac ischaemic chest pain are well recognised. It may have any one of a number of characteristics. The pain may vary in severity from mild compressive discomfort to sharp, severe pain. It may be located in the anterior chest, particularly substernally, or predominantly involve the mandible, neck, shoulders, either or both arms, the back or epigastrium. It may or may not be associated with shortness of breath, perspiration, nausea or vomiting. None of these features predicts the severity of the underlying problem. The pain will generally be brief but may last longer than 30 minutes without resulting in myocardial infarction.

In ACS the chest pain is frequently spontaneous in onset, and unrelated to the usual stressors known to precipitate stable angina pectoris. It may occur with no or less than the usual amount of provocation and be more severe or more prolonged. Less frequently, ACS may present with little or no chest pain but rather with atypical pain, or be accompanied by the features of an acute transient reduction in cardiac output (tachycardia, hypotension and poor peripheral circulation), pulmonary venous congestion (breathlessness or pulmonary oedema), or, rarely, a potentially lethal ventricular tachyarrhythmia (a rapid heart rate with a weak or impalpable pulse).

Male gender, an age above 50 years, and in women early menopause, as well as a history of smoking, dyslipidaemia, hypertension, diabetes mellitus and/or a family history of coronary disease, all increase the likelihood of ACS in a given patient with chest pain.

Repeated attacks of chest pain or ongoing chest pain before admission or pain which recurs on treatment, is associated with a worse outcome.

**Physical examination** often fails to contribute to the diagnosis of ACS. There may be no abnormal findings. However, a fourth heart sound or a mitral regurgitant murmur or signs of pulmonary congestion are important signs that suggest transient ischaemic myocardial dysfunction. Although pre-existing myocardial dysfunction is one of the characteristics of the high-risk patient, new-onset heart failure of whatever cause and/or tachycardia and hypotension with poor peripheral perfusion and/or cardiogenic shock imply the

#### ACS patients with:

- Sinus tachycardia
- hypotension
- poor peripheral perfusion
- new-onset heart failure or
- cardiogenic shock

**are at extremely high risk and merit urgent, intensive therapy.**



involvement of a large volume of myocardium in the ischaemic process. Such patients are at extremely high risk and require urgent, intensive treatment.

### 3.2 The electrocardiogram

A 12-lead ECG must be recorded immediately and then repeated at intervals of 4 - 6 hours. The important signs are ST-segment depression or transient ST-segment elevation or T-wave inversion, in two or more contiguous leads. These changes are diagnostic of ACS in the presence of chest pain. Although the ECG may be normal on presentation in 26 - 60% of patients,<sup>3,5</sup> it is especially important to obtain further tracings in the group with an initially normal ECG, as the diagnostic ST-segment and T-wave changes may appear some hours later. ECGs recorded during subsequent bouts of chest pain are particularly valuable in revealing transient ST-segment and T-wave changes.

If there are difficulties in the interpretation, the ECG should be referred for urgent interpretation by a specialist. Facsimile transmission is helpful when the patient is being assessed at a distance from a specialised centre.

ST-segment shifts and/or T-wave inversion in the ECG characterise a group of patients who have a worse prognosis.<sup>6,7</sup>

### 3.3 The serum markers of myocardial injury and infarction

Not all patients presenting with ACS will have elevated serum markers. The serum markers at the time of the initial assessment may be within their normal ranges, especially when they have been obtained very shortly after the onset of chest pain. All patients who have normal serum marker results on presentation must have a second assessment of their levels 4 - 6 hours later or 8 hours after the onset of symptoms, whichever is longer. Elevated levels of creatine kinase (CK), creatine kinase MB iso-enzyme (CK-MB), troponin T or I, and myoglobin are indicators of myocardial injury/infarction. High levels confirm the occurrence of myocardial infarction. Myoglobin is the earliest marker of an infarct event to appear in the serum. Although myoglobin is a very sensitive indicator of infarction, its clinical usefulness as the sole marker of myocardial injury/infarction is limited by the high incidence of false-positive results. CK in conjunction with CK-MB, CK-MB alone<sup>8</sup> and the troponins<sup>5</sup> are all sensitive and specific markers of myocardial injury/infarction that appear within the serum in raised amounts from about 4 hours after the onset of the ischaemic event. Whereas CK and CK-MB are cleared from the serum within 2 - 3 days, an elevation of the troponin level may persist for up to 14 days after an event, making the troponins poor markers of early re-infarction. Rapid bedside testing of troponin T or I (e.g. the TropT test)<sup>9</sup> during the initial evaluation is encouraged. The bedside use of a 'multimarker strategy' that evaluated CK-MB, troponin I or T and myoglobin

in combination proved much superior to any 'single-marker strategy' and was also better than CK-MB and troponin *without* myoglobin in reaching an earlier diagnosis and identifying those at higher risk of death or MI by 30 days.<sup>10</sup>

Elevated levels of troponin T or I<sup>11-14</sup> or CK-MB<sup>8</sup> on admission indicate a poorer outcome. The later appearance of an elevated troponin level is also associated with higher risk.<sup>14</sup> Why a raised troponin level indicates a high risk is not known. It is postulated that a fissured plaque is associated with platelet-rich thrombi that embolise into the distal circulation and cause micro-infarctions and, in consequence, a rise in the troponin level. According to this view, an elevated troponin level is a surrogate marker for the presence of developing intracoronary thrombus.

UA and NSTEMI can be distinguished from one another only when the magnitude of the serum enzyme marker rise in the first day is known. Infarction is diagnosed if the serum markers have risen above the 99th percentile of the values for a reference control group during the first 24 hours after the onset of the index event. Elevation in the serum markers above normal that do not reach the diagnostic threshold for infarction nonetheless indicates the presence of a lesser degree of myocardial injury and is associated with an increased risk of death and myocardial infarction. The initial treatment decisions are the same in all those whose serum marker levels are above normal, whether or not they reach the diagnostic level for infarction.

### 3.4 Other serum markers

Elevations in high-sensitivity C-reactive protein (CRP), alone and in combination with troponin T<sup>15</sup> and von Willebrand factor,<sup>16</sup> are associated with a worse outcome in ACS within the first month after presentation. Whereas troponin T predicts early cardiac risk (within the first 72 hours of presentation), CRP does not.<sup>17</sup> An elevated CRP is a powerful and independent predictor of risk over the next 6 months. Markers such as CRP and von Willebrand factor are not recommended for incorporation into the routine clinical assessment of ACS at present.

## 4. THE TREATMENT OF UNSTABLE ANGINA AND NSTEMI

All patients should be evaluated for systemic factors such as febrile illness, anaemia or hyperthyroidism that might precipitate or aggravate cardiac ischaemia. If present, they should be treated aggressively.

Several therapeutic modalities are used in the immediate treatment of ACS. Firstly there are those that influence the

Recognise and treat factors precipitating or aggravating cardiac ischaemia.



pathogenesis: the anti-platelet drugs and anti-coagulants, and then there are those that provide symptomatic relief: the anti-anginal agents, analgesics and sedatives. Most patients should receive aspirin, some should be treated in addition with one of the heparin preparations, and some should also undergo early revascularisation during treatment with a GPIIb/IIIa inhibitor. In each case these decisions are based on the outcome of individual risk factor stratification.

**The therapeutic modalities for treating ACS are:**

- anti-platelet agents
- anti-coagulants
- anti-anginal drugs
- analgesics
- revascularisation in association with IV GPIIb/IIIa inhibition.

#### 4.1. Risk stratification

ACS encompasses a wide variety of clinical presentations. These vary from a minor exacerbation of anginal symptoms, which after careful clinical evaluation will require only an alteration or addition to outpatient treatment, to potentially life-threatening impending myocardial infarction for which intensive inpatient therapy is mandatory.

The treatment given to a patient with ACS is based upon the individual's risk factor profile.

**The risk stratification of patients with ACS is the key to appropriate treatment.** Risk stratification ensures that all those at high risk are correctly identified and intensively treated while it minimises inconvenience to those at lowest risk. Correct risk stratification will promote cost-effective care. There is general agreement among the many risk factor models that have been proposed,<sup>18</sup> that three major aspects should be evaluated: (i) clinical features; (ii) ST-segment changes; and (iii) elevation of cardiac markers such as CK-MB and troponin T. Each model that has been proposed is highly dependent upon the selection criteria applied in the trial population upon which it is based.

Antman *et al.*<sup>19</sup> recently developed a risk stratification model from a trial of LMWH in ACS and found it to be applicable in another similar patient population with ACS. The risk factors for death, myocardial infarction and urgent revascularisation within 14 days that they identified were: age more than 65 years, the presence of at least 3 classic risk factors for coronary artery disease, a previously identified coronary stenosis greater than 50%, more than two attacks of angina within 24 hours, the use of aspirin within the preceding 7 days, ST-segment

deviation, and elevated serum cardiac enzymes. This TIMI Risk Factor Score assigns an equal weighting to each of these factors. The risk of an adverse outcome rose from 4.7% if none or only one of the risk factors was present, to 40.9% if there were 6 or 7 present. Ohman *et al.*<sup>18</sup> have pointed out that this model omits troponin evaluation and the recognition of congestive heart failure.<sup>18</sup>

In retrospective analyses, the absolute benefit achieved by various therapies (LMWH,<sup>19</sup> GPIIb/IIIa inhibition,<sup>20</sup> and PCI<sup>21</sup>) has been found to be proportional to the magnitude of the TIMI Risk Factor Score. The greater the risk, the greater was the benefit of treatment. Although no specific threshold level in the risk factor score has been established, these treatments all showed a benefit when the risk factor score was 3 or more.

The TIMI Risk Factor Score and others like it have been developed from patient groups in which the diagnosis of ACS has been established on entry to the trial. These trials typically enrol patients with chest pain accompanied by either ST-segment depression or elevated serum markers. This process thus pre-selects higher-risk patients, but may also exclude those admitted with haemodynamic instability. For these reasons, such risk factor scores cannot be generalised to an overall group of patients presenting with acute chest pain. Furthermore, by assigning an equal value to each risk factor, the TIMI Risk Factor Score would attribute greater risk, for example, to a patient whose chest pain has settled, who is above the age of 65 years, who has taken aspirin within a week of admission and who smokes cigarettes, is diabetic and hypertensive (3 TIMI risk factors) than to the patient of 60 years who has ongoing chest pain and ST-segment depression in the ECG (2 TIMI risk factors).

The ACS risk stratification model in this guideline therefore recognises that ongoing or recurrent symptoms, evidence of any new ischaemia in the ECG,<sup>6,7</sup> elevation of the serum markers of myocardial injury/infarction, *including troponin T/I*,<sup>8,11-14</sup> and haemodynamic instability are the more important indicators of high risk. These factors are designated the *event-related indicators* of high risk. There are other factors, not produced by the acute disease state, that also indicate an adverse outcome in ACS. They are: patients who are 65 years or older, the presence of 3 or more risk factors for CAD, the onset of ACS despite the recent use of aspirin,<sup>22</sup> the previous recognition of CAD, and prior congestive heart failure. These have been designated as the *pre-existing indicators* of high risk. All the ACS risk factors should be enumerated at each clinical assessment of the patient. The presence of haemodynamic instability or any 2 of the other event-related risk indicators or 3 or more of the pre-existing risk indicators or the combination of 1 event-related and 2 pre-existing risk indicators identifies a high-risk patient. If only 1 event-related plus 1 pre-existing risk indicators, or only 1 or 2 of the pre-existing risk indicators, are present, the patient is assigned intermediate risk status. Table I



## The risk indicators of a poor outcome in ACS:

### Event-related

- Ongoing or recurring chest pain
- ST-segment depression/new ischaemia in the ECG
- Raised serum markers of cardiac injury/infarction
- Haemodynamic instability.

### Pre-existing

- Age over 65 years
- Multiple risk factors for CAD ( $\geq 3$ ), especially diabetes
- Aspirin use within 7 days
- Known CAD
- Prior left ventricular dysfunction.

shows the risk factor stratification and Figs 3 - 6 show its application in guiding the therapy proposed in this guideline.

If a scoring system is preferred, then by scoring 6 for haemodynamic instability, 3 for each event-related risk factor and 2 for each pre-existing risk factor, a total score of 6 or more assigns the patient to high risk and a total score of 5 or less assigns the patient to intermediate risk. The low-risk patient will have a risk factor score of zero.

## Formula for assigning high, intermediate or low risk:

- For haemodynamic instability, score = 6
- For each event-related risk indicator, score = 3
- For each pre-existing risk indicator, score = 2

**High risk** = total score 6 or more

**Intermediate risk** = total score 5 or less

**Low risk** = score zero

### 4.1.1 High risk

#### High-risk patients are defined by:

- The presence of haemodynamic instability
- The presence of any two of the other event-related risk factors *or*
- The presence of 3 or more of the pre-existing risk factors *or*
- The presence of one event-related and 2 pre-existing risk factors.

In this guideline, high-risk ACS patients are defined by the presence of haemodynamic instability or any 2 of the following: recurring or refractory chest pain, an ischaemic ECG and elevated serum markers or one of these latter with 2 pre-existing ACS risk factors *or* 3 or more of the pre-existing ACS risk factors occurring in isolation in a patient presenting after symptoms suggesting ACS.

### 4.1.2 Intermediate risk

Diabetics, older patients and those with previously recognised CAD are less likely to respond to medical therapy.<sup>23</sup>

**Table I. The risk stratification of unstable angina and non-ST elevation myocardial infarction**

#### Early risk

##### High risk

The following factors should be summated to estimate the intensity of risk.

##### Event related:

The presence of haemodynamic instability alone in proven ACS confers high risk

The presence of two of these other factors defines high risk

- Recurring chest pain or symptoms refractory to treatment
- ST depression/transient ST elevation/T wave inversion
- Elevation of troponin T/I or other serum markers of cardiac injury

##### Pre-existing:

The presence of three or more of these factors defines high risk

- Age > 65 years
- 3 or more risk factors for coronary artery disease
- Use of aspirin within 7 days
- Known CAD
- Prior congestive heart failure

##### Combinations of event-related and pre-existing:

The presence of one event-related and two pre-existing risk factors also defines high risk

#### Intermediate risk

- 1 event-related ACS risk factor (refractory chest pain or ischaemic ECG or elevated serum marker) with/without 1 pre-existing risk factor *or*
- 1 or 2 pre-existing ACS risk factors occurring in isolation (age > 65 years, 3 or more risk factors for CAD (especially diabetes), use of aspirin within 7 days, known CAD, prior congestive heart failure)

#### Low risk

- Chest pain settled, normal cardiac markers, normal/unchanged ECG
- No pre-existing risk factors present

#### Late risk

##### Reversible ischaemia on functional testing

- ST segment depression in the stress ECG
- Wall motion abnormality induced in stress echo
- Reversible defect with myocardial perfusion imaging

##### Left ventricular dysfunction

##### Elevated high-sensitivity CRP

Others at higher risk are those with 3 or more risk factors for CAD, those who have developed ACS despite having taken aspirin in the past week, and those with prior left ventricular dysfunction. If one event-related risk factor with/without one of these pre-existing risk factors, *or* one or two of these pre-

Intermediate risk patients are characterised by being haemodynamically stable *and* having one other event-related with or without one pre-existing *or* one or two of the pre-existing ACS risk factors.

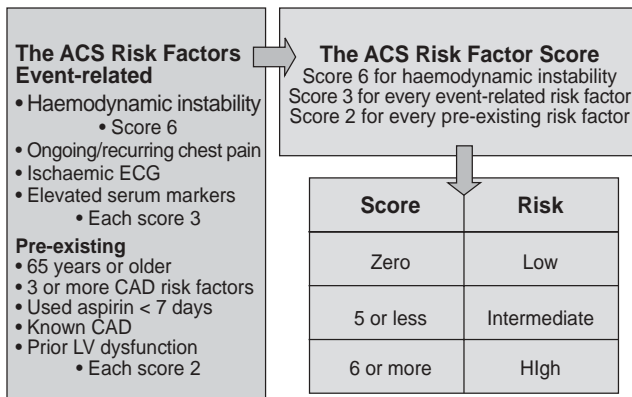


Fig. 3. Algorithm for the risk stratification of patients with unstable angina/non-ST-segment elevation myocardial infarction.

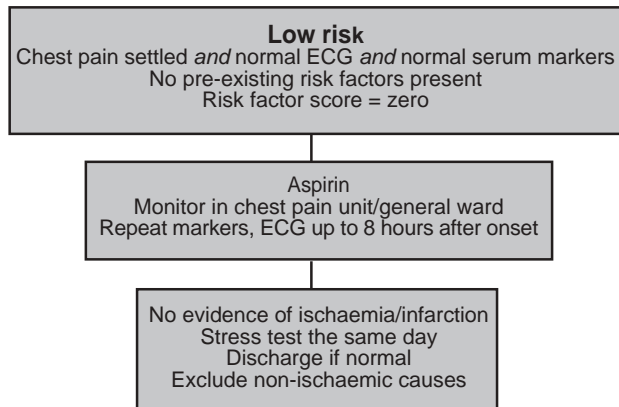


Fig. 4. Algorithm for the treatment of low-risk patients with unstable angina/non-ST-segment elevation myocardial infarction.

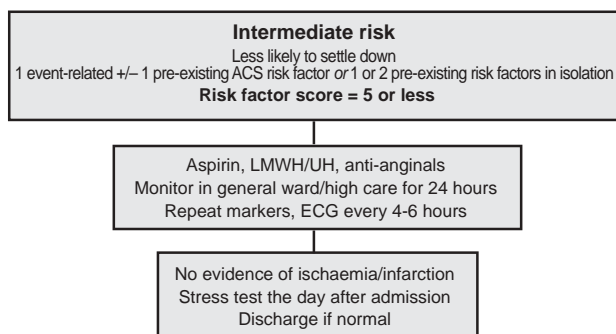


Fig. 5. Algorithm for the treatment of intermediate-risk patients with unstable angina/non-ST-segment elevation myocardial infarction.

existing factors, is present in isolation, the patient should be assigned an intermediate risk status. The presence of 3 or more of the pre-existing risk factors places the patient in the high-risk category. Intermediate-risk patients merit a longer period of observation and a higher level of care than the low-risk patients.

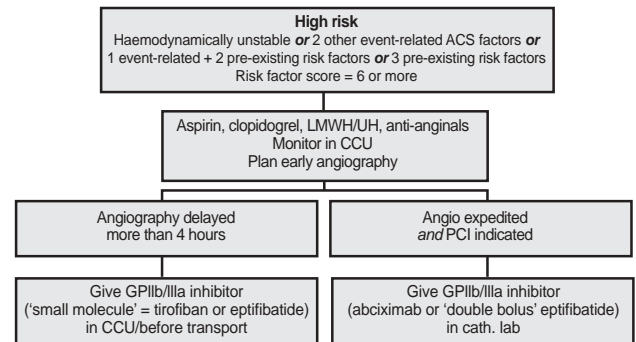


Fig. 6. Algorithm for the treatment of high-risk patients with unstable angina/non ST-segment elevation myocardial infarction.

4.1.3 Low risk

**Low-risk patients:**

- no longer have chest pain and
- have a normal ECG and
- have normal serum markers of cardiac infarction/injury and
- are haemodynamically stable.

**Low-risk patients have none of the pre-existing ACS risk factors.**

Patients whose symptoms have settled by the time of the initial assessment, with a normal ECG and normal cardiac markers and with none of the secondary ACS risk factors, are at low risk and may be suitable for early discharge.

4.1.5 Escalation of risk

The ACS risk factors status should be reviewed periodically.

Given the variations in clinical course in ACS, the risk status of any particular patient should be reviewed and updated periodically throughout the hospital stay.

4.2 Initial management of the patient suspected to have ACS

The dosing and special precautions pertaining to the most commonly used anti-platelet and anti-coagulant agents are summarised in Table II.

4.2.1 Oral anti-platelet agents

4.2.1.1 Aspirin

ACS patients should receive aspirin immediately unless contra-indicated.

The Anti-platelet Trialists' Collaboration found beneficial effects of aspirin in atherosclerotic coronary disease, including

**Table II. Commonly used antiplatelet and anticoagulant agents in unstable angina and NSTEMI — drug doses and special precautions**

Agent	Dose	Precautions
Oral anti-platelet agent		
Aspirin	Initially 300 mg p.o. then 75 - 150 mg daily	<ul style="list-style-type: none"><li>• GI bleeding</li><li>• Peptic ulceration</li><li>• Aspirin allergy</li></ul>
Clopidogrel (Plavix)	Initial loading dose of 300 mg then 75 mg daily	<ul style="list-style-type: none"><li>• Increased bleeding risk</li><li>• Antiplatelet therapy contraindicated</li></ul>
Heparins		
Unfractionated heparin		
Heparin sodium (Heparin Novo, Intramed Heparin Sodium)	60 U/kg IV bolus to a maximum of 4 000 units; then 12 units/kg/h infusion to a maximum of 1 000 units/h	<ul style="list-style-type: none"><li>• Monitor PTT: keep at 50 - 70 seconds</li><li>• Any abnormal bleeding</li><li>• Any major surgery &lt; 30 days</li><li>• Thrombocytopenia</li></ul>
Low-molecular-weight heparin		
Dalteparin (Fragmin) Enoxaparin (Clexane)	120 IU/kg subcut 12-hrly 1 mg/kg subcut 12-hrly	<ul style="list-style-type: none"><li>• Risk of bleeding</li><li>• As above</li></ul>
Glycoprotein IIb/IIIa inhibitors		
Eptifibatide (Integrilin)	180 µg/kg IV over 1 - 2 min then 2 µg/kg/min infusion over 72 h or until hospital discharge, whichever occurs first When initiating immediately before PCI, as above but repeat 180 µg/kg IV bolus 10 min after the first bolus	<ul style="list-style-type: none"><li>• Bleeding disorder</li><li>• Thrombocytopenia</li><li>• Surgery &lt; 6 weeks</li><li>• Abnormal bleed &lt; 30 d</li><li>• Active GI ulceration</li><li>• Puncture of a non-compressible vessel</li><li>• Prior stroke, organic CNS pathology</li><li>• Any systolic BP &gt; 180 mmHg during the acute event</li></ul>
Tirofiban	0.4 µg/kg/min IV over 30 min then 0.1 µg/kg/min infusion for 48 - 108 h	<ul style="list-style-type: none"><li>• As above</li><li>• 1/2 dose in renal insufficiency</li></ul>
Abciximab (ReoPro)	0.25 mg/kg IV bolus 10 - 60 min before PCI, than 10 µg/min IV infusion for 12 h	<ul style="list-style-type: none"><li>• As above</li></ul>

unstable angina and myocardial infarction.<sup>24</sup> Aspirin should be given to all patients suspected of having ACS unless contraindicated by allergy, active bleeding or active peptic ulceration. Aspirin has antiplatelet effects in low doses. Although aspirin affects many of the pathways that lead to platelet aggregation, it acts predominantly through the inhibition of cyclo-oxygenase activity that in turn reduces the platelet synthesis of thromboxane A<sub>2</sub>.

Aspirin treatment should be started as early as possible. In the absence of any dose-finding studies, we recommend a starting dose of 300 mg daily of soluble or chewable aspirin, tapering to 75 - 150 mg daily thereafter. Slow-release formulations of aspirin should not be used for emergency treatment because their onset of action is too slow.

Those patients who develop ACS despite taking treatment with aspirin are presumed to be aspirin-resistant and are at higher risk of complications.<sup>20</sup>

#### 4.2.1.2 Thienopyridines (inhibitors of ADP-mediated platelet aggregation)

The thienopyridines, ticlopidine (Ticlid) and clopidogrel (Plavix), have antiplatelet effects that are mediated through the inhibition of ADP-stimulated platelet aggregation.

Ticlopidine reduced death and myocardial (re)infarction in one trial,<sup>25</sup> but given its delayed onset of action and the incidence of side-effects, it is not recommended for routine use.

Clopidogrel added to aspirin therapy in ACS patients with chest pain and ST-segment deviation and/or elevated serum markers effected a 2.1% reduction (20% relative risk reduction) in the combined endpoint of cardiovascular death, recurrent myocardial infarction and stroke when compared with aspirin alone.<sup>26,27</sup> Given in a dose of 300 mg orally immediately after admission and continued at 75 mg per day thereafter for 3 - 12 months, the onset of this effect was observed within hours and continued to accrue throughout the trial period. There was a





1% excess of major bleeding requiring transfusion of at least 4 units of blood both during the index admission and in the post-hospital phase. A sub-group that underwent PCI in this trial were found to have a 1.9% reduction (30% relative risk reduction) in the composite end-point of cardiovascular death, myocardial infarction or urgent target vessel revascularisation. Most of these patients had stent implantation. The procedure was performed at a median time of 6 days after admission. The early post-procedural benefit was mainly due to pretreatment with clopidogrel from the time of admission.<sup>28</sup>

Clopidogrel should be given in combination with aspirin to all high-risk patients from the time of admission.

We recommend that clopidogrel be added to aspirin therapy at the time of admission in all high-risk patients. It should be continued for at least 6 months thereafter and may be considered for longer-term use in the patient considered to be at continuing high risk.

A thienopyridine may also be used as alternative therapy if there is an absolute contraindication to or intolerance of aspirin. A thienopyridine may be added to aspirin therapy if aspirin resistance is suspected.

The dose of ticlopidine is 250 mg bd and clopidogrel 300 mg immediately and then 75 mg daily.

#### 4.2.1.3 Other agents

Dipyridamole (Persantin), despite its antiplatelet activity, has no evidence to support its use in ACS.

#### 4.2.2 Sublingual nitrates

Sublingual nitrates should be given to alleviate chest pain.

The patient should receive a sublingual nitrate tablet or spray if still having chest discomfort and not hypotensive. Thereafter, nitrates should be given as needed to control pain.

### 4.3 Management of the patient according to risk status

#### 4.3.1 The low-risk patient

Low-risk patients should be observed for changes in the ECG or a rise in the serum markers for 8 hours after onset of symptoms; if these remain normal, they should have stress testing the same day, before discharge.

The low-risk patient should be kept under observation in a chest pain unit or general ward, to undergo re-evaluation of the ECG and cardiac markers 8 hours following the onset of symptoms. If these are found to have remained normal, inducible myocardial ischaemia should be ruled out by

functional testing. Thereafter it is safe to discharge the patient on aspirin and, if considered necessary, anti-anginal therapy. If functional testing cannot be arranged before the patient is discharged, it should be performed at the earliest possible date thereafter. The patient should be instructed to report any recurrence of symptoms immediately.

Exercise stress testing is the most appropriate functional test in the South African context. Early-onset symptoms during exercise, a short exercise time, a fall in blood pressure during exertion, ST-segment elevation, new post-exercise ST-segment depression in excess of 1 mm in two adjacent leads of the ECG and/or prolonged ST-segment depression are the characteristics of a strongly positive test. Stress echocardiography and/or myocardial perfusion imaging should be reserved for the patient with a particular clinical problem, when such specialised facilities are available locally.

If the functional test demonstrates ischaemia, investigation by coronary angiography should be advised. The more strongly positive the test, the earlier angiography should be undertaken. Angiography defines the nature and extent of the coronary disease and enables the planning of appropriate revascularisation.

Patients with a negative functional test may have minor coronary artery disease, other cardiovascular causes of chest pain or a chest pain of non-cardiovascular origin. Additional diagnostic tests may be required to identify the cause.

#### 4.3.2 The patient at intermediate risk (Fig. 5)

Patients at intermediate risk should receive either low-molecular-weight heparin or unfractionated heparin in addition to aspirin.

In addition to aspirin, patients at intermediate risk should receive antithrombin therapy with either LMWH or unfractionated heparin (UH). Anti-anginal agents should be given as required.

These patients should be observed and treated in a general ward or high-care facility. They may require transport to a hospital in which cardiac monitoring and resuscitation are available. Their ECG and serum markers should be repeated every 4 - 6 hours for 12 hours and at any later time if there are further symptoms.

Most patients will remain free of chest pain on treatment. They may be transferred to general ward care once free of chest

Patients at intermediate risk should be observed for 24 hours.

If free of chest pain, with a normal ECG and normal serum markers, they should have stress testing prior to discharge.



pain for 24 hours. They should be continued on treatment with aspirin, LMWH or UH and, as needed, anti-anginal agents. Once mobilised, these patients should be submitted to functional testing as soon as possible. Those with a positive functional test should undergo elective coronary angiography. The patient without evidence of ischaemia may be discharged on treatment.

#### 4.3.3 The patient at high risk (Fig. 6)

##### Patients at high risk should receive:

- Aspirin
- Clopidogrel
- Low-molecular-weight heparin or unfractionated heparin and
- Anti-anginal therapy

These patients will frequently have ongoing or recurring symptoms, be haemodynamically unstable, and have marked ST changes in the ECG and raised levels of troponin and other serum markers. They should be kept at bed rest. Oxygen should be administered if the patient is dyspnoeic, cyanosed or hypoxic. An intravenous infusion should be commenced to allow rapid venous access in the event of an emergency. The patient should have continuous electrocardiographic rhythm monitoring and nursing surveillance in an intensive care unit. The patient should be observed for the development of cardiac decompensation and/or ventricular arrhythmias. All should be treated with aspirin and clopidogrel, subcutaneous LMWH (or IV UH), and IV/oral anti-anginal therapy according to the physician's preference. Nitrates and  $\beta$ -blockade are most frequently used, alone or in combination, in doses that achieve symptom relief. We recommend that IV beta-blockade be reserved for situations in which continuous heart rate and blood pressure monitoring are available.

There is a diversity of opinion as to the best treatment options in high-risk ACS patients.

The management of the high-risk patient is challenging. There is a diversity of opinion as to the best treatment options, regarding both what constitutes optimal medical therapy and the place and timing of coronary angiography and revascularisation.

## 4.4 Anticoagulants

### 4.4.1 Unfractionated heparin

The combination of aspirin and unfractionated heparin has been standard therapy for ACS.

Until recently, the combination of oral aspirin and IV UH has been the standard therapy for ACS. The superiority of heparin

treatment over placebo in unstable angina has been demonstrated.<sup>29,30,31</sup> UH achieves its anticoagulant effects *inter alia* through the indirect inhibition of thrombin. UH should be given as an initial bolus of 60 U/kg IV to a maximum of 4 000 units and followed by a continuous IV infusion of 12 U/kg/h to a maximum of 1 000 U/h. The rate of the infusion must be adjusted to maintain the partial thromboplastin time (PTT) within a range of 50 - 70 seconds. Meticulous monitoring of the PTT is mandatory. However, even within the setting of a clinical trial, the target PTT range could be achieved in only 40 - 50% of patients, despite using a weight-adjusted dosage regimen.<sup>32</sup> Heparin-induced thrombocytopenia (HIT) is an occasional complication of UH therapy.

### 4.4.2 Low-molecular-weight heparins

Low-molecular-weight heparin may be used as an alternative to unfractionated heparin.

Enoxaparin (Clexane) and dalteparin (Fragmin) are the two LMWHs that are commercially available in South Africa. They are derived from the fractionation of heparin. Their smaller molecules not only inhibit thrombin but also factor X. Anticoagulation is achieved by giving enoxaparin 1 mg/kg subcutaneously 12-hourly or dalteparin 120 units/kg subcutaneously 12-hourly. It is not only very complex but also unnecessary to monitor LMWH therapy. The rate of haemorrhage with unmonitored LMWH is similar to that of carefully monitored UH treatment. Trials that compared dalteparin to placebo treatment in ACS<sup>33,34</sup> showed that the efficacy of dalteparin was similar to that of UH, based on a comparison to the results of earlier trials of UH treatment. Trials in ACS that directly compared enoxaparin to UH therapy<sup>32,35</sup> and a meta-analysis of these two trials<sup>36</sup> suggest that enoxaparin is superior to UH, reducing the composite end-point of death and non-fatal myocardial infarction by approximately 20%. However, another meta-analysis that incorporated the other LMWHs such as dalteparin and nadroparin found no convincing difference in efficacy or safety between LMWH preparations as a class and UH.<sup>37</sup>

There is a lower incidence of HIT with LMWH treatment. It may also be more cost-effective to give LMWH than standard UH therapy. LMWH treatment beyond the first 3 - 6 days after presentation does not influence the outcome in patients with ACS.<sup>34</sup>

### 4.4.3 Hirudin

The hirudins are potent, specific thrombin inhibitors that were initially isolated from the saliva of the medicinal leech. Hirudin in medium doses is superior to heparin therapy in preventing ischaemic outcomes in unstable angina and acute myocardial infarction without ST-segment elevation.<sup>2</sup> Given the modest benefit reported, a higher rate of bleeding and the higher cost, recombinant hirudin (lepirudin, Refludan) will not



supplant heparin as routine therapy at present. It is useful in managing those patients who develop HIT.

#### 4.4.4 Warfarin

Warfarin reduced recurrent ischaemic events in ACS in two trials.<sup>38,39</sup> However, even within the setting of a trial, the participating physicians were reluctant to use warfarin because its slow offset of action might complicate the management of patients requiring PCI. Furthermore, the patients did not comply satisfactorily with the anti-coagulant treatment.<sup>39</sup>

#### 4.5 Anti-anginal agents

Anti-anginal agents can provide symptom relief. No trial has evaluated the effect of these agents on survival.

Nitrates,  $\beta$ -adrenergic blockade and calcium channel blockade have been used to treat patients with ACS. These therapies aim to control symptoms, to reduce myocardial ischaemia and to prevent the dire complications of this syndrome. Relatively few randomised trials have evaluated the effects of an anti-anginal agent against placebo therapy or compared one class of anti-anginal agent with another in ACS. All were relatively small trials. None was powered to detect a reduction in mortality.

##### 4.5.1 Beta-blockers

Beta-blockers are recognised to be both negatively chronotropic and negatively inotropic. Beta-blockade reduces myocardial oxygen demand and diminishes ischaemia. Although there are large trials that have demonstrated the benefit of  $\beta$ -blockade following acute myocardial infarction, there has been very limited evaluation of this treatment in UA/NSTEMI. The effects of  $\beta$ -blockade upon subsequent myocardial infarction and survival are uncertain. The drugs that have been scrutinised in smaller trials or retrospective subgroup analysis are metoprolol (Lopresor),<sup>40</sup> propranolol (Inderal)<sup>41</sup> and esmolol (Brevibloc).<sup>42</sup> Whichever  $\beta$ -blocker is selected, the dose should be adjusted to obtain a resting heart rate of 50 - 60 per minute while maintaining an adequate blood pressure and satisfactory peripheral perfusion.

##### 4.5.2 Nitrates

Nitrates act by reducing pre- and afterload, promoting coronary vasodilation and relieving coronary vasospasm, and by putative effects upon platelet aggregability. These effects combine to improve myocardial blood flow and relieve ischaemia. Although nitrates effectively relieve cardiac ischaemic pain, they have not been found to improve the outcome in ACS.<sup>43</sup> They may be administered sublingually, orally or intravenously in standard doses.

##### 4.5.3 Calcium-channel blockers

Calcium-channel blockers are a diverse group of compounds

that cause smooth-muscle relaxation by blocking calcium entry into the cell. Their action results in coronary vasodilation and afterload reduction. The dihydropyridine group of calcium-channel blockers may increase the resting heart rate whereas the non-dihydropyridine group (diltiazem and verapamil) reduce the resting heart rate and thus tend to diminish myocardial oxygen demand.

The Holland Interuniversity Nifedipine/Metoprolol Trial<sup>40</sup> showed that the short-acting dihydropyridine, nifedipine (Adalat capsules), was detrimental in comparison with placebo in unstable angina.

Calcium-channel blockers should be reserved for the control of intractable chest pain or hypertension that cannot be alleviated by other means. Diltiazem (Tilazem) is a non-dihydropyridine calcium-channel blocker that is superior to placebo treatment in reducing re-infarction and post-infarction angina in non-Q-wave myocardial infarction.<sup>44</sup> Mortality was unaffected in the trial. A comparison of diltiazem treatment to propranolol found no differences in outcome in groups of patients with unstable angina or Prinzmetal angina.<sup>45</sup> In a trial that compared intravenous glyceryl trinitrate with intravenous diltiazem, the combined end-point of refractory angina and myocardial infarction was less with diltiazem than with the nitrate.<sup>46</sup> Although verapamil (Isoptin) has similar effects to diltiazem, its effects in ACS have not been evaluated in any large trial.

Dihydropyridines should be used only in combination with  $\beta$ -blockade. The combination avoids the induction of tachycardia. Short-acting dihydropyridine calcium-channel blockers should not be used at all. The non-dihydropyridine calcium-channel blocker diltiazem may be used alone as an alternative therapy if it is not possible to use  $\beta$ -blockade. However,  $\beta$ -blockers should be preferred in all other patients as they have marked benefits in those who go on to develop MI. Furthermore, the use of any calcium-channel blocker is contraindicated when there is left ventricular dysfunction.

#### 4.6 Analgesics and sedatives

While analgesics have no influence on the pathophysiological process, narcotic analgesia with IV morphine sulphate and/or sedation with oral benzodiazepines in standard doses may assist in alleviating the patient's pain and anxiety. As morphine may induce nausea and vomiting, it is advisable to pre-medicate the patient with IV metoclopramide (Maxolon) prior to commencing the IV morphine titration. It is important to take cognisance of other analgesic treatment such as tramadol (Tramal) that may have been administered by paramedical staff during transport. Adverse interactions might arise if a narcotic analgesic were administered inadvertently shortly thereafter.

IV injection of analgesics and other drugs should be preferred as intramuscular injection may perturb certain of the serum markers of cardiac injury/infarction.



#### 4.7 The glycoprotein IIb/IIIa inhibitors

The GPIIb/IIIa inhibitors block the final common pathway of platelet aggregation, the GPIIb/IIIa receptor, which when activated binds both von Willebrand factor and fibrinogen, the two principal proteins which are involved in platelet-to-platelet linking during aggregation.

Eptifibatide,<sup>47</sup> a peptide compound, and tirofiban<sup>48,49</sup> and lamifiban,<sup>50</sup> two non-peptide compounds, have undergone controlled trials in ACS. Abciximab, a Fab antibody fragment, has been employed in a trial of patients with ACS refractory to therapy who were destined to undergo percutaneous revascularisation.<sup>51</sup> As the abciximab treatment was given for 24 hours before the percutaneous intervention, the early effect of 'medical therapy only' with abciximab could be analysed within that time period. A combined analysis of the trials with abciximab, eptifibatide and tirofiban<sup>52</sup> demonstrated an absolute reduction of death and non-fatal MI of 1.3% (relative risk reduction 34%) during the period of medical treatment of these high-risk patients with ACS. In one of these trials, a raised troponin T/I at the time of presentation reliably identified those patients who would benefit from GPIIb/IIIa inhibition.<sup>53</sup> These retrospective analyses were taken to indicate that high-risk patients, and in particular those with an elevated troponin T/I, benefit from the early introduction of GPIIb/IIIa inhibition into their therapy.

However, this has not been confirmed by the trial that compared the GPIIb/IIIa receptor blocker abciximab in combination with aspirin and heparin to standard aspirin-heparin therapy. Both 24- and 48-hour infusions of abciximab (ReoPro) were compared with placebo in ACS patients with recent ischaemic chest pain and ST-segment depression and/or a positive troponin T. As planned, there was a very low incidence of coronary intervention (only 1.2%) during the first 48 hours of the trial. The abciximab infusions had no effect on outcome in this group of patients.<sup>54</sup> Whereas the value of GPIIb/IIIa inhibition as routine 'stand-alone' medical treatment in ACS *without intervention* must remain in question, there is therefore secure evidence for the so-called 'upstream' use of a GPIIb/IIIa inhibitor when coronary intervention is imminent.<sup>22</sup>

Clinical trials have demonstrated the safety and efficacy of commercially available eptifibatide (Integrilin) and tirofiban (Aggrastet) in ACS. Lamifiban is unlikely to be released for clinical use. Both eptifibatide<sup>47</sup> and tirofiban<sup>49</sup> (the so-called 'small-molecule' GPIIb/IIIa inhibitors) were effective when the GPIIb/IIIa inhibitor was given for periods of up to 72 hours and 48 hours respectively before angiography. No such trial has been conducted with abciximab. A comparison between abciximab and tirofiban treatment in association with coronary stenting<sup>55</sup> has shown a 1.54% worse outcome with tirofiban in respect of death, myocardial infarction and urgent revascularisation (a relative risk increase of 26%) at 30 days.<sup>56</sup> The authors commented that this difference was especially pronounced in the group with ACS.

#### Recommendations for IV GPIIb/IIIa inhibitor therapy:

- High-risk patients in whom angiography is delayed more than 4 hours — eptifibatide or tirofiban
- Patients found at angiography to require PCI and not already on GPIIb/IIIa inhibitor — abciximab or 'double-bolus' eptifibatide
- Adjunctive medical therapy in the high-risk patient unable to undergo angiography — eptifibatide or tirofiban.

**Do not use a GPIIb/IIIa inhibitor in intermediate- and low-risk patients.**

We recommend that GPIIb/IIIa inhibitor therapy be used as follows:

Firstly, patients who have high-risk features, and in particular those who do not settle down on standard treatment, should be commenced on 'small-molecule' intravenous GPIIb/IIIa inhibition (either eptifibatide or tirofiban) before being transferred for coronary angiography if there is to be a delay of more than 4 hours in performing the procedure. This would apply to instances when access to the local cardiac catheterisation laboratory is delayed or when the patient requires inter-hospital transfer for the procedure. Coronary angiography should be planned to coincide with the infusion period as the combined risk of death and non-fatal MI in the patients requiring PCI is reduced by 3.1% (relative risk reduction 41%) when parenteral GPIIb/IIIa inhibition is given concurrently.<sup>52</sup>

Secondly, all high-risk patients, including those whose symptoms have settled, *and* who are found after angiography to require PCI *and* who are not already receiving a GPIIb/IIIa inhibitor, should be commenced on either abciximab<sup>57</sup> or 'double-bolus' eptifibatide<sup>58</sup> immediately prior to PCI.

Thirdly, either of the small-molecule GPIIb/IIIa inhibitors may be a useful adjunct to standard medical therapy in the exceptional circumstance of the patient with very-high-risk features in whom coronary angiography is not possible.

Finally, GPIIb/IIIa inhibitors should *not* be used in intermediate- and low-risk patients as there is no proven benefit in these groups and the treatment will increase the risk of bleeding.

It should be noted that no trial data are available that *exactly* support these recommendations. The recommendations are made on the basis of the best evidence that has been presented to date.

Eptifibatide is given as an initial intravenous bolus of 180 µg/kg over 1 - 2 minutes followed immediately by a continuous infusion of 2 µg/kg/min. If eptifibatide is started immediately prior to PCI then the so-called 'double-bolus' regimen should be followed. This entails repeating the 180 µg/kg bolus dose after 10 minutes. Tirofiban is given as a loading dose of 0.4 µg/kg/min intravenously for 30 minutes



followed by a continuous infusion of 0.1 µg/kg/min. Abciximab should be restricted to administration in the cardiac catheterisation laboratory immediately before PCI, giving a 0.25 mg/kg IV bolus 10 - 60 minutes before the procedure, followed immediately by a continuous IV infusion of 10 µg/min.

In the published trials, the infusion of eptifibatide was given for up to 72 hours before angiography and for at least 24 hours after PCI.<sup>47</sup> The tirofiban infusion was administered for between 48 and 108 hours before angiography and for 12 - 24 hours thereafter.<sup>49</sup> Abciximab should be commenced 10 - 60 minutes before PCI and continued for 12 hours thereafter.

All GPIIb/IIIa inhibitors are given with either LMWH or UH. Until recently, the safety of combining GPIIb/IIIa inhibitors with LMWH was unknown. Abciximab and the low-molecular-weight heparin dalteparin have now been evaluated in a clinical trial and found to be safe.<sup>59</sup> A non-randomised observational study has also demonstrated the safety of combining enoxaparin with various GPIIb/IIIa inhibitors.<sup>60</sup> A previous smaller study suggests that there might be a therapeutic benefit in combining enoxaparin and tirofiban.<sup>61</sup> On this basis, we recommend that the patient who is already receiving LMWH therapy may be continued thereon when GPIIb/IIIa inhibition is commenced.

There are no published data on the effects of combining one GPIIb/IIIa inhibitor with another. Once a certain agent has been administered, no other GPIIb/IIIa inhibitor should be administered within the period in which the initial agent might still be active.

Information based on patients treated in the USA suggests that GPIIb/IIIa inhibition in ACS is cost-effective and falls within the commonly accepted limit of affordable treatment.<sup>62</sup>

#### 4.8 Coronary angiography

Only a skilled operator working within a setting in which angiography and percutaneous intervention is common practice, should undertake coronary angiography in the patient with ACS.

Angiography should be undertaken only to evaluate the potential for revascularisation and only in those patients in whom there is no contraindication to do so.

Some authorities have argued that all patients with ACS should have coronary angiography to establish a firm diagnosis and ensure the early discharge of those without coronary disease and appropriate revascularisation for those discovered to have the extent of coronary disease that confers a poor prognosis. However, one prospective study found that a policy of routine and early cardiac catheterisation did not improve patient outcome.<sup>63</sup>

In the high-risk group, the more high-risk factors present, the higher the imminent risk of another ischaemic event.

Troponin-positive patients have been shown to be at particularly high risk not only before but also following intervention when treated conventionally with aspirin, heparin and anti-anginal agents.<sup>23</sup>

The hazard of intervention is diminished when a GPIIb/IIIa inhibitor is administered concurrently.<sup>52</sup> Even so, PCI does increase the rate of ischaemic events above that prevailing immediately before the intervention.

A trial of LMWH therapy has shown that an 'early interventional' approach in high-risk patients (angiography within 4 - 7 days after presentation) yielded an improved outcome in respect of both mortality and (re)infarction.<sup>64</sup> This result contradicts earlier moderate-sized randomised studies, which found that early intervention had no impact on the incidence of death or myocardial infarction.<sup>65,66</sup> In the trial, LMWH was discontinued 12 hours before the procedure.

Intervention in patients on LMWH also was associated with an increased early hazard. This early hazard was outweighed by the eventual rate of death and myocardial (re)infarction at 3 months observed in the patients who did not undergo revascularisation.

A sub-analysis of this trial population found that the greatest benefit from early revascularisation occurred in those who had both ST-segment depression and a raised troponin T. Early revascularisation in this sub-group reduced the combined rate of death and myocardial infarction at 1 year from 21.6% to 13.2%.<sup>67</sup>

While angiography within 24 - 48 hours of admission has often been the practice, there have until recently been no data to support this approach as opposed to allowing the patient first to 'cool down' on medical therapy and LMWH and then proceeding to angiography within the first week.

The benefit of coronary angiography and appropriate revascularisation within 4 - 48 hours of admission in high-risk patients with ACS was demonstrated recently.<sup>21,68</sup> All patients were treated with tirofiban whether they were in the early intervention or conservative treatment arms of the trial. Almost all patients in the early intervention group had angiography; 60% required early revascularisation. Two-thirds had PCI and one-third had coronary bypass surgery. The 'early invasive' strategy reduced death, myocardial infarction and rehospitalisation for ACS at 6 months by 3.5% (relative risk reduction 22%) when compared with the conservative treatment and 'selective invasive' policy where revascularisation was driven by ischaemia. The 'early hazard' noted in the earlier trials of both GPIIb/IIIa inhibitors and LMWH was not encountered in this study.

All high-risk patients should be considered for early coronary angiography to decide on the appropriateness of revascularisation.



On the basis of these findings, we recommend that all high-risk patients should be considered for early coronary angiography to decide upon the appropriateness of revascularisation.

Intermediate- and low-risk patients with significant cardiac ischaemia on stress testing or with left ventricular dysfunction have a poor long-term prognosis and require elective diagnostic coronary angiography.

The intermediate- and low-risk patients who demonstrate features of significant cardiac ischaemia on functional testing and/or in whom left ventricular dysfunction is detected have a poor long-term prognosis and require elective diagnostic coronary angiography.

## 4.9 Revascularisation

Angiography will be undertaken in patients found to be at imminent high risk of another ischaemic event or to have inducible ischaemia. Revascularisation is indicated when a culprit high-grade stenosis of a major vessel is identified or when the extent of the coronary disease and the state of the left ventricular function indicate that the prognosis is poor and is modifiable by revascularisation. Revascularisation may be achieved by PCI or by coronary bypass surgery.

Revascularisation may be achieved by percutaneous coronary intervention or by coronary bypass surgery.

If percutaneous revascularisation is undertaken while the patient is receiving a GPIIb/IIIa inhibitor, the infusion should be continued after the procedure for the period specified for each of the agents (12 hours for abciximab, 12 - 24 hours for tirofiban and 24 hours for eptifibatide).

If coronary bypass surgery is planned, the GPIIb/IIIa inhibitor should be discontinued timeously to allow for the recovery of platelet function. Patients on clopidogrel in combination with aspirin may be at higher risk of intra-operative bleeding.

## 5. SECONDARY PREVENTION

All patients with evidence of coronary artery disease should be strongly advised to stop smoking. The value of a low saturated fat diet and regular moderate exercise should be stressed.

Participation in physical rehabilitation programmes combined with risk factor intervention should be encouraged and continued long-term.<sup>69-71</sup>

All patients who tolerate aspirin should take 75 - 150 mg daily long-term. If clopidogrel was commenced in hospital, it should be continued for at least 6 months.

### Secondary preventive measures:

- Stop smoking
- Low-fat diet
- Regular moderate exercise
- Aspirin
- Beta-blocker after myocardial infarction
- Antihypertensive to control BP at 140/90 mmHg or lower
- A statin to control LDL cholesterol at 3.0 mmol/l or lower
- ACE inhibitor.

All patients who have sustained an MI should have  $\beta$ -blockade long-term if they are tolerant of the treatment.<sup>72</sup>

Hypertensive patients should have their blood pressure tightly controlled.<sup>73</sup> Expert opinion is that the blood pressure should be lowered to at least 140/90 and preferably to 135/85 mmHg.<sup>74-76</sup>

All patients should have their serum cholesterol controlled at 5.0 mmol/l or less and their LDL cholesterol at 2.6 - 3.0 mmol/l.<sup>77,78</sup> Statin therapy will very often be required to reach these goals. Statin therapy with simvastatin (Zocor)<sup>79</sup> and pravastatin (Prava)<sup>80</sup> after myocardial infarction has reduced mortality and morbidity. Trials of intensive lipid-lowering therapy with atorvastatin (Lipitor),<sup>81,82</sup> and pravastatin in combination with colestyramine or niacin,<sup>83</sup> commenced immediately after admission in ACS patients, demonstrate that the benefits appear soon after starting treatment and emphasise the importance of initiating the lipid-lowering therapy while the patient is still in hospital. The lipid-lowering treatment should be continued long-term.

A study using ramipril (Ramace, Tritace) 10 mg/d<sup>84,85</sup> showed that ACE inhibition reduced major cardiovascular events in patients with CAD whose blood pressure was controlled and who were not in heart failure. The same study found no benefit from vitamin E. All patients with CAD should therefore receive an ACE inhibitor in addition to other secondary preventive measures, irrespective of their baseline blood pressure and left ventricular function.

## 6. DISCLAIMER

This national clinical guideline is for reference and education only and is not intended to be a substitute for the advice of the appropriate health care professional or for independent research and judgement. SAMA relies on the source of the national clinical guideline to provide updates and to notify us if the guideline protocol becomes outdated. SAMA accepts no responsibility or liability arising from any information contained in or any error in or omission from the protocol or from the use of any information contained in it.



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## ANNEXURE A. ACUTE CORONARY SYNDROME WORKING GROUP

South African Medical Association: Chairperson — R W Charlton; Critical Care Society: D Smith; DENOSA: S Labuschagne; Department of Health: Directorate Medical Schemes, Supplies and Pharmaceutical Services (EDL): J Ludick; Heart Foundation of South Africa: S Biesman-Simons; Hypertension Society of SA: S Middlemost; National Pathology Group: H Rossouw; Non-Metropolitan Forum Working Group: F A Ahmed, S J Anie, G J A Beetge, P Burger, H J R Colyn, R C Conradie, M S H Khan, A J Kock, D I Duncan, S W Hardcastle, L G Herbst, C P Jameson, O T Jannasch, D M Kelbe, J T K S Kibowa, P L Kotze, L L Latakomo, G E Letcher, H J Matthews, J H Mynhardt, E J Solomon, J J Steyn, C H Teichler, K S van Eeden, L J van Zyl; Pharmacy Association of South Africa: J Bothma; Radiological Society of South Africa: G Wagoner; Resuscitation Council of SA/Emergency Medical Society: W Kloock; SA Academy of Family Practice: S Mazaza; SA Association of Cardiovascular Rehabilitation: H Joughin, F Gerber; SA Heart Association: P Blomerus, A J Dalby, A Doubell, I Khan, J King, E Klug, P Manga, L H Opie, E Klug, J J Patel; SAMA Nominee: J Snyman; SAMA Centre for Quality Care: V Pinkney-Atkinson; **Observer delegates:** Schering-Plough (Pty) Ltd: G Nel, S Langenegger, C. Stoltz; Medscheme: H Seftel.

## ANNEXURE B: METHODOLOGY

In 1999 SAMA and the South African Society of Cardiac Practitioners agreed to collaborate on the development of a national Acute Coronary Syndrome Clinical Guideline. The first draft of the guideline was presented to a forum of non-metropolitan physicians by members of SASCP on 11 September last year. The proposals of this group were included in the next draft of the guideline. Thereafter SASCP's responsibility for the development of the guideline passed into the hands of the South African Heart Association that formed from the amalgamation of the SASCP and the Southern African Cardiac Society. A nationally representative acute coronary syndrome consensus meeting was held on 26 November 1999 in Gauteng. The invited participants were representatives of professional, government and consumer groups with an interest in the acute coronary syndrome. All participants





received the revised copy of the draft guideline together with the relevant references before the meeting. The meeting was chaired by a neutral person. The purpose of the meeting was to consider the content of the draft and either endorse or amend the document. The proceedings were recorded for future reference.

The document was revised according to the proceedings of the national consensus meeting. It also incorporated further comments received after the meeting. The Endorsement Draft was then circulated to all participants and to other interested persons, including the members of the Executive Committee and the Ethics and Guidelines Committee of SA Heart, and posted on SAMA's Internet site, SAMA-On Line, for further comment.

Recently further amendments have been made to the guideline based on new published evidence and certain presentations of clinical trial results that are as yet unpublished

(references 20, 59, 60 and 67). The Editor gratefully acknowledges the significant input and critical commentary that Professor L H Opie has made in this phase of the document's development. The final document was submitted to the SAMA's Guideline Committee for endorsement according to set criteria. The endorsed guideline is published in the *SA Medical Journal* and will also be available in the Compendium and on the Centre for Quality Care's Internet site ([www.samedical.org/cqc](http://www.samedical.org/cqc)).

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This guideline is endorsed by the South African Medical Association.

## ANNEXURE C.

Treatment options in ACS according to the patient's risk stratification and indicating the evidence base underpinning the recommendation					
	Low risk	Intermediate risk	High risk	Trial acronym	Text reference
Oral antiplatelet agents	Aspirin	Aspirin	Aspirin	Antiplatelet Trialists Collaboration	24
	-	-	Clopidogrel	CURE	26, 27
Heparin: <i>either</i> UH <i>or</i> LMWH	-	UH	UH	Various	29-31
		LMWH	LMWH	FRISC ESSENCE TIMI 11B	33 35 32
Anti-anginal therapy	-	Beta-blocker Nitrate CCB	Beta-blocker Nitrate CCB	Various	40 - 46
Impending intervention	-	-	GPIIb/IIIa inhibitor	PURSUIT PRISM PLUS GUSTO-IV ACS CAPTURE EPISTENT ESPRIT	47 49 54 51 57 58
Early invasive strategy	-	-	PCI	FRISC-II TACTICS-TIMI 18	64 21