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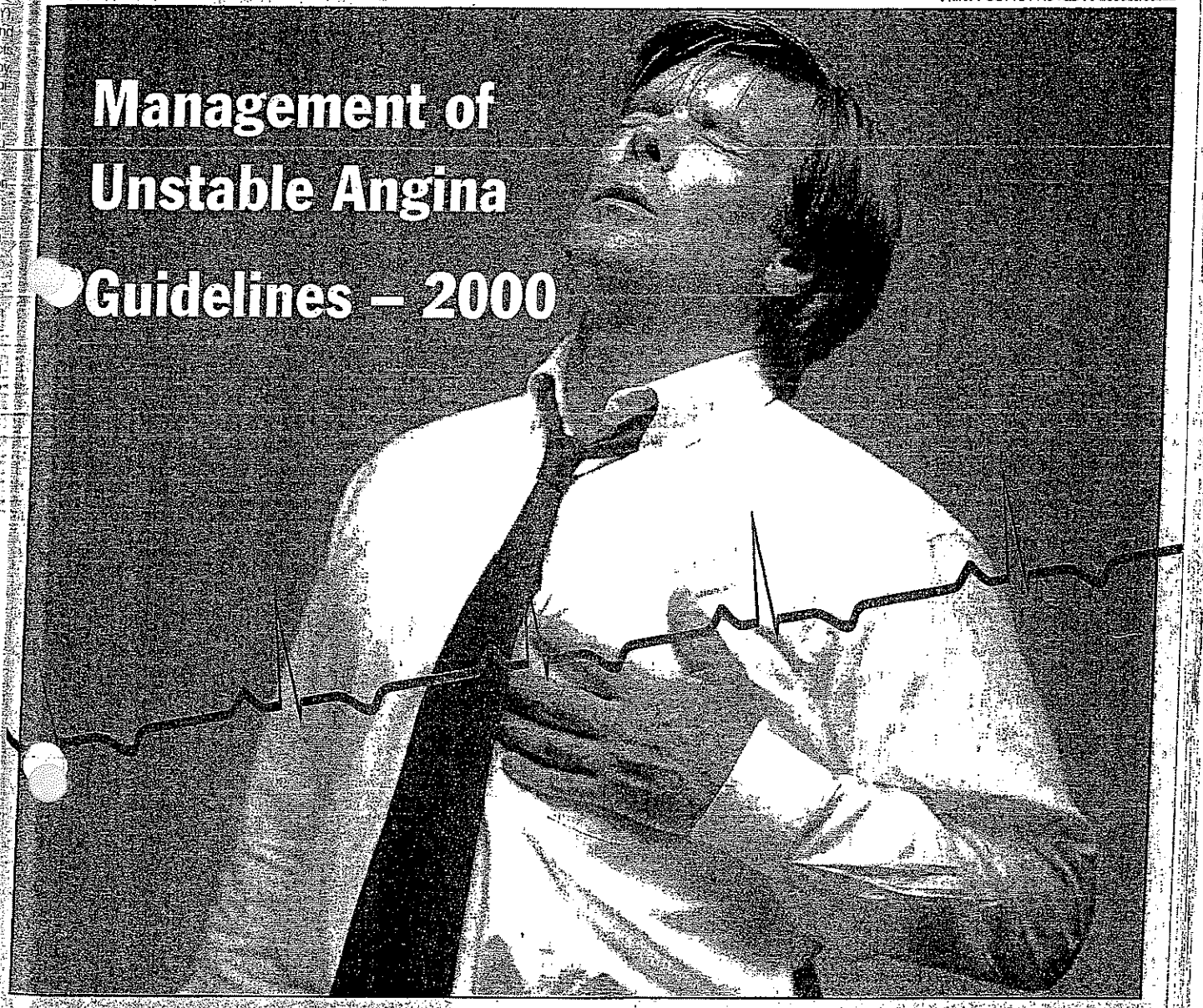
Management of Unstable Angina Guidelines – 2000



The National Heart Foundation of Australia

The Cardiac Society of Australia and New Zealand

Heart Foundation

Management of Unstable Angina

Guidelines – 2000

The National Heart Foundation of Australia
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Management of Unstable Angina Guidelines – 2000

THE PURPOSE OF THESE GUIDELINES is to incorporate contemporary information on the diagnosis and management of unstable angina into a set of recommendations that defines the boundaries of the highest-quality care in July 2000. The guidelines are directed at caring for patients presenting with the acute coronary syndrome without electrocardiographic ST-segment elevation, and therefore include patients with unstable angina and non-Q-wave myocardial infarction. The emphasis in the guidelines is on developments that have arisen since the previous National Health and Medical Research Council (NHMRC) Australian guidelines, *Diagnosis and management of unstable angina*, published in 1996. The current guidelines are an entirely local synthesis of more recent evidence.

The guidelines provide a general framework for appropriate practice, to be followed subject only to the medical practitioner's judgement in each individual case. They are directed primarily at doctors in a hospital environment (emergency physicians, rural doctors, and cardiologists) who manage patients with unstable angina, but also contain information relevant to general practitioners. The guidelines are designed to provide information to assist decision-making and are based on the best information available up to July 2000. It should be understood that the context in which clinical trials are performed and the local environment in which practice is undertaken must always be considered when assessing the evidence base for guidelines and, at times, their local implementation.

The guidelines were developed on a foundation of evidence-based criteria, using a consensus approach. They are the outcome of a workshop of representatives of key expert groups and stakeholders held in November 1999, followed by written submissions and further meetings of writing group members during January–July 2000.

Level-of-evidence codes

Evidence in the guidelines is graded according to the level of evidence classifications endorsed by the National Health and Medical Research Council (NHMRC) in 1995.

These are:

E1 Level I: Evidence obtained from a systematic review of all relevant randomised controlled trials.

E2 Level II: Evidence obtained from at least one properly designed randomised controlled trial.

E3 Level III: Evidence obtained from well-designed controlled trials without randomisation, well-designed cohort or case–control analytic studies, preferably from more than one centre or research group, or from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

E4 Level IV: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

The 1995 evidence classifications allow the inclusion of opinions of respected authorities (E4). In the 1999 NHMRC guidelines level of evidence E4 has been removed. This makes it difficult to categorise the evidence for unstable angina, some of which is still empiric and not based on clinical trial evidence. Hence the writing group has used the 1995 NHMRC levels of evidence.

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Summary of recommendations

Prehospital care

- Patients with a history of rest or prolonged chest discomfort (longer than 10 minutes, not relieved by sublingual nitrates), recurrent chest discomfort, or discomfort associated with syncope or heart failure are considered a medical emergency and should be transferred by ambulance to a hospital for urgent assessment.

Acute hospital assessment and triage

- The following investigations should be carried out for patients presenting with rest or prolonged chest or arm discomfort:
  - Baseline tests: electrocardiography (ECG), serum cardiac troponin (I or T) level (or serum CK-MB level if troponin testing is not available), full blood count, serum creatinine and electrolyte levels, serum CK levels, serum lipid levels (within 24 hours of onset of acute coronary syndrome), blood glucose level and chest x-ray.
  - The ECG is the sole test required to select patients for emergency reperfusion (thrombolytic therapy or direct PCI).
  - Continuous ECG monitoring of heart rhythm (ST segment monitoring is desirable, if available) and serial ECGs should be performed in patients with high and intermediate risk features.
  - Ongoing chest discomfort requires frequent follow-up 12-lead ECGs (15 minutes apart if continuous ST segment monitoring is unavailable) to rapidly diagnose eligibility for a reperfusion strategy.
  - A repeat serum troponin assay (unless already positive) should be performed at least six hours after presentation.
  - In patients with myocardial infarction, serial measurements of total CK should be performed for 48 hours, so that if reinfarction is suspected later total CK can be remeasured to confirm a second event. (A specific marker, such as CK-MB, is not required for the diagnosis of reinfarction, and troponin is not useful for diagnosing early reinfarction, as it remains elevated for 7–10 days.)
- All patients presenting with chest discomfort should have an ECG completed within five minutes of arrival at a medical facility and be assessed by the most appropriately qualified available person.
- Patients with chest discomfort should be evaluated with a careful history and physical examination completed within 10 minutes of arrival at a medical facility.
- High and intermediate risk patients should be admitted for continuous ECG monitoring, intensive medical therapy and observation by appropriately qualified nursing and medical staff.
- Recurrent chest discomfort (including in patients observed in a general ward environment) requires urgent reassessment, including immediate ECG, by the most appropriately qualified person.
- Patients whose ECG shows ST segment elevation or left bundle branch block should be immediately considered for reperfusion therapy.

Management

Low risk patients

- Low risk patients with a history of a moderate increase in angina frequency or severity, or angina onset more than two weeks before presentation, can be referred for cardiac assessment within two weeks.

Intermediate risk patients

- Intermediate risk patients who develop further ischaemia (pain or dynamic ST deviation) or positive serum markers are reclassified as high risk.
- Intermediate risk patients need not be treated with low molecular weight heparin unless reclassified into a high-risk group.
- Intermediate risk patients who have no further pain, have a normal ECG for the period of observation, have normal serum markers at baseline and six hours after presentation and a normal stress test may be reclassified as being at low risk.
- Patients with documented coronary artery disease without high-risk features are usually managed by increasing anti-anginal therapy, followed by a period of observation for clinical stability. Investigation will depend on the clinical context.
- Patients with symptoms strongly suggestive of myocardial ischaemia, but normal ECGs and serum markers, may be considered for either further provocative testing (stress radionuclide or stress echocardiography) and outpatient cardiac follow-up or coronary angiography in selected patients.

continued over

High risk patients

Intensive medical management

- In addition to aspirin, either LMW heparin or intravenous tirofiban with unfractionated heparin is recommended in high risk patients, and in geographically isolated patients requiring transfer to a tertiary facility, or patients not suitable for an invasive approach (very elderly, severe comorbidities).
- Intravenous tirofiban and unfractionated heparin are particularly recommended where LMW heparin fails and in high-risk patients for whom an invasive strategy is planned.

Early invasive approach

- With the exception of patients of advanced age or with severe or multiple comorbidities, an early invasive approach should be considered in patients with the following high-risk features:
  - pain or ischaemia refractory to medical therapy;
  - electrocardiographic changes (ST-segment depression or T-wave inversion in multiple leads);
  - positive serum markers (troponin I or T);
  - associated heart failure or haemodynamic instability;
  - high-risk features on early exercise testing; or
  - recent myocardial infarction or revascularisation.

  In rural centres and units that lack invasive facilities, these markers may be used to determine which patients may benefit from transfer for an invasive approach.
- The complementary use of aggressive medical and invasive approaches should be considered in all patients with high-risk features.

Long term management

- Statin therapy should be considered in all patients following unstable angina or non-ST elevation myocardial infarction if serum cholesterol level is less than 4 mmol/L.
- Angiotensin-converting enzyme (ACE) inhibitors should be considered, particularly if hypertension or diabetes is present.
- All patients with a diagnosis of unstable angina or myocardial infarction should be referred to, and participate in, an appropriate cardiac rehabilitation and prevention program.

1. Background

A non-structured approach to the diagnosis of chest pain leads to a rate of missed myocardial infarction of 1% to 5%,[1,2] and the unnecessary hospital admission of more than 50% of patients.[3] The sequelae of non-Q-wave myocardial infarctions include recurrent angina with the need for re-admission to hospital (and possibly revascularisation if not already undertaken) in 40%–50% of patients,[4] reinfarction in 9.8%[5] of patients at six months, and mortality of 11.1% at one year.[5] The aims of management should reflect these issues; that is, to:

- reduce the incidence of death and myocardial infarction;
- reduce the incidence of recurrent angina and readmission to hospital and improve long term functional health outcomes; and
- provide the most useful and cost-effective diagnostic and management strategies, which may be readily adapted to local conditions.

2. New terminology

New terminology for acute coronary syndromes is emerging to:

- more accurately describe these at the time of presentation; and
- describe a newly identified group of patients with an adverse prognosis who have elevated serum cardiac troponin levels without elevation of total serum creatine kinase levels.

Rather than making a retrospective diagnosis of Q or non-Q myocardial infarction at the time of the patient's discharge from hospital, the description of infarction in terms of the presence or absence of significant ST elevation at presentation is now considered more appropriate. This classification also reflects differences in pathophysiology between ST elevation and non-ST elevation infarction. It also reflects management, which is determined by the presence or absence of ST elevation and not by the presence of Q waves. Thus, the new terminology (Box 1) to more accurately describe the acute coronary syndromes at the time of presentation is *ST elevation myocardial infarction* (STEMI) and *non-ST elevation myocardial infarction* (non-STEMI), rather than Q or non-Q myocardial infarction.

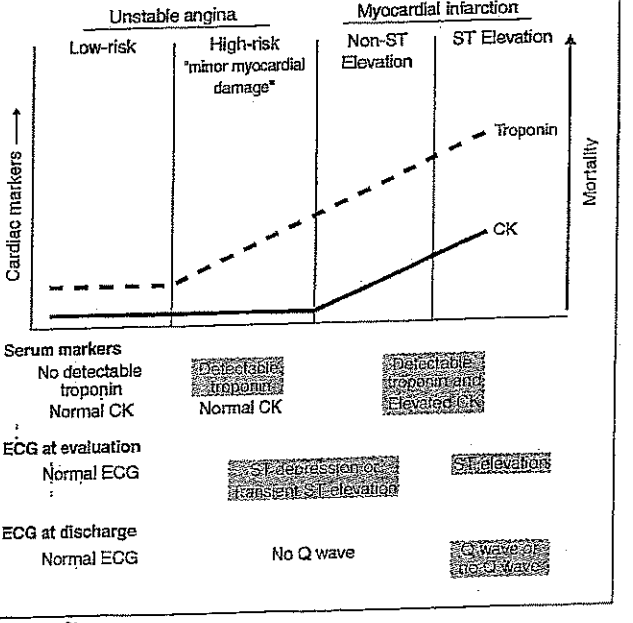
The differentiation between the diagnosis of unstable angina and non-STEMI has become clouded, with the subgroup of patients with elevated serum cardiac troponin levels without elevated serum creatine kinase (CK) or CK-MB levels being labelled as having *minor myocardial damage*.[1] These patients with "minor myocardial damage" who have an adverse cardiac prognosis[2] are a newly identified subgroup of patients with an acute coronary syndrome. The diagnoses of unstable angina, minor myocardial damage and non-STEMI may therefore be considered a continuum, with prognosis closely correlated with troponin level (Box 1). This entire diagnostic continuum will be considered in these guidelines. Patients presenting with persistent STEMI will not be considered, as, although they may "evolve" into non-Q wave myocardial infarctions, their pathophysiology and management are very different.[3]

3. Pathophysiology

Unstable angina is a syndrome that incorporates rest angina, new onset or crescendo effort angina, post-infarct angina, or angina early after percutaneous coronary intervention (PCI) or bypass surgery. The pathophysiology of acute coronary syndromes has been described in detail elsewhere.[6] Essentially, the established coronary plaque contains extracellular and intracellular lipid (the latter within foam cells), collagen and other connective tissue matrix proteins synthesised by smooth muscle cells, and inflammatory cells including macrophages derived from monocytes, T lymphocytes and mast cells. Foam cells in the plaque produce large numbers of cytokines and inflammatory mediators, including proteolytic enzymes, such as metalloproteinases. This inflammation is in response to modification (probably oxidation) of low-density lipoproteins in the subendothelial (intimal) space and to local monocyte adhesion and migration. Ongoing inflammation may, in part, be mediated by platelet interaction with leukocytes, and identified by inflammatory markers such as C-reactive protein, which is a predictor of poor long term outcome.

The extracellular lipid core in the plaque is encapsulated by a collagen cap, which can be infiltrated by macrophages. Intracoronary ultrasound has demonstrated that atheromatous plaques, which are vulnerable to plaque rupture and the development of acute coronary syndromes, are more likely to be eccentric, with a shallow, lipid-rich echolucent zone.[7] In unstable angina and non-ST or ST elevation myocardial

1: New terminology for coronary syndromes



infarction, there is a reduction in coronary perfusion due to plaque rupture or erosion and associated platelet aggregation, leading to varying degrees of coronary thrombosis and vasospasm and distal platelet microembolisation. Whether the patient develops unstable angina or non-ST or ST elevation myocardial infarction is determined by the degree and duration of reduction in coronary flow, the quality of collateral flow to the jeopardised myocardium, and the nature of the thrombus forming at the site of plaque rupture.

Patients with unstable angina or non-ST elevation infarction usually develop white (platelet) thrombi, whereas 80% of ST elevation infarctions are associated with red (fibrin with entrapped erythrocytes) thrombi.[8] These differences in pathophysiology are reflected by the effectiveness of platelet glycoprotein IIb/IIIa receptor antagonists in unstable angina and non-ST elevation infarction compared with the utility of fibrinolytic therapy for ST elevation infarction.

4. Serum markers

Cardiac troponins

The cardiac troponins have changed ideas regarding the pathophysiology of unstable angina, improved diagnostic accuracy, enhanced risk stratification and identified patients who respond to specific therapies.

The cardiac troponins are sensitive and specific markers of myocardial cell injury, with demonstrated value for prediction of cardiac events and outcomes in the short and longer term. It has been shown that 6%–8% of cardiac troponin T (cTnT)[9,10] and 3%–8% of cardiac troponin I (cTnI)[10,11] is present in the cytosol of the cardiac myocyte, with the rest being structurally bound to the contractile elements. Unlike CK-MB, cTnI and cTnT are specific for myocardial injury or necrosis, and, with usual current techniques, any circulating level of cTnI or cTnT is considered as abnormal. It is controversial whether cytosolic troponin is released with reversible myocardial ischaemia, but accepted that with myocyte necrosis the structurally bound troponins are released.

Prognostic value

Any circulating level of cardiac troponin (greater than 0.1 μg/L) is associated with greater mortality at 30 days than in patients with no detectable level (11.8% v. 3.9%; $P<0.001$).[12] In one study, after a five-month follow-up of patients presenting with unstable angina, the risks of cardiac death and myocardial infarction for cTnT levels < 0.06 μg/L, 0.06–0.18 μg/L, and > 0.18 μg/L were 4.4%, 11.4% and 14.1%, respectively.[13] A further study has shown a strong correlation between baseline cTnI level and mortality alone at 42 days in patients admitted with unstable angina (< 0.4 μg/L, 1%; 1–2 μg/L, 3.4%; 5–9 μg/L, 6%).[14]

On multivariate analysis, electrocardiography (ECG) is the strongest predictor of 30-day mortality ($\chi^2=11.5$), followed by cTnT ($\chi^2=9.2$). CK-MB appears to add no prognostic information after correction for ECG and cTnT findings.[12] Long term risk of death or myocardial infarction in patients without ST elevation is also predicted by an elevated cTnT level (41.9% v. 23.1% at three years).[15]

There is additional prognostic value in measuring a 6–8 hour troponin level, particularly if the baseline level is normal. In the GUSTO IIa study, 30-day mortality was 10% with a positive baseline cTnT, 5% with a late positive level, and zero in patients with both normal baseline and normal late troponin levels.[16]

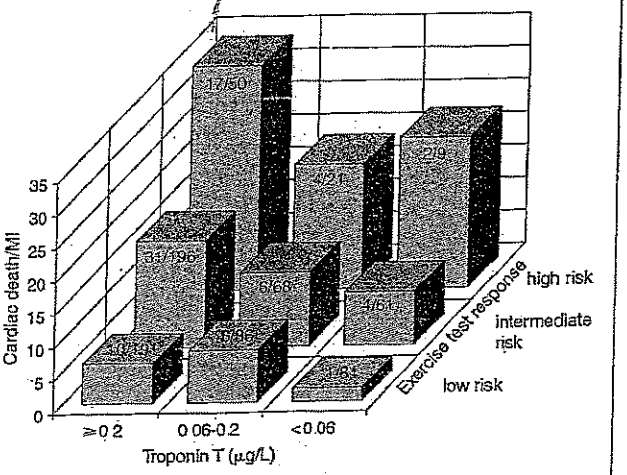
Risk stratification

The importance of negative troponin assays in identifying low-risk individuals was shown in a study of 773 consecutive patients presenting with acute chest pain and no new ST segment changes on ECG.[17] Patients with normal troponin levels at baseline and at least six hours later were discharged from the emergency department, and their 30-day event rates for death or myocardial infarction were 1.1% for cTnT and 0.3% for cTnI. This suggests that a policy of early discharge of such patients without elevated troponin levels is relatively safe. Bedside assays of both cTnT[18,19] and cTnI,[20] which provide point-of-care testing, may allow for earlier discharge and reduce hospital stay.

Late troponin level is predictive of left ventricular function. In one study, a cTnT level of 2.8 μg/L measured 12–48 hours following admission was predictive of a left ventricular ejection fraction of 40% or less, with a sensitivity of 100% and a specificity of 93%.[21] If initial troponin levels are negative, the assay should be repeated after 6–8 hours. Following myocardial infarction, troponin levels remain elevated for at least a week and CK levels may be used to diagnose (re)infarction in this period.

The combination of troponin level and exercise testing is

2: Five-month risk of cardiac death or myocardial infarction (MI) in relation to exercise test response and maximal cardiac troponin T levels during the first 24 hours



From *European Heart Journal*, Vol 18, B Lindahl B, Andren B, Ohlsson J, et al. Risk stratification in unstable coronary artery disease. Additive value of troponin T determinations and pre-discharge exercise tests 18 p. 768 1997. by permission of the publisher WB Saunders

also useful in the categorisation of risk. The risk of death or infarction at five months was 1% in patients with cTnT < 0.06 µg/L and with a negative exercise stress test, compared with 34% in patients with cTnT > 0.2 µg/L and a "high risk" stress test (Box 2).[22,23]

Cardiac troponins can also predict response to therapy. Patients with positive troponin levels will benefit from treatment with dalteparin,[24] tirofiban,[25] and from abciximab if they undergo PCI.[26]

Diagnostic utility

Around a third of patients with a positive troponin level but normal CK and CK-MB levels will develop an adverse outcome.[27] It has been suggested that, with the advent of the troponins as the preferred markers of myocardial injury, CK-MB level should be regarded as an obsolete assay.[28] As it is not cost-effective to measure both cardiac troponin and CK-MB, and because of the superior prognostic value of the troponins, many cardiac units have abandoned the use of CK-MB assays.

The International Federation of Clinical Chemistry has suggested the use of two cut-off levels for the optimum use of serum troponin: a low abnormal level to confirm minimal myocardial damage, and a higher level to make a definitive diagnosis of myocardial infarction.[29] The levels, specific assay, and time from presentation or symptom onset for the specimen to be discriminative have not yet been decided.

Of the cardiac troponins, only cTnI is never detected in skeletal muscle, either at any point in fetal development or in any pathologic state.[30-32] Troponin levels are sometimes elevated in patients with renal failure[25,26,30] and it was originally thought this may reflect a false positive result. However, a newer assay of cTnT has demonstrated that these elevated levels in renal failure do not represent a false positive finding,[33] but represent subclinical myocardial injury and predict an adverse cardiac prognosis.[34,35] As troponin levels indicate myocardial injury of any cause, they have been documented to be elevated in patients with myocarditis,[36] including heart transplant rejection[20] and the acute phase of Kawasaki disease.[37] An elevated cTnT level predicted an adverse outcome in patients with severe cardiac failure in the absence of acute ischaemia,[28] with a one-year mortality of 40%, compared with 10% in those without an elevated cTnT level. This may represent a subgroup of patients with ongoing myocyte loss. Elevation of cardiac troponin levels is also documented in acute pulmonary embolism, possibly caused by severe acute right ventricular ischaemia.[20,38,39]

C-reactive protein

Instability of coronary plaques is associated with macrophage accumulation,[40] inflammation, and an increase in acute phase proteins such as high sensitivity C-reactive protein and serum amyloid A.[41] Both baseline[42-47] and discharge[48] elevated high sensitivity C-reactive protein levels are independent predictors of subsequent events and, in the future, may also be used in risk stratification. However, a high sensitivity commercial assay required to detect minimal elevations of C-reactive protein has only recently been released. Although it is the subject of intense clinical research, there is insufficient evidence to recommend it for risk stratification at this stage.

5. Initial evaluation

Initial assessment is based on the clinical history, physical examination, and 12-lead ECG. The two objectives are to define the likelihood of significant coronary heart disease and to determine the risk of adverse short term outcomes.

Defining the likelihood of significant coronary heart disease

Patients with myocardial ischaemia or infarction can present with chest pain or pressure, syncope, palpitations, dyspnoea, or sudden death. Many patients deny a history of pain, but instead complain of pressure, tightness, or constriction, or place a fist over the central chest. The discomfort may radiate to the neck or one or both arms. Prolonged pain or discomfort occurring at rest or after physical exertion is mostly characteristic of unstable angina or myocardial infarction. The severity of this discomfort is not strongly correlated with the degree of ischaemia, with about a quarter of myocardial infarcts being painless.[49]

There are several features of pain which are characteristic of a non-ischaemic aetiology;[50] however, atypical presentations, such as dyspnoea, diaphoresis, interscapular or pleuritic pain, and nausea and vomiting, may occur, particularly in the elderly or people with diabetes.[49,51] Sharp or pleuritic pain has been described in 5%–19%[52,53] of patients with myocardial infarction and in 17% of patients with unstable angina.[52] About 15% of patients with myocardial infarction have tenderness on chest wall palpation.[53] Patients presenting with atypical symptoms often have a delayed diagnosis and treatment and an increased mortality

Summary: serum markers for coronary syndromes

- Cardiac troponin T or I are considered serum markers of choice in acute coronary syndromes.
- The presence in the serum of cardiac troponin T or I indicates myocardial damage.
- The level of cardiac troponin correlates with early risk of cardiac death and myocardial infarction.
- Baseline measurements of cardiac troponin level should be repeated after 6–9 hours, particularly if the baseline level is normal.
- Cardiac troponins predict response to therapy with low molecular weight heparin, tirofiban, or the adjunctive use of abciximab with percutaneous coronary intervention.
- Current assays of cardiac troponin T and I offer about equivalent information; the choice of assay and appropriate cut-off of abnormality is dependent on local expertise and laboratory facilities.
- At this stage, there is insufficient evidence to recommend C-reactive protein for risk stratification.

3: Risk stratification of unstable angina

High risk features
- Prolonged (>10 min) ongoing chest pain/discomfort.
- ST elevation or depression (≥ 0.5 mm) or deep T wave inversion in three or more leads.
- Elevated serum markers of myocardial injury (especially cardiac troponin I or T).
- Associated syncope.
- Associated heart failure, mitral regurgitation or gallop rhythm.
- Associated haemodynamic instability (systolic blood pressure <90 mmHg, cool peripheries, diaphoresis).

Intermediate risk features
- Prolonged but resolved chest pain/discomfort.
- [illegible]rmal pain.
- Ne[illegible]onset grade III or IV chest pain* in the previous two weeks.
- Age > 65 years.
- History of myocardial infarction or revascularisation.
- Electrocardiography (ECG) normal or pathologic Q waves.
- No significant (<0.5 mm) ST deviation, or minor T wave inversion in less than three leads.

Low risk features
- Increased angina frequency or severity.
- Angina provoked at a lower threshold.
- New onset angina more than two weeks before presentation.
- Normal ECG and negative serum troponin.
- No high or intermediate risk features.

* Grade III: Marked limitation of ordinary physical activity. Grade IV: Inability to carry out any physical activity without discomfort. Grading of angina by the Canadian Cardiovascular Society. Campeau L. Grading of angina pectoris. *Circulation* 1976; 54: 522-523.

(50% [illegible]mpared with patients presenting with typical symptoms [illegible]%).[54]

Age is very important in determining diagnosis. The high prevalence of coronary disease in older people in Western societies means that the presence (or otherwise) of cardiac risk factors adds little to the accuracy of the diagnosis in middle-aged or elderly patients with a history suggestive of unstable angina. Coronary disease will account for more than 50% of cases of all chest pain presentations in patients aged over 40 years,[55] and only 7% in patients younger than 35 years.[56] In contrast, in these younger patients, cardiac risk factors (particularly smoking and family history),[57] as well as a history of physical stress before pain onset, increase the likelihood of unstable angina or myocardial infarction.

4: Simplified risk-assessment algorithm

	Six-month risk of death or myocardial infarction		
	Low risk (<2%)	Intermediate risk (2%–10%)	High risk (>10%)
Any pain	[illegible]	[illegible]	[illegible]
Rest, repetitive or prolonged pain	–	[illegible]	[illegible]
ECG changes or elevated troponin level	–	–	[illegible]

Defining the risk of adverse short term outcomes

Patients with unstable angina can be classified into high-, intermediate- and low-risk groups (Box 3). Physical examination is normal in most patients with unstable angina, but evidence of heart failure, mitral regurgitation or an extra heart sound are considered very high risk features. A simplified risk algorithm that could be used in emergency departments is shown in Box 4.

6. Accelerated chest pain assessment of intermediate risk patients

Almost two-thirds of patients with chest pain presenting to emergency departments are admitted, many to coronary care units, with only about 15% proven to have myocardial infarction.[3] Of the third of patients discharged from the emergency department, 1%–5% have a myocardial infarction,[1,2] and these "missed" infarcts carry a high mortality — up to 16% in one study.[2] One approach to this problem has been the development of an accelerated chest pain assessment strategy for intermediate-risk unstable angina patients.

Depending on the hospital, the chest pain assessment service might be located in the coronary care unit, emergency department, or a monitored bed in a country hospital. Irrespective of the location, patients with chest pain should be observed by staff who are specifically trained in coronary care practice, and should undergo accelerated diagnostic evaluation and risk stratification. Patient care is facilitated by integration of care between the emergency medical services, emergency medicine department, coronary care unit and cardiac diagnostic laboratories. Accurate assessment can be improved by the use of structured admission and continuing evaluation forms.

During the evaluation process, intermediate risk patients should be observed with frequent ECG and, often, continuous ST segment monitoring for six or more hours. After this period, serum troponin level is assayed and, if this is negative, an exercise stress test should be performed.[58] Following this period of observation and assessment, the patients are reclassified as high or low risk.

Reclassification of intermediate risk patients after a period of observation

Intermediate risk patients without ECG changes, further ischaemia, or a positive serum troponin level need not be treated with heparin,[24] but may be given aspirin during a period of observation, and other medical therapy may be commenced or upgraded if there is previous evidence of coronary artery disease.

The presence of dynamic ST depression is an independent marker of high risk, and carries a worse prognosis than T wave inversion (7% v. 2% death in GUSTO IIa).[59] ST

depression of 0.5 mm has the same prognostic significance as 1 mm of depression.[60,61] However, some investigators consider that dynamic T inversion in five or more leads suggests a high degree of risk.[62] In the TIMI IIIB study, rest pain occurring in the first 48 hours following admission was associated with a significantly increased incidence of adverse cardiac events at both six weeks and one year.[63] In GUSTO-IIb, recurrent ischaemia occurred in 35% of patients without ST elevation and nearly tripled the number of late adverse cardiac events.[5] Thus, patients who have recurrent pain or dynamic ECG changes during the period of observation should be immediately reclassified as high-risk.

After at least six hours of observation,[58] serum troponin level should be assayed, with a positive level also leading to a reclassification as high risk.[17] Finally, in patients with no further ischaemia and a negative troponin assay, an exercise stress test[64,65] or other provocative study should be performed. The combination of cardiac troponin level and exercise stress test is particularly useful in risk stratification (Box 2).

Patients reclassified as low risk and discharged should be instructed to return to the emergency department if symptoms recur. They may also benefit from early follow-up by their local doctor or cardiologist.

Advantages of a structured chest pain assessment service

A structured period of observation and investigation is likely to reduce the number of patients discharged with a "missed infarct". There are also clear opportunities to more rapidly identify and apply a reperfusion strategy to patients who develop ST elevation after being admitted to hospital, and to enhance the treatment of those who develop other high risk features. Effective and rapid risk stratification should also reduce length of stay of low risk patients. A structured chest pain assessment service has demonstrated a reduction in missed myocardial infarctions (from 4.5% to 0.4%) while also reducing total hospital admissions (from 57% to 47%) and costs.[66,67] Units employing this strategy have already been established in a number of Australian centres.

This strategy has the advantages of:

- allowing the rapid diagnosis of patients who develop high risk features during the observation period, facilitating rapid, specific therapy of these patients;
- avoiding the discharge of patients with "missed" infarcts; and
- promoting the prompt discharge of patients reclassified as being at low risk after the observation period.

7. Evidence for medical therapies

Aspirin and dipyridamole

Aspirin irreversibly inhibits cyclooxygenase, preventing platelet synthesis of thromboxane A_2, a potent vasoconstrictor and stimulator of platelet aggregation. Part of the benefit of aspirin could relate to its anti-inflammatory properties, which could reduce plaque rupture and its sequelae, as, in the Physicians' Health Study, benefits of aspirin were shown, particularly in those with higher serum levels of C-reactive protein, an inflammatory marker.[68]

The use of aspirin in acute coronary syndromes has been clearly established,[69-71] and it reduces the rate of death or myocardial infarction by about 50%.[72] Despite clear evidence of benefit in all patient subgroups with acute coronary syndromes, aspirin is frequently underutilised. In the GUARANTEE registry of unstable angina patients, only 82% of patients received aspirin.[73] Aspirin should be given to all patients unless there is intolerance.

In patients with unstable angina, dipyridamole does not confer benefit when added to aspirin.[74,75]

Ticlopidine and clopidogrel

Ticlopidine, an ADP-receptor antagonist, is useful where there is intolerance to aspirin,[76] but is associated with severe side effects, including neutropenia and thrombotic thrombocytopenic purpura.

Clopidogrel, another ADP-receptor antagonist, may be a safer alternative in patients who are unable to tolerate aspirin, and is currently being assessed in patients with unstable angina (CURE trial). Unlike ticlopidine, clopidogrel is not associated with neutropenia. It also produces less gastrointestinal bleeding than aspirin. Clopidogrel is more effective than aspirin in preventing vascular events in patients with recent stroke, myocardial infarction or symptomatic peripheral vascular disease.[77] At 1.9 years' follow-up, there was an 8.7% reduction with clopidogrel compared with aspirin, with the incidence of ischaemic stroke, myocardial infarction or vascular death corresponding to an extra five events prevented per 1000 patients treated with clopidogrel for one year. However, clopidogrel has not been assessed in acute coronary syndromes and its increased cost precludes general use when aspirin has proven efficacy in cardiovascular disease.

Nitroglycerine and nicorandil

Nitroglycerine has systemic and coronary effects. The systemic effects include venous pooling, which reduces left ventricular preload and end-diastolic pressure, as well as having a more modest effect on reducing afterload. The coronary effects include vasodilatation of normal and atherosclerotic coronary arteries, an increase in coronary artery collateral flow, redistribution of flow from subepicardial to subendocardial regions, and antiplatelet activity.

There are no large randomised trials of intravenous nitroglycerine in unstable angina, although several small studies have demonstrated symptomatic relief with open label nitroglycerine.[78-80] The combination of intravenous or transdermal nitroglycerine and N-acetylcysteine has been shown to be superior to nitroglycerine alone, but is associated with increased side effects.[81,82]

Nicorandil is a newly available agent with nitrate and potassium channel opening activity, with effects in reducing both preload and afterload as well as causing coronary

vasodilatation.[83] There is preliminary evidence that, unlike intravenous nitroglycerine, nicorandil may not lead to tolerance after 24 hours of administration.[84] In a study of 188 patients with unstable angina, the addition of nicorandil to medical therapy reduced the incidence of recurrent myocardial ischaemia and ventricular and supraventricular arrhythmias.[85]

β-Blockers

The primary benefits of β blockade in unstable angina are owing to its effects on β_1 receptors, resulting in decreased cardiac work and myocardial oxygen demand.

Randomised studies[86-88] have shown no definite reduction in mortality, but a meta-analysis[89] has shown a 13% reduction in progression to myocardial infarction. Patients with significant AV block (first degree heart block with PR interval > 0.24 seconds, 2nd or 3rd degree heart block), bradycardia < 60 bpm, hypotension (systolic blood pressure < 90 mmHg), a history of asthma, or uncontrolled heart failure should not be given β-blockers until these conditions have resolved. Intravenous administration of β-blockers may be particularly useful in patients with uncontrolled ischaemia and hypertension, and when used in conjunction with nitrates.

Calcium channel blockers

Calcium channel blockers may exert a beneficial effect in unstable angina by promoting coronary vasodilatation, reducing heart rate (verapamil and diltiazem) and reducing cardiac work and myocardial oxygen demand.

There are a number of small trials of calcium channel blockers demonstrating relief of symptoms of ischaemia in patients with unstable angina.[90-92] The largest study [illegible] tested nifedipine, metoprolol, and the combination of both. Nifedipine increased the risk of myocardial infarction and recurrent angina relative to placebo by 16%, metoprolol reduced it by 24%, and the combination reduced it by 20%. It is not recommended that dihydropyridine calcium channel blockers be used without the concomitant use of β-blockers. If a calcium channel blocker alone is considered (eg, in patients with obstructive airways disease), then one which reduces heart rate (verapamil or diltiazem) is recommended.

Perhexiline

Perhexiline is believed to reduce myocardial ischaemia by causing a shift from fatty acid to glucose metabolism.[93]

Addition of perhexiline to standard medical therapy improves anginal symptoms and exercise tolerance in patients with severe refractory angina.[94] There is preliminary evidence that perhexiline is useful in the treatment of unstable angina.[95]

Unfractionated heparin

Heparin binds with antithrombin, enhancing its ability to inactivate factor Xa and thrombin.

The evidence for benefit of unfractionated heparin for the treatment of unstable angina is weak, particularly when compared with the proven benefits of low molecular weight heparins. A meta-analysis of six randomised short-term trials has assessed the value of the addition of unfractionated heparin to aspirin for the treatment of unstable angina in 1353 patients.[96] There was a trend towards reduced death and myocardial infarction (risk ratio, 0.67; 95% CI, 0.44–1.02; $P = 0.06$) in the patients receiving heparin. However, only four studies reported results to 12 weeks, when much of the trend in benefit was attenuated (risk ratio, 0.82; 95% CI, 0.56–1.20; $P = 0.76$).

Although it has not been definitively established that the combination of heparin and aspirin is superior to either aspirin or heparin alone, guidelines usually recommend their combined use in patients with unstable angina or non-STEMI who are considered to be at higher risk. Rebound ischaemia on cessation of treatment may occur, particularly in patients not taking aspirin. The target activated partial thromboplastin time (aPTT) is recommended to be in the range of 45–60 seconds on the basis of TIMI IIIB.[97] Control may be facilitated by the use of bedside monitoring and dosing titrated to patient weight.

A number of factors may contribute to limited efficacy of unfractionated heparin. These include the need for antithrombin for its action, and reduced effectiveness of the heparin–antithrombin complex in the presence of fibrin monomers. The release of platelet factor 4 in response to heparin may also contribute to reactivating acute ischaemia. Other limitations of unfractionated heparin are the need for continuous infusions and difficulty in achieving target aPTTs because of wide variation in antithrombotic response. Heparin-induced thrombocytopenia syndrome occurs in about 1%–3% of patients.[96]

Low molecular weight heparins

Low molecular weight (LMW) heparins are derived from unfractionated heparin by depolymerisation. They have a number of practical advantages, including greater activity against factor Xa than thrombin, and greater bioavailability than unfractionated heparin because of less binding to plasma proteins and endothelial cells. This leads to a more predictable antithrombotic dose–response relationship without the need for factor Xa monitoring, which is not recommended. The long half-life of about four hours after subcutaneous injection allows twice-daily subcutaneous injection.

Trials do not show a lower incidence of bleeding compared with unfractionated heparin; indeed, there may be an increase in minor (cutaneous) bleeding. However, LMW heparins have distinct advantages in that they do not require aPTT monitoring, they have a reduced rate of heparin-induced thrombocytopenia,[98] and intravenous site infections are avoided. Because of the long half-life of LMW heparins and difficulties in achieving rapid reversal of effect, unfractionated heparin is often preferred in patients in whom early or immediate intervention is planned. However, administration of protamine sulfate results in about 60% reversal of

the antifactor Xa effects of LMW heparins, and may result in decreased bleeding.[99,100]

The only clinical trial of LMW heparin (dalteparin) compared with placebo in patients taking aspirin (FRISC)[101] showed a benefit in death and myocardial infarction (1.8% v. 4.8%) at six days, which persisted at 40 days. For inclusion in that study, patients were required to have an unstable coronary syndrome and transient or persistent ECG changes (ST depression of 1 mm or more, or T wave inversion of 1 mm in two adjacent leads). A positive cTnT level (≥ 0.1 µg/L) differentiated between patients who responded to dalteparin (48% less death or MI at 40 days) and those who did not.[24]

Several major clinical studies of LMW heparins have examined their efficacy compared with intravenous unfractionated heparin. Both the FRIC study (dalteparin)[102] and the FRAXIS study (nadroparin)[103] demonstrated equivalence but no advantage of LMW heparins over unfractionated heparin. Two studies of enoxaparin (ESSENCE[104] and TIMI 11B)[105] demonstrated superiority over unfractionated heparin, with reduction in the composite endpoint of death, infarction, recurrent angina, or revascularisation. A prospectively planned meta-analysis[106] of the two trials of enoxaparin (ESSENCE and TIMI 11B) demonstrated superiority, with a 20% reduction in the combination of death and myocardial infarction when compared with unfractionated heparin ($P=0.05$) at 8, 14 and 43 days. Benefit has been confirmed to persist at one year.[107] Economic analyses of data from ESSENCE show cost savings at both 30 days[108] and one year[109] in patients treated with enoxaparin.

The LMW heparins differ in their ratio of anti-Xa to anti-IIa activity, with enoxaparin having relatively greater anti-Xa activity (3.5:1) than dalteparin (2.5:1).[110] The LMW heparins also vary in their pharmacological effects,[111,112] including their rates of clearance, the amount of non-specific binding, as well as duration of effect and effects on Von Willebrand factor. In the absence of direct comparisons in clinical trials, the relative effectiveness of the different LMW heparins is uncertain. Current evidence, however, demonstrates the clinical benefit of enoxaparin[106] over unfractionated heparin; this is not proven with dalteparin or nadroparin.

It was hoped that the LMW heparins might be particularly effective for prolonged therapy in low-dependency areas or in outpatients. However, this has not been substantiated, with a three-month study of twice-daily dalteparin compared with placebo (FRISC II) showing a reduction in the composite endpoint of death and myocardial infarction at one month, which was not sustained at six-month follow-up.[113] Another study (TIMI 11B) of prolonged enoxaparin for 35 days after initial stabilisation demonstrated persistence of the early benefit at 43 days (without convergence of the event curves), but was associated with an increased risk of major bleeding.[105]

Direct antithrombins

Hirudin, hirulog, inogatran and argatroban are selective antithrombin agents that have been subject to clinical trial but are not available for clinical use in Australia. They differ from heparin in that they do not require interaction with an intermediate enzyme; instead, they bind directly to the catalytic site of thrombin. Their proposed benefits over heparin include the ability to inactivate clot-bound thrombin, and reduction in thrombin-induced platelet activation, factor V and factor VIII activation, and endothelin release. The direct antithrombins are not inhibited by platelet factor 4, remain active in platelet-rich environments, and are not associated with thrombocytopenia.

Despite these "laboratory" advantages, large-scale trials of direct antithrombins have been disappointing. Only a small, incremental benefit has been shown over standard unfractionated heparin in large-scale studies. A meta-analysis[114] of the hirudin trials from the OASIS pilot, OASIS-2 and GUSTO-IIb studies of non-ST elevation acute coronary syndrome patients demonstrated a trend to benefit (risk ratio, 0.90; $P=0.06$). Compared with heparin, hirudin was associated with a higher rate of bleeding requiring transfusion. Similarly, a study of inogatran[115] showed no improvement in ischaemic end-points, despite a clear dose-related improvement in activated partial thromboplastin time.

Early benefit at seven days[114,116] may be attenuated by 30 days because of rebound activation of the coagulation system after termination of treatment.[115,117] Owing to low event rates in these large trials, it has been difficult to demonstrate significant differences in outcomes, and apparent gains appear to be small. In addition, these agents are associated with an increase in major bleeding and are more expensive than heparin. These agents are not available for clinical use in Australia.

Thrombolytic therapy

In the TIMI IIIB study,[118] 1473 patients with unstable angina or non-Q myocardial infarction were randomised to receive tissue-type plasminogen activator (tPA) or placebo, in addition to unfractionated heparin and aspirin. It was found that tPA did not lead to an improvement in clinical endpoints, but was associated with an increase in fatal and non-fatal myocardial infarction at six weeks and one year (7.5% v. 4.9%; $P=0.04$). Cerebral haemorrhage occurred in four patients with tPA but not in control patients ($P=0.06$).

Warfarin

Two randomised trials of combined aspirin and warfarin compared with aspirin alone have been reported.[119,120] The ATACS trial[119] randomised 214 patients to 162.5 mg aspirin alone or aspirin plus heparin for 3–4 days followed by warfarin with a target INR of 2–3. There was no significant difference in the combined endpoint of ischaemic events at 12 weeks (28% v. 19%; $P=0.09$) and an excess of major and minor bleeds in the warfarin group. In phase I of the OASIS pilot study,[120] 309 patients were randomised to aspirin or aspirin and warfarin (low intensity anticoagulation with target INR of 1.5) after three days of intravenous heparin or hirudin. Of patients in the warfarin group, 6.5% experienced a primary ischaemic end-point (cardiovascular

death, new myocardial infarction, or refractory angina) at six months, compared with 3.9% in the aspirin group ($P=0.31$). Phase II of this study employed moderate intensity warfarin (target INR, 2–2.5). Of patients in the warfarin group, 5.1% experienced a primary ischaemic end-point, compared with 12.1% of patients in the aspirin group ($P=0.08$). There was an excess of minor bleeds in the warfarin group in both phases of the study.

Glycoprotein IIb/IIIa receptor antagonists

Platelets are central to coronary thrombosis. Their aggregation may be stimulated by a variety of substances, but the common final mechanism is activation of the glycoprotein IIb/IIIa receptor, the platelet membrane receptor for fibrinogen.

The first glycoprotein IIb/IIIa receptor antagonist to reach clinical practice was abciximab, a murine monoclonal Fab antibody fragment. Subsequently, both peptide (eptifibatide) and non-peptide (tirofiban, lamifiban, sibrafiban, xemilofiban and orbofiban) small molecules have been assessed in clinical trials. Abciximab has been mainly studied with PCI, and these agents have not been compared directly. However, results of trials with the agents support their place as a major advance in medical therapy for patients with unstable angina.

In the PRISM-PLUS study,[121] the combination of aspirin, heparin and tirofiban (compared with aspirin and heparin alone) reduced the composite end-point of death, non-fatal infarction and refractory ischaemia at seven days (12.9% v. 17.9%; $P=0.004$), 30 days (18.5% v. 22.3%; $P=0.03$) and six months (27.7% v. 32.1%; $P=0.02$). Death and non-fatal infarction were reduced at seven days (4.9% v. 8.3%; $P=0.006$) and 30 days (8.7% v. 11.9%; $P=0.03$), but not at six months (12.3% v. 15.3%; $P=0.06$). Similarly, the combination of aspirin, heparin and eptifibatide[122] reduced the combination of death and myocardial infarction from 15.7% to 14.2% ($P=0.042$) at 30 days compared with heparin and aspirin alone. Low-dose lamifiban, heparin and aspirin (compared with heparin and aspirin alone) led to a reduction in death or myocardial infarction at six months (12.6% v. 17.9%; $P=0.025$).[123]

In the PRISM study, 13% of patients who were cTnI-positive had a cardiac event (death, myocardial infarction) at 30 days, compared with 4.9% in cTnI-negative patients ($P<0.0001$).[25] At 30 days, among cTnI-positive patients, tirofiban had lowered the risk of death (adjusted hazard ratio, 0.25; 95% CI, 0.09–0.68; $P=0.004$) and myocardial infarction (adjusted hazard ratio, 0.37; 95% CI, 0.16–0.84; $P=0.01$). This benefit was seen in medically managed patients (adjusted hazard ratio, 0.30; 95% CI, 0.10–0.84; $P=0.004$) and those undergoing revascularisation (adjusted hazard ratio, 0.37; 0.15–0.93; $P=0.02$) after 48 hours' infusion treatment. However, no treatment effect was seen for cTnT-negative patients. Similar benefits were seen for cTnT-positive patients.

The benefits of the glycoprotein IIb/IIIa receptor antagonists tirofiban[121,124] eptifibatide[122] and lamifiban[123] have been consistent in patients with acute coronary syndromes, with early decrease in death, myocardial infarction and refractory ischaemia, but there was some attenuation of benefit at six months. Tirofiban is currently available in Australia for the treatment of unstable angina or non-STEMI, and abciximab is available for adjunctive therapy with PCI. The combination of glycoprotein IIb/IIIa receptor antagonists together with LMW heparins has not yet been studied in large clinical trials, although this is being actively assessed. A small study of tirofiban in combination with enoxaparin demonstrated more consistent inhibition of platelet aggregation than when combined with unfractionated heparin.[125] There are no head-to-head studies of glycoprotein IIb/IIIa receptor antagonists compared with LMW heparins.

Some glycoprotein IIb/IIIa receptor antagonists may have other clinically important effects on long term inflammation and hyperplasia. Abciximab binds the leukocyte Mac-1 receptor,[126,127] which may have long term benefits in reducing inflammation. It also blocks the vitronectin receptor,[128,129] which is an integrin involved in tissue hyperplasia.

Although oral glycoprotein IIb/IIIa receptor antagonists

Summary: evidence for medical therapy in unstable angina

- Aspirin reduces progression to myocardial infarction and cardiac mortality by about 50% (E1).
- Dipyridamole does not confer any additional reduction in coronary events when added to aspirin (E1).
- Clopidogrel may be a useful alternative when there is intolerance to aspirin (E4).
- Intravenous nitroglycerine can achieve symptomatic relief (E3).
- β-Blockers reduce progression to myocardial infarction (E1).
- Calcium channel blockers that increase heart rate should not be used without concomitant β-blockers (E2).
- When used alone, only calcium channel blockers that reduce heart rate should be used (E2).
- Unfractionated heparin, when used with aspirin, only marginally reduces death and myocardial infarction compared with placebo (E1).
- Dalteparin reduces death and myocardial infarction when compared with placebo (E2).
- Enoxaparin is superior to unfractionated heparin in reducing death and myocardial infarction (E1), whereas dalteparin and nadroparin are not (E2).
- Prolonged use of low molecular weight heparins shows no additional benefit over short term use (E1).
- Direct antithrombins appear to have a marginal advantage over heparin and have the risk of increased bleeding (E1).
- Intravenous thrombolytic therapy is ineffective and may be harmful (E2).
- Warfarin has minimal benefits over aspirin (E2).
- Glycoprotein IIb/IIIa receptor antagonists in combination with aspirin and unfractionated heparin reduce death and myocardial infarction in the first months after treatment, but with attenuation of effect at six months (E1).
- The benefits of glycoprotein IIb/IIIa receptor antagonists are additive to the use of revascularisation (E1).

could provide prolonged receptor inhibition and thus have potential value in prevention of chronic recurrent ischaemia, they have thus far been disappointing.

Antibiotics

There is serological evidence that *Chlamydia pneumoniae* is associated with atherosclerosis.[130] Furthermore, *C. pneumoniae* has been shown to localise in coronary plaque and to promote LDL-cholesterol oxidation.

A report of the use of roxithromycin in patients with unstable angina demonstrated a reduction in ischaemic events at 30 days,[131] with continued benefit apparent at six months.[132] However, more data are required on the role of antibiotics.

8. Evidence for early angiography and revascularisation

Direct randomised comparisons of invasive versus conservative strategies

The recent large FRISC II study[4] (Box 5) has attracted considerable attention. It examined an early invasive strategy in 2457 patients with unstable angina who had ECG changes or positive serum markers. Patients first received dalteparin for at least two days before a randomised comparison of an early invasive strategy employing early PCI (stenting in 61%–70%) or bypass surgery, which significantly reduced death and myocardial infarction (the primary end-point) by 22% (from 12.1% to 9.4%) ($P=0.03$) at six months, compared with a conservative strategy in which revascularisation was driven by recurrent or ongoing ischaemia. The event curves continued to diverge at six months after randomisation. In addition, there was a strong trend to reduction (by 35%) in total mortality alone (from 2.9% to 1.9%; $P=0.10$). Total mortality was significantly reduced in men but not women treated with the invasive strategy. Myocardial infarction alone was significantly reduced (from 10.1% to 7.8%) ($P<0.05$) at six months. At six months, there were highly significant reductions in angina (22% v. 39%; $P<0.001$), class III–IV angina (3% v. 8%; $P<0.001$), requirement for long-acting nitrates (17% v. 38%; $P<0.001$) and hospital readmission rates (31% v. 49%; $P<0.001$) in the invasive compared with the non-invasive group (Box 5).

PCI was performed at a median of four days (10th and 90th percentiles being at 2 and 7 days, respectively) and coronary bypass surgery at a median of seven days (10th and 90th percentiles being at 5 and 13 days, respectively). It is possible, but not proven, that this complementary medical therapy with an average of four days of "early plaque passivation" (with LMW heparin and aspirin) before angiography and intervention may have been synergistic in leading to an improved outcome. The benefits of an immediate invasive strategy without at least two days of medical therapy are unknown.

The TIMI IIIB[118] and VANQWISH[133] studies, two earlier and smaller studies (1473 and 920 patients, respectively) that included the use of balloon angioplasty before the widespread availability of intracoronary stents, did not demonstrate an overall reduction in death or infarction from an early invasive approach. Whereas there was a large difference in intervention rates between invasive and conservative groups in the FRISC II study (71% v. 9% at 10 days, and 77% v. 37% at six months), there was only a small difference in intervention rates between invasive and conservative groups in both the TIMI IIIB (61% v. 49% at six weeks)[118] and VANQWISH (44% v. 33%)[133] studies. Thus, these studies have been criticised because of the similar intervention rates of their "invasive" and conservative arms. VANQWISH has also been heavily criticised because 78% of adverse events in the early "invasive" group occurred in patients who had not undergone an intervention. However, like the FRISC II study, the TIMI IIIB study showed that an invasive strategy reduced readmission to hospital by 45% at six weeks, and reduced death and myocardial infarction by 47% in the subgroup of patients aged 65 years and over.[118]

Coronary artery bypass surgery is considered appropriate in patients in whom angiography has demonstrated left main coronary artery disease or triple vessel disease with left ventricular dysfunction. Registry data show operative mortality is increased when patients undergo surgery while they are still unstable; thus, where possible, the timing of coronary artery bypass surgery may be delayed until symptoms are controlled. The third major criticism of the VANQWISH study[133] is that patients treated with early coronary artery bypass surgery had a very high (12%) mortality. Even though patients in the VANQWISH study having early PCI had no early mortality, the high surgical complication rate led to an overall worse outcome in the invasive group. However, this early risk with bypass surgery has not been verified in other studies (1.2% in FRISC II).[4] Even though recurrent angina and readmission to hospital are the most common adverse events occurring after an initial presentation with unstable angina, these events were not assessed in the VANQWISH

5: The FRISC II Study:[4] status at six months

	Invasive	Conservative	Risk ratio (95% CI)	*P*
Number	1222	1235		
Intervention				
PCI	43%	18%		
CABG	34%	19%		
Outcome				
Death or myocardial infarction	9%	12%	0.78 (0.62–0.98)	0.031
Any angina	22%	39%	0.56 (0.50–0.64)	<0.001
CCS class 3/4 angina	3%	7%	0.38 (0.25–0.56)	<0.001
Any readmission	31%	49%	0.62 (0.60–0.69)	<0.001

PCI = percutaneous cardiac intervention, CABG = coronary artery bypass grafting, CCS = Canadian Cardiovascular Society

study; however, they were significantly reduced in the invasive arms of both the TIMI IIIB and FRISC II studies.

Aggressive medical management used with an invasive strategy

Contemporary clinical trials of medical therapy for unstable angina usually incorporate a high rate of coronary angiography and revascularisation. In the PRISM-PLUS study[121] of intravenous heparin with tirofiban versus heparin, coronary angiography was encouraged at 2–4 days after randomisation, leading to a 90% rate of early angiography. Consequently, there was a 54% rate of early revascularisation overall (31% angioplasty and 23% bypass surgery). Although there was no randomisation between invasive and medical strategies, the reduction in the composite endpoint with heparin and tirofiban was only significant in patients undergoing angioplasty (risk ratio, 0.55; 95% CI, 0.32–0.94) and not in patients treated medically (risk ratio, 0.87; 95% CI, 0.60–1.25). This suggests that the major benefit of this aggressive medical management accrues when it is used as a complement to an early invasive strategy.

An angiographic assessment of patients treated with heparin and tirofiban in the PRISM-PLUS study demonstrated persistent thrombus in 45% of patients.[134] Persistent thrombus was associated with an increase in both death (risk ratio, 2.4; 95% CI, 1.3–4.3) and myocardial infarction (risk ratio, 2.0; 95% CI, 1.3–3.1) at 30 days. This problem illustrates the need for possible complementary mechanical revascularisation, as well as a need for continued research to develop more effective medical regimens.

PCI and adjunctive medical therapy

Platelets play a central role in complications after PCI or stenting. Use of the glycoprotein IIb/IIIa platelet receptor antagonist abciximab improves outcomes in patients undergoing PCI and stenting, particularly in patients with unstable angina or myocardial infarction.[135-139] Troponin level can predict which patients will benefit from abciximab therapy, with a risk ratio of myocardial infarction at six months of 0.23 (95% CI, 0.12–0.49; $P < 0.001$) for troponin-positive patients receiving abciximab compared with placebo.[26] Improved outcomes are maintained for three years following treatment.[140]

After stent implantation, treatment with the combination of aspirin and clopidogrel[141,142] for 2–4 weeks provides excellent protection against thrombotic complications.

Invasive therapy in post-infarction angina

Although a trial assessing an invasive versus conservative strategy in patients with post-infarction angina has not been carried out, invasive therapy has been evaluated in a group of post-infarction patients with exercise-induced myocardial ischaemia.[143] In this study (DANAMI), there was a reduction in readmission for unstable angina at one year (17.9% v. 29.5%; $P < 0.001$), stable angina (21% v. 43%; $P < 0.001$) and reinfarction (5.6% v. 10.5%; $P < 0.004$) in patients being treated invasively.

Summary: evidence for early invasive strategies

In high-risk patients, an early invasive strategy employing angiography and percutaneous coronary intervention (PCI) or bypass surgery:

- reduces anginal symptoms and need for nitrates by 50% (E1);
- reduces subsequent hospitalisation by 45%–50% (E1);
- reduces subsequent death or myocardial infarction by 22% (E2);
- provides definitive early diagnosis and prognostic stratification;
- provides for an early clear therapeutic plan;
- reduces hospital length-of-stay overall, and especially promotes early discharge and return to normal activities of patients with low-risk coronary anatomy;
- defines patients without obstructive coronary disease, where other diagnoses should be considered (60% of these will have gastrointestinal disease, especially gastro-oesophageal reflux).

The benefit from PCI is enhanced by peri-procedural heparin/tirofiban (E2), or by concomitant administration of abciximab (E1).

Patients with minor coronary disease or "normal" coronary arteriograms

In TIMI IIIA, 14% of patients enrolled with a diagnosis of unstable angina did not have a coronary obstructive lesion of 60% or greater.[144] Of this group, half had no detectable disease and a third had "slow-flow" (TIMI flow grade 1 or 2). Prognosis was much better than in patients with severe obstructive lesions. Lipid-lowering therapy has been shown to reduce cardiac events, at least in part, by the stabilisation of minor or moderate coronary lesions.[145] Clearly, patients with even minor coronary artery lesions should be managed with aggressive risk factor modification.

In patients with "normal" coronary arteries, other pathology should be considered. Oesophageal disease, especially reflux oesophagitis, has been reported in up to 36% of patients presenting with chest pain,[146] and should be considered when myocardial ischaemia has been excluded.

9. Management strategies

Prehospital care

Patients experiencing chest discomfort for more than 10 minutes, chest discomfort at rest, or chest discomfort associated with syncope or heart failure, should call an ambulance and be transferred to hospital. Because of the time-critical nature and increased potential for cardiac arrest in these patients, ambulance services should respond as a medical emergency. All ambulances responding to patients with chest pain should be equipped with a defibrillator. When a patient experiencing chest discomfort calls his or her GP, an ambulance should also be called immediately and the patient instructed to take aspirin if available. In rural and remote centres, it may be more expedient for the patient to

be taken by private transport to the nearest healthcare facility. Local doctors in these centres should discuss an appropriate "action plan" with their patients to deal with these emergencies.

The prehospital management by ambulance services for patients with chest pain of presumed cardiac origin should include rest and reassurance, oxygen, monitoring vital signs and cardiac rhythm, aspirin, nitrates, and analgesia.

High and intermediate risk patients should be transferred to a hospital; low risk patients may be treated medically and referred for non-urgent cardiac assessment (Box 6). However, depending on the expertise and assessment by the medical practitioner or other healthcare professional who first evaluates the patient in the community environment, many patients will need to be assessed in a hospital, irrespective of this classification. The imperatives in management are to prevent out-of-hospital cardiac arrest and to avoid a delay in application of a reperfusion strategy for patients with acute STEMI (Box 6). A definitive positive diagnosis should not be sought at the expense of a delay in transfer. Nor should the possibility of non-cardiac pain prevent urgent triage when high-risk features are present.

Acute hospital assessment and triage

Patients who are admitted to the emergency department with chest pain or discomfort should be treated as emergencies and should be regarded as qualifying for the Australasian College for Emergency Medicine triage category 2. An ECG should be completed within five minutes of arrival and reviewed immediately by a medical officer, and a careful history and physical examination completed within 10 minutes of arrival.

A normal ECG is found initially in up to 50% of patients with acute coronary syndromes and can not be used to exclude the diagnosis.[147-149] In one study, patients who were diagnosed with definite or probable unstable angina on clinical history alone had myocardial ischaemia proven in 95%, and, in patients with a normal ECG, myocardial ischaemia was still confirmed in 89%.[147] ST segment elevation is a marker of jeopardised myocardium and signifies a medical emergency. Patients with ST segment elevation (without response to sublingual nitrates) or left bundle branch block should be considered for an emergency reperfusion strategy (thrombolytic therapy or PCI) (E1). Where available, previously recorded ECGs should be used for comparison.

Always consider other diagnoses such as pulmonary embolism (especially in patients with associated syncope and precordial ST depression), aortic dissection, and pericarditis, possibly with tamponade and pneumothorax. Consider also secondary causes of angina, including arrhythmias, anaemia, hyperthyroidism, aortic stenosis and hypertrophic cardiomyopathy. In some patients, critical aortic stenosis may be associated with only a soft systolic murmur.

Management of patients initially assessed as being at low risk

Patients who can be definitely classified as low risk can be managed in an outpatient setting. These patients should be referred for semi-urgent cardiology assessment, preferably within two weeks. However, if there is uncertainty regarding the risk category, patients should be immediately transferred to an acute care setting.

Aspirin should be administered to all patients with unstable angina (its use reduces the risk of further events by 50%) (E1). If there is a contraindication to aspirin, clopidogrel should be considered. Patients should also be provided with buccal nitroglycerine (E4) and instructed in its use. β-Blockers should also be commenced, unless contraindicated (E1). If β-blockers are contraindicated, and if there is no evidence of heart failure or heart block, a heart-rate-slowing calcium channel blocker (diltiazem or verapamil) may be used (E2).

Education about angina and myocardial infarction should be provided, and patients instructed to contact the ambulance service directly in the event of discomfort not relieved by nitroglycerine and lasting longer than 10 minutes. These patients are at low risk of short-term infarction, but are at increased risk of further cardiovascular events in the medium to long term. Consequently, reversible risk factors (eg, cholesterol level, hypertension, diabetes) need to be actively managed.

Management of intermediate risk patients

Intermediate risk patients require observation for at least 6–8 hours (E2). During or after this period, they may be reclassified into low or high risk categories, on the basis of the development of further pain, ST depression of 0.5 mm or more (12 lead ECG or continuous ST segment monitoring), evolution of T wave inversion in multiple leads, positive serum markers (especially troponin) obtained at least six hours after presentation, and the results of exercise stress testing (Box 2). Comparisons with earlier ECGs should be performed where these are available, and significant changes indicate a high-risk classification.

Management of high risk patients

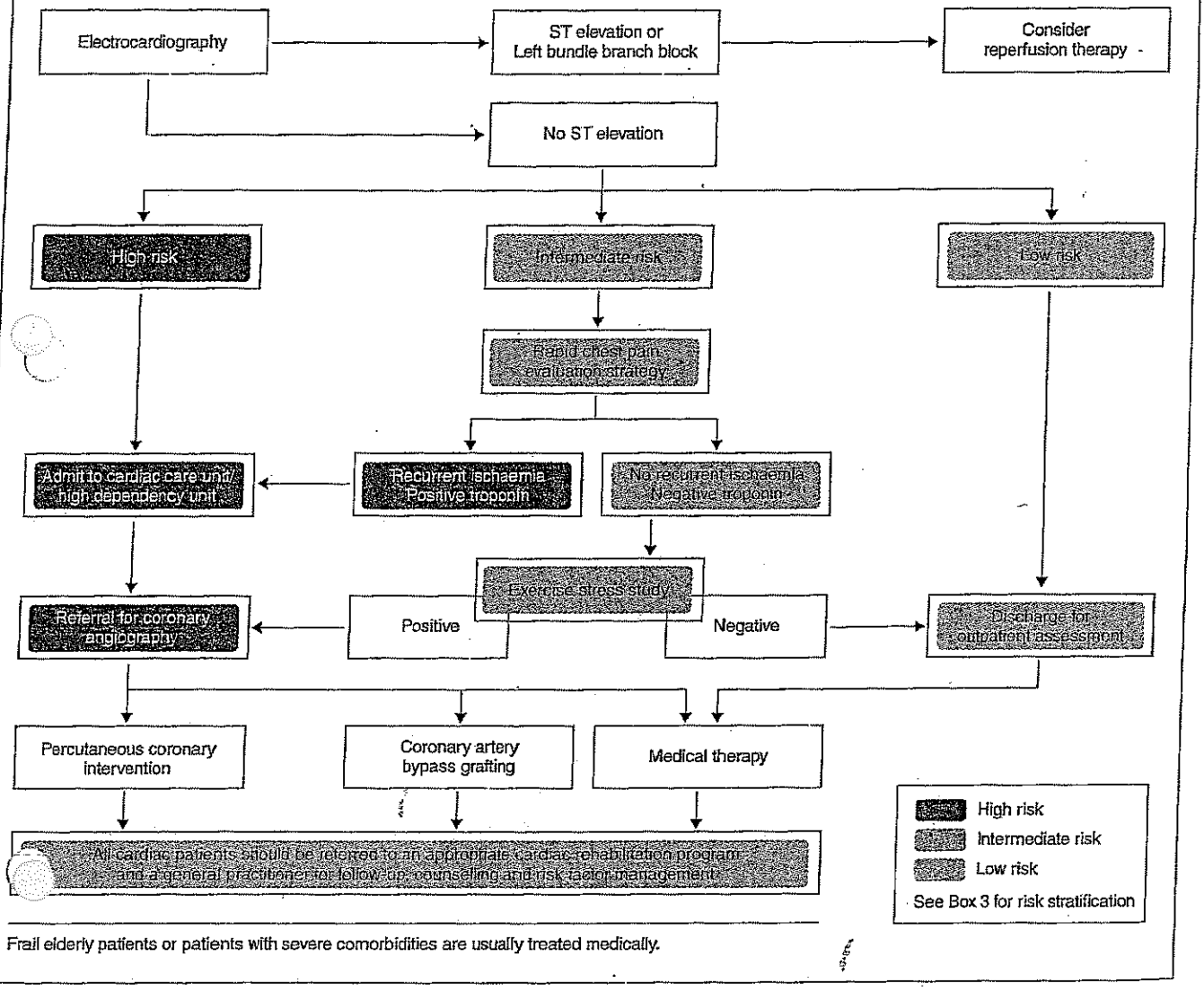
Intensive medical management

Patients with prolonged or rest angina should be treated with sublingual nitroglycerine, aspirin and supplemental oxygen. Ongoing pain should be treated with intravenous nitroglycerine and intravenous or oral β-blockers titrated to heart rate and blood pressure (E3).

Patients with any high-risk features, especially ST depression (0.5 mm or more) or elevated serum troponin levels, should be treated with LMW heparin[24] (E1) or tirofiban and heparin[121] (E1). Patients in cardiogenic shock should be considered for intravenous dopamine, and a very early invasive strategy, including intra-aortic balloon counterpulsation (E2).[150,151] This strategy should also be considered for patients with severe widespread ST depression (which suggests critical left main or three vessel coronary artery disease) and ongoing evidence of ischaemia despite maximal medical therapy. In these patients, intravenous heparin and tirofiban is suggested before emergency coronary angiography (E3).

In addition to treatment with aspirin and β-blockers,

6: Recommended management of a patient presenting with chest pain or discomfort



Frail elderly patients or patients with severe comorbidities are usually treated medically.

patients who develop an elevated serum cardiac troponin level should be treated with LMW heparin for at least 3–4 days (E1). Refractory angina may be defined as the recurrence of ischaemia after the commencement of optimal treatment with aspirin, LMW heparin and β-blockers. Refractory angina, particularly dynamic ECG changes (ST depression or transient ST elevation), is considered an indication for a change to intravenous tirofiban with heparin (E1). In these patients, referral for invasive investigations is also recommended, usually after a period of stabilisation on medical therapy, if possible.

Tirofiban and heparin are particularly beneficial in patients for whom an invasive strategy is planned (E2), and may be useful in facilitating the safe transfer of high-risk isolated and rural patients for invasive management. They may also be beneficial in patients who are unsuitable or unwilling to undergo invasive therapy.

Patients who develop acute STEMI while taking intravenous heparin and tirofiban should be considered for either direct PCI or half-dose thrombolytic therapy with alteplase, reteplase or TNK, but not streptokinase (E4).

Amlodipine or long-acting nifedipine may be added to β-blockers,[152] and nitrate therapy increased to maximally tolerated doses. Oral nicorandil added to standard therapy has been shown to reduce transient myocardial ischaemia and tachyarrhythmias.[85] Perhexilene should also be considered. Nocturnal pain can often be controlled by switching oral or cutaneous long-acting nitrates from a morning to an evening dosing schedule.

Early invasive approach

It was hoped that intensive medical therapy of unstable angina with antiplatelet and antithrombin therapy might "passivate" the coronary plaque. However, results have been disappointing, with a 6–9-month failure rate of about 12%

of death or myocardial infarction and 40% of ischaemia-driven revascularisation.[4] Therefore, it appears to be appropriate to consider an early strategy of direct intervention in patients with high-risk features. However, the complementary use of aggressive medical and invasive approaches should be considered in all patients with high-risk features (ongoing ischaemia and positive serum markers). Early coronary angiography and revascularisation with either PCI or coronary artery bypass surgery is associated with significant and sustained reductions in death, infarction, recurrent angina and readmission to hospital.[4] These benefits are most apparent in patients with high-risk features.

PCI and adjunctive medical therapy

Patients undergoing PCI or stenting should be considered for concomitant administration of intravenous glycoprotein IIb/IIIa receptor antagonist therapy (E1). From a practical point of view, patients already taking intravenous tirofiban before PCI may be continued on this treatment for a further 12–24 hours (E2), whereas patients undergoing PCI without having received tirofiban should be considered for intravenous abciximab. Patients undergoing stent implantation are also treated with additional oral antiplatelet therapy: clopidogrel for 2–4 weeks[141,142] and aspirin long term (E2). In most cases, patients having PCI even after having unstable angina can return to light activities in a few days and full activities at one month.

Long term management after control of myocardial ischaemia

All patients with unstable angina, particularly those with documented coronary disease (even minor lesions)[145] should be considered for treatment with lipid-lowering therapy if the total cholesterol level is 4 mmol/L or more. In the 4S, CARE and LIPID studies, lipid lowering with simvastatin and pravastatin improved outcomes in patients following myocardial infarction[153–155] (E1). The LIPID study included patients with previous unstable angina (3–36 months previously). Benefits of pravastatin were the same as in patients following myocardial infarction. The LIPID study also included patients with average cholesterol levels in the range of 4.0–7.0 mmol/L, following an eight-week run-in period during which dietary advice was given. Statins also improve endothelial function in diseased coronary arteries, but their role in the early (within three months) treatment of unstable angina is unproven and is currently being evaluated in several studies.

In a recent large study,[156] patients older than 55 years with evidence of vascular disease or diabetes plus one other cardiac risk factor were randomised to 10 mg of the angiotensin-converting enzyme (ACE) inhibitor ramipril or to placebo for a mean of five years. Ramipril reduced cardiac death (6.1% v. 8.1%; relative risk, 0.74; $P<0.001$), myocardial infarction (9.9% v. 12.3%; relative risk, 0.80; $P<0.001$), stroke (3.4% v. 4.9%; relative risk, 0.68; $P<0.001$), death from any cause (10.4% v. 12.2%; relative risk, 0.84; $P=0.005$), and revascularisation procedures (16.3% v. 18.8%; relative risk, 0.85; $P<0.001$). These benefits are being assessed in two further trials, but, at present, ACE inhibitors should be considered in patients with vascular disease and diabetics, particularly if hypertension is present.

Obesity and diabetes should be controlled, smoking should be proscribed, and, once ischaemia is controlled, a regular exercise program should be instituted. All patients with a diagnosis of unstable angina or myocardial infarction should be referred to, and participate in, an appropriate cardiac rehabilitation and prevention program.[157] Meta-analyses have shown that coordinated cardiac rehabilitation programs improve functional health outcomes, reduce recurrent coronary events, and may result in reduced early mortality.[158,159]

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Summary of recommendations with levels of evidence

Prehospital care

- Patients with a history of rest or prolonged chest discomfort (longer than 10 minutes, not relieved by sublingual nitrates), recurrent chest discomfort, or discomfort associated with syncope or heart failure are considered a medical emergency and should be transferred by ambulance to a hospital for urgent assessment (*E4*).

Acute hospital assessment and triage

- The following investigations should be carried out for patients presenting with rest or prolonged chest or arm discomfort:
  - Baseline tests: electrocardiography (ECG), serum cardiac troponin (I or T) level (or serum CK-MB level if troponin testing is not available), full blood count, serum creatinine and electrolyte levels, serum CK levels, serum lipids levels (within 24 hours of onset of acute coronary syndrome), blood glucose level and chest x-ray.
  - The ECG is the sole test required to select patients for emergency reperfusion (thrombolytic therapy or direct PCI).
  - Continuous ECG monitoring of heart rhythm (ST segment monitoring is desirable, if available) and serial ECGs should be performed in patients with high and intermediate risk features.
  - Ongoing chest discomfort requires frequent follow-up 12-lead ECGs (15 minutes apart if continuous ST segment monitoring is unavailable) to rapidly diagnose eligibility for a reperfusion strategy.
  - A repeat serum troponin assay (unless already positive) should be performed at least six hours after presentation.
  - In patients with myocardial infarction, serial measurements of total CK should be performed for 48 hours, so that if reinfarction is suspected later total CK can be remeasured to confirm a second event. (A specific marker, such as CK-MB, is not required for the diagnosis of reinfarction, and troponin is not useful for diagnosing early reinfarction, as it remains elevated for 7–10 days.)
- All patients presenting with chest discomfort should have an ECG completed within five minutes of arrival at a medical facility and be assessed by the most appropriately qualified available person (*E4*).
- Patients with chest discomfort should be evaluated with a careful history and physical examination completed within 10 minutes of arrival at a medical facility (*E4*).
- High and intermediate risk patients should be admitted for continuous ECG monitoring, intensive medical therapy and observation by appropriately qualified nursing and medical staff (*E1*).
- Recurrent chest discomfort (including in patients observed in a general ward environment) requires urgent reassessment, including immediate ECG, by the most appropriately qualified person.
- Patients whose ECG shows ST segment elevation or left bundle branch block should be immediately considered for reperfusion therapy (*E1*).

Management

Low risk patients

- Low risk patients with a history of a moderate increase in angina frequency or severity, or angina onset more than two weeks before presentation, can be referred for cardiac assessment within two weeks (*E4*).

Intermediate risk patients

- Intermediate risk patients who develop further ischaemia (pain or dynamic ST deviation) or positive serum markers are reclassified as high risk (*E1*).
- Intermediate risk patients need not be treated with low molecular weight heparin unless reclassified into a high-risk group (*E2*).
- Intermediate risk patients who have no further pain, have a normal ECG for the period of observation, have normal serum markers at baseline and six hours after presentation and a normal stress test may be reclassified as being at low risk (*E1*).
- Patients with documented coronary artery disease without high-risk features are usually managed by increasing anti-anginal therapy, followed by a period of observation for clinical stability. Investigation will depend on the clinical context (*E4*).
- Patients with symptoms strongly suggestive of myocardial ischaemia, but normal ECGs and serum markers, may be considered for either further provocative testing (stress radionuclide or stress echocardiography) and outpatient cardiac follow-up or coronary angiography in selected patients (*E4*).

continued over

High risk patients

Intensive medical management

- In addition to aspirin, either LMW heparin or intravenous tirofiban with unfractionated heparin is recommended in high risk patients (*E1*), and in geographically isolated patients requiring transfer to a tertiary facility, or patients not suitable for an invasive approach (very elderly, severe comorbidities) (*E4*).
- Intravenous tirofiban and unfractionated heparin are particularly recommended where LMW heparin fails (*E4*), and in high-risk patients for whom an invasive strategy is planned (*E2*).

Early invasive approach

- With the exception of patients of advanced age or with severe or multiple comorbidities, an early invasive approach should be considered in patients with the following high-risk features:
  - pain or ischaemia refractory to medical therapy (*E4*);
  - electrocardiographic changes (ST-segment depression or T-wave inversion in multiple leads) (*E2*);
  - positive serum markers (troponin I or T) (*E2*);
  - associated heart failure or haemodynamic instability (*E3*);
  - high-risk features on early exercise testing (*E3*); or
  - recent myocardial infarction or revascularisation (*E3*).

  In rural centres and units that lack invasive facilities, these markers may be used to determine which patients may benefit from transfer for an invasive approach.
- The complementary use of aggressive medical and invasive approaches should be considered in all patients with high-risk features (*E1*).

Long term management

- Statin therapy should be considered in all patients following unstable angina or non-ST elevation myocardial infarction if serum cholesterol level is less than 4 mmol/L (*E2*).
- Angiotensin-converting enzyme (ACE) inhibitors should be considered, particularly if hypertension or diabetes is present (*E2*).
- All patients with a diagnosis of unstable angina or myocardial infarction should be referred to, and participate in, an appropriate cardiac rehabilitation and prevention program (*E1*).

E1 Level I: Evidence obtained from a systematic review of all relevant randomised controlled trials.

E2 Level II: Evidence obtained from at least one properly designed randomised controlled trial.

E3 Level III: Evidence obtained from all well-designed controlled trials without randomisation; well-designed cohort or case–control analytic studies, preferably from more than one centre or research group; or from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

E4 Level IV: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

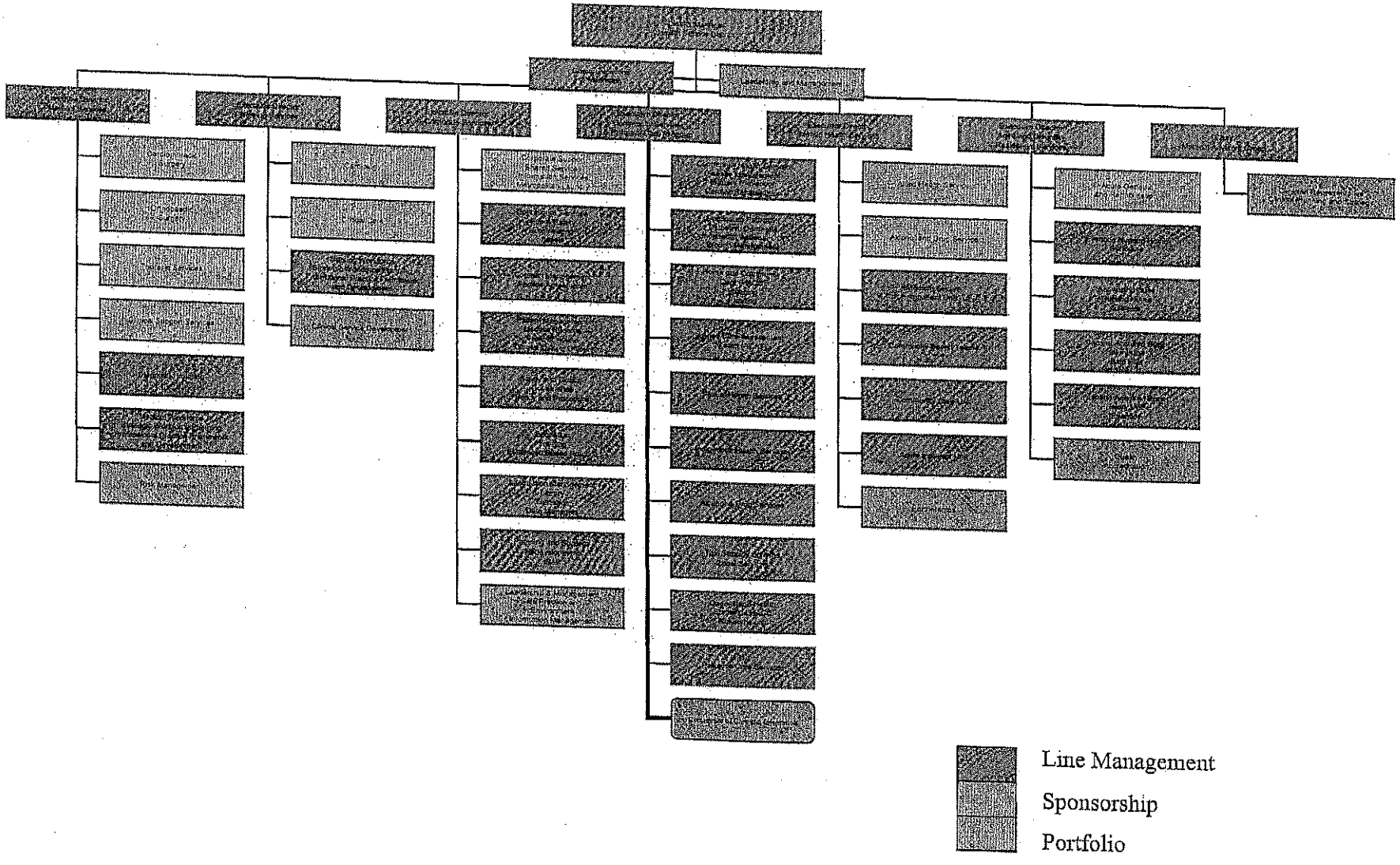
National Health and Medical Research Council, 1995

Bundaberg Hospital Commission of Inquiry

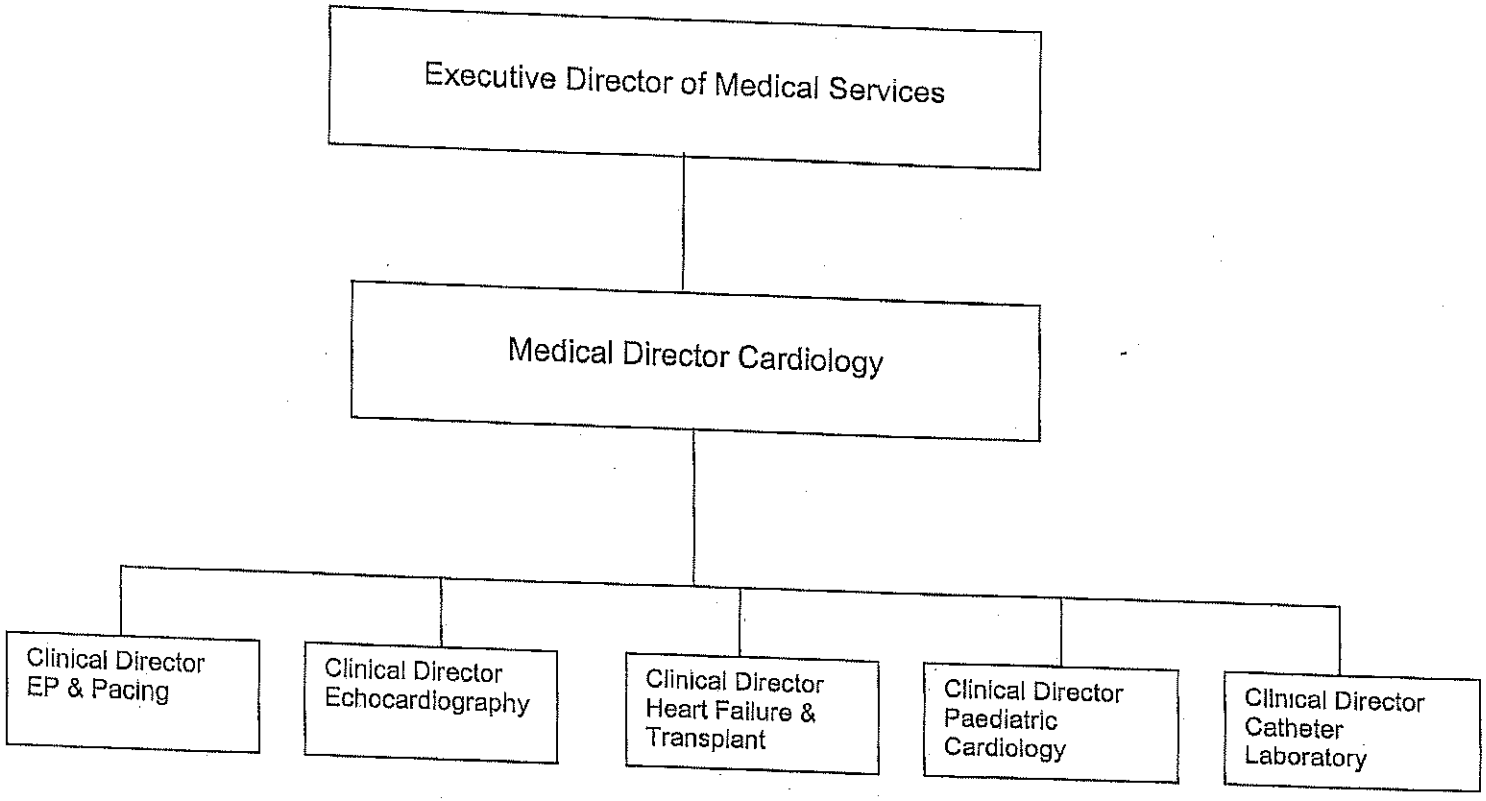
Statement of Michael Ian Cleary

Attachment MIC-2

The Prince Charles Hospital Health Service District Organisational Structure



ORGANISATIONAL STRUCTURE DIAGRAM:



Bundaberg Hospital Commission of Inquiry

Statement of Michael Ian Cleary

Attachment MIC-3

CARDIAC SURGERY SERVICES WORKING PARTY

Terms of Reference

PURPOSE:
To facilitate the allocation of resources to PAH to enable a targeted increase of 300 cardiac surgery cases in the Southern Zone.

ROLE:
- To review the business case developed by PAH.
- Determine an appropriate volume and mix of resources to be transferred to PAH from TPCH to support a sustainable, efficient and equitable service delivery at both sites.
- Establish ad-hoc working parties to address specific issues that may arise.
- Review the impact of strategies to manage the impact of resource re-allocation of service delivery at TPCH and recommend appropriate courses of action.
- Establish an appropriate mechanism for transfer of resources and increase in activity at PAH from 1 January 2004.
- Oversee the implementation and evaluation of the transfer of services.

MEETINGS:
Location: As indicated on agenda
Frequency: Monthly or as required by the demands of business
Duration: One hour or as required
Agenda: Developed and circulated to members one week prior to meeting

MEMBERSHIP:
Karen Roach, Zonal Manager, Southern Zone (Chair)
Dan Bergin, Zonal Manager, Central Zone
Richard Ashby, A/District Manager, PAHHSD
Sean Birgin, A/Director of Nursing – Surgery, PAH
Michael Cleary, Executive Director Medical Services, TPCH
Corelle Davies, Principal Project Officer, CZMU
Leuwin Ferguson, Team Leader, Clinical Services, SZMU
Andrew Galbraith, Cardiologist, TPCH
Paul Garrahy, Director, Cardiology, PAH
Andrew McAuliffe, Team Leader, Service Development and Support, SZMU
Hayley Middleton, Senior Project Officer, TPCHHSD
Julie Mundy, Director, Cardiac Surgery, PAH
Deb Podbury, District Manager, TPCHHSD
Jon Roberts, Finance Controller, TPCH
Greg Stafford, Chair, Cardiac Surgery, TPCH
John Wakefield, Deputy Director Medical Services - Surgery, PAH
Mary Wheeldon, Director of Nursing - Critical Care, TPCH

SECRETARIAT:
Southern Zone Management Unit