Unstable angina
assessment and management

An aggressive approach, with early investigation and revascularisation as appropriate, has led to reduced cardiac events and hospital readmissions for patients with unstable angina.

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It is important that unstable angina is diagnosed early and accurately because the condition carries a significant risk of early and late cardiac events. The management of unstable angina has undergone major changes in recent years, with greater attention now being paid to risk factor stratification and cardiac enzyme changes, particularly troponin levels.[1] (The cardiac troponins are sensitive and specific markers of myocardial cell injury, and predict cardiac events and outcomes in the short and longer term.)

A more aggressive approach (earlier intervention) and the new agents that have become available have led to a significant reduction in acute infarction rates and mortality, particularly in high risk groups. Long term risk factor management and drug therapy can reduce rehospitalisation, ongoing angina and recurrent events. These changes have led to new Australian and American guidelines.[2,3]

Diagnosis

Patients with unstable angina present with one of the following:[4]

- an increasing frequency and severity of pre-existing angina on effort
- new onset effort angina
- rest or nocturnal angina.

These patients have an increased risk of death or acute myocardial infarction (AMI) over the next 12 months (see the box on page 38).[5]

The underlying pathology is usually a change in an underlying atheromatous coronary artery plaque, with plaque ulceration, local platelet aggregation and then secondary thrombus formation. There may also be vasoconstriction or spasm at the site or embolisation of material downstream.

Instability may also be due to other factors that aggravate a stable angina pattern, such as anaemia, infection or thyrotoxicosis. Some patients may not have typical chest pain symptoms, presenting instead with effort dyspnoea or atypical pain patterns (pain in the neck, jaw, arms, epigastrium or back).

The diagnosis of unstable angina is usually based on the history, typical ischaemic electrocardiogram (ECG) changes (flat or downsloping ST

IN SUMMARY

- **An early and accurate diagnosis of unstable angina is essential.**
- **The underlying pathology is usually an ulcerated plaque, with local platelet aggregation and thrombus, without complete vessel occlusion.**
- **ECG changes and a raised troponin level place patients in a high risk group.**
- **Management is influenced by the patient's risk profile.**
- **Stress testing may help in diagnosis and directing future management.**
- **New medical management to stabilise high risk patients includes low molecular weight heparin, clopidogrel and tirofiban via an infusion.**
- **After initial stabilisation, early angiography followed by coronary intervention can significantly improve patient outcomes.**
- **Long term risk factor management and drug therapy can control symptoms and reduce future cardiovascular events.**

Mortality of unstable angina

Patients with unstable angina have an increased risk of death or acute myocardial infarction (AMI) over the 12 months after presentation. The Braunwald classification grades patients with unstable angina according to severity of expected outcome on the basis of the clinical manifestations and circumstances of their presentation (Table A). Risk stratification based on this classification has been validated by the Thrombolysis in Myocardial Infarction (TIMI) III Registry (Figure A).[4,5]

Table A. Braunwald clinical classification of unstable angina[4]

Severity	
Class I	New onset of severe angina or accelerated angina; no rest pain
Class II	Angina at rest within past month but not within preceding 48 hours (angina at rest, subacute)
Class III	Angina at rest within 48 hours (angina at rest, acute)
Clinical circumstances	
A (secondary angina)	Develops in the presence of extra-cardiac condition that intensifies MI
B (primary angina)	Develops in the absence of extra-cardiac condition
C (post infarction angina)	Develops within two weeks after AMI
ECG changes	Patients with unstable angina may be further subdivided into those with and those without transient ST–T wave changes during pain

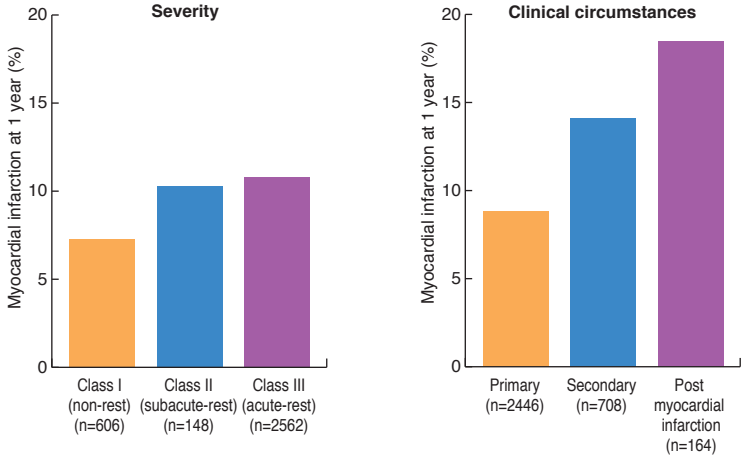


Figure A. Unstable angina: one-year mortality, from the TIMI III registry (according to the Braunwald classification).[5]

segment depression (≥ 1 mm) or T wave inversion) during pain and exclusion of infarction on serial cardiac enzymes.

Classification

The Braunwald classification gives an indication of the clinical factors that reflect on risk for patients with unstable angina. Elevation of troponin I or T levels in the absence of an elevation of creatine kinase (CK) levels is an independent and significant increased risk factor.

The 2000 Australian guidelines for the management of unstable angina divide acute coronary syndromes into:

- low risk unstable angina – all cardiac enzymes normal
- high risk unstable angina – mild elevation of serum troponin I or T, with normal CK levels (also labelled 'minor myocardial damage')
- non-ST elevation or ST elevation myocardial infarction (non-STEMI and STEMI, respectively) – elevation of both troponin and CK levels with evolving ECG changes (see Table 1).[2]

The diagnoses of low risk unstable angina, minor myocardial damage and non-STEMI may be considered a continuum, with prognosis closely correlated with troponin level.[2]

In planning management it is important to stratify patients into low, intermediate and high risk groups (Table 2).[2] A complete history and examination are necessary to exclude other pathology and to assess the patient's clinical state. If the patient has prolonged rest or effort related pain lasting more than 10 minutes and not relieved by sublingual glyceryl trinitrate (Anginine, Nitrolingual Pumpspray), recurrent ischaemic chest pain or pain associated with syncope or heart failure, then urgent assessment in hospital is required.

Investigations

An ECG is the important initial investigation to exclude acute ST elevation

myocardial infarction and to look for features of ischaemia. Cardiac enzymes should then be taken (both troponin I or T and CK) with enzymes repeated at six hours. An elevation of troponin levels in the absence of a CK elevation puts the patient in an increased risk group.

Urea and electrolytes, full blood examination, liver function tests, fasting glucose and lipids (including HDL and LDL cholesterol) are useful in planning drug therapy and long term management.

Stress testing and coronary angiography

Other investigations to confirm the diagnosis or assess the degree of ischaemia may also be required.

Stress ECG

Treadmill or bicycle exercise testing may be useful if the initial ECG is normal, with normal serial enzymes, and the patient has a suspicious but not classic history of ischaemia. The stress test is best done when the patient is clinically stable.

If the patient has classic symptoms of angina that have not settled with therapy, then angiography may be the preferred investigation.

Stress thallium or sestamibi

Ischaemia can be induced by bicycle or treadmill exercise, or using intravenous dipyridamole (Persantin) or intravenous dobutamine (Dobutamine Hydrochloride Injection, Dobutrex) in patients who are unable to exercise. Nuclear stress testing is more sensitive and specific than exercise ECG testing as both radiolabelled thallium (thallium-201) and sestamibi (technetium-99m) allow an assessment of myocardial perfusion and are able to assess the site and extent of the region of ischaemia.

Nuclear testing is also useful in patients who have resting ECG changes where the diagnostic value of a stress ECG alone is limited.

Table 1. Classification of acute coronary syndromes[2]

	Unstable angina		Myocardial infarction	
	Low risk	**High risk ('minor myocardial damage')**	**Non-ST elevation**	**ST elevation**
Troponin	Not detectable	Detectable (+)	Detectable (++)	Detectable (+++)
Creatine kinase	Normal	Normal	Elevated (+)	Elevated (++)
ECG at evaluation	Normal	ST depression or transient ST elevation	ST depression or transient ST elevation	ST elevation
ECG at discharge	No Q wave	No Q wave	No Q wave	May be a Q wave
Mortality	→			

Table 2. Risk stratification of unstable angina[2]

High risk features

- Prolonged (>10 minutes) 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)

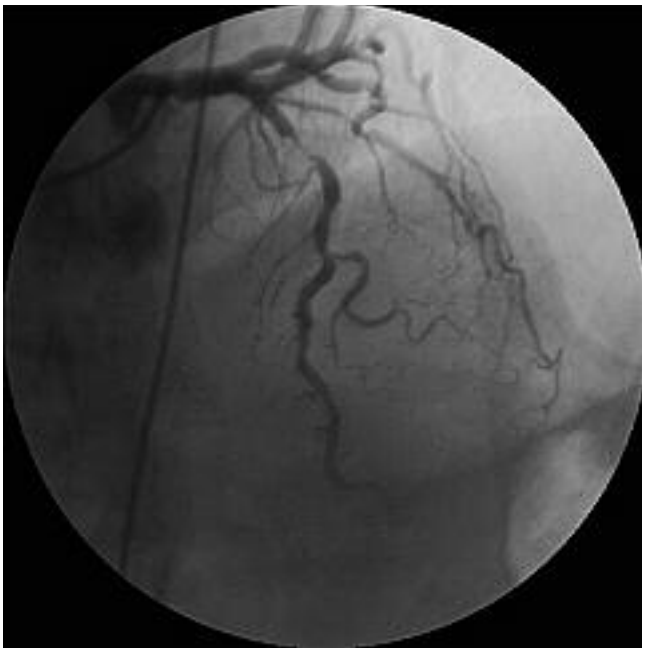
Intermediate risk features

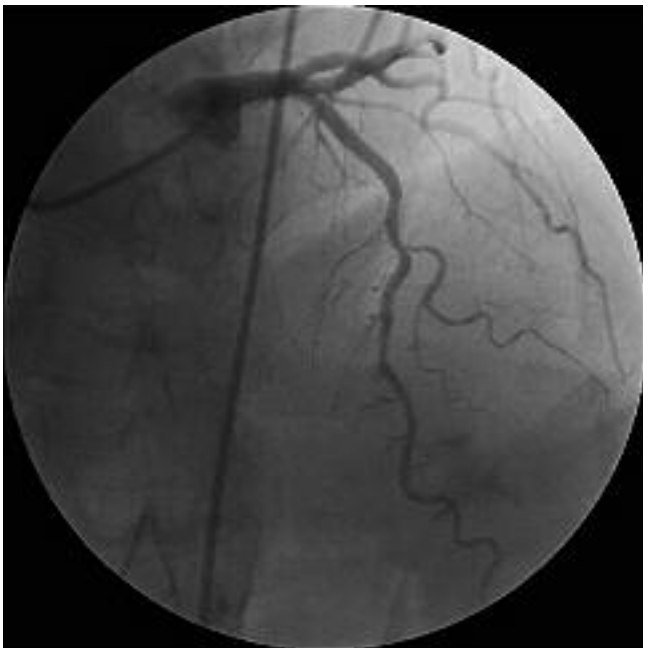
- Prolonged but resolved chest pain/discomfort
- Nocturnal pain
- New onset grade III or IV chest pain in the previous two weeks*
- Age >65 years
- History of MI or revascularisation
- ECG normal or pathological Q waves
- No significant (<0.5 mm) ST deviation, or minor T wave inversion in fewer than 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. *Circulation* 1976; 54: 522-523.)





Figures 1a and b. Coronary angiograms before (a, left) and after (b, right) a successful angioplasty and stenting procedure to a tight proximal stenosis in the left anterior descending coronary artery.

Stress echocardiogram

A stress echocardiogram assesses the development of wall motion abnormalities with exercise, or by the use of intravenous dobutamine, to confirm the site and extent of ischaemia. Sensitivity and specificity are similar to stress thallium.

Coronary angiography

Coronary angiography is an invasive test that defines the coronary anatomy and the extent and severity of coronary artery disease. It helps to direct the best interventional therapy in appropriate patients – either percutaneous transluminal coronary angioplasty (PTCA) with or without stenting or coronary artery bypass grafting (CABG; Figures 1a and b). In some patients, ongoing medical therapy may be the best alternative.

Coronary angiography should be performed in most high risk patients and also in intermediate risk patients who have a significantly positive stress study or who have ongoing symptoms on medical therapy (see the flowchart on page 42).[2]

Management

Patients with unstable angina will usually require referral for rapid diagnosis and appropriate management. At the time of presentation to the GP, the patient should receive soluble aspirin 300 mg orally (if not already on aspirin) and be started on beta blockers (or nondihydropyridine calcium channel blockers such as verapamil or diltiazem if beta blockers are contraindicated), plus oral or topical nitrates (Table 3). If the patient is hospitalised, heparin should be commenced, plus intravenous glyceryl trinitrate (Glyceryl Trinitrate for Injection).

If the patient has ongoing angina, the addition of intravenous IIb/IIIa receptor antagonists or oral clopidogrel (Iscover, Plavix) should be considered, plus calcium channel blockers or nicorandil (Ikorel). Dihydropyridine calcium channel blockers are best used with concomitant beta blocker therapy.

Following initial stabilisation with drug therapy, an early decision should be made as to the need for medical therapy alone, non-invasive testing (stress ECG, stress thallium or stress echocardiography) or early coronary angiography and/or coronary intervention (see the flowchart on page 42).

In high risk patients, an early aggressive approach is indicated if clinically appropriate. These patients should have early coronary angiography with a view to PTCA or CABG.

Medical therapy

Antiplatelet agents

- **Aspirin.** Aspirin acts as a cyclo-oxygenase inhibitor, preventing platelet synthesis of thromboxane A2, and also helps to stabilise the coronary plaque. It has been shown to be highly effective in unstable angina, reducing the risk of acute myocardial infarction or death by about 50%.[6]
- **Clopidogrel.** An ADP receptor antagonist, clopidogrel is useful as an aspirin substitute when aspirin is contraindicated. It has also been shown to be beneficial when combined with

aspirin in acute coronary syndromes (the Clopidogrel in Unstable angina to prevent Recurrent Events [CURE] study).[7]

- **Glycoprotein IIb/IIIa receptor antagonists.** Antagonists acting at the glycoprotein IIb/IIIa receptor on the platelet surface, the final common pathway to induce platelet aggregation, are very useful agents in patients with acute coronary syndromes. Currently they are only available as intravenous agents, all oral compounds tested to date having not proven beneficial. Tirofiban (Aggrastat), a nonpeptide small molecule, is a valuable agent in unstable angina patients who do not settle on conventional therapy. The Platelet Receptor Inhibition in ischemic Syndrome Management (PRISM) and Platelet Receptor Inhibition in ischemic Syndrome Management in Patients Limited by Unstable Signs and symptoms (PRISM-PLUS) studies showed that tirofiban significantly reduced the primary composite endpoints of death, nonfatal myocardial infarction and refractory ischaemia at seven days.[8,9] In patients aged less than 65 years, 8.5% of patients on tirofiban, heparin and aspirin achieved this endpoint, compared with 12.4% of those on heparin and aspirin; respective figures for patients aged over 65 years were 17.8% and 23.5%. Tirofiban is also useful for stabilising patients awaiting coronary intervention, particularly when they are in a rural or non-interventional centre awaiting transfer. Abciximab (ReoPro), a murine monoclonal Fab antibody fragment, reduces complications during coronary angioplasty and stenting procedures in patients with unstable angina. It has been shown to be superior to tirofiban when given for the first time during coronary interventional procedures (the do Tirofiban And ReoPro Give similar Efficacy Trial [TARGET]).[10]

Heparin

- **Unfractionated heparin.** Although of value in acute coronary syndromes when combined with aspirin, the use of unfractionated heparin has reduced recently because of the increased use of low molecular weight heparin (LMWH).[11] Unfractionated heparin still has advantages in patients in whom early or acute intervention is planned, as its effects can be acutely reversed with protamine (Protamine Sulphate Injection BP) if required. It may be easier to monitor dosage with unfractionated heparin than with LMWH in those patients with impaired renal function as LMWH has a prolonged half-life in such patients.
- **Low molecular weight heparins.** The major action of LMWHs is against factor Xa, compared with unfractionated heparin's action against both factor Xa and thrombin. LMWHs have a greater bioavailability than unfractionated heparin and have the convenience of administration by twice daily subcutaneous injections, without the need for blood monitoring in most cases. Studies have shown equivalence for dalteparin (Fragmin) and superiority with enoxaparin (Clexane), compared with intravenous unfractionated heparin.[11]

Beta blockers

Beta blockers reduce myocardial work by slowing the heart rate and the force of the myocardial contraction, thereby reducing myocardial oxygen demand. They are helpful in reducing symptoms and in reducing progression to infarction, but have not been shown to reduce mortality in this setting. They may be given orally or intravenously, but are contraindicated in patients with significant atrio-ventricular block (marked 1st degree, or 2nd or 3rd degree heart block), severe airways disease (particularly if bronchospasm is present), bradycardia, hypotension or uncontrolled cardiac failure.

Nitrates

Nitrates predominantly reduce myocardial preload and have a lesser reduction on afterload. Left ventricular end diastolic pressure is lowered and there is a direct effect on dilating coronary vessels to improve subendocardial blood flow and improve collateral flow. Angina symptoms are improved, but there is no evidence for improved mortality. These agents may be given sublingually, orally, transdermally or intravenously. The major disadvantages are headaches and the development of tolerance with continual use.

Nicorandil is a newer agent with nitrate-like properties but which also acts as a potassium channel opener. It has been shown to improve symptoms in unstable angina and has the advantage over other nitrates of fewer problems with tolerance.[12]

Table 3. Unstable angina: medical management

Presentation

- Soluble aspirin 300 mg
- Beta blockers (nondihydropyridine calcium channel blockers if beta blockers are contraindicated)
- Nitrates (topical or oral)

Hospitalisation

- Intravenous unfractionated heparin or subcutaneous low molecular weight heparin
- Intravenous glyceryl trinitrate

Ongoing angina in hospital (one or more episodes)

- Intravenous glycoprotein IIb/IIIa receptor antagonists
- Clopidogrel orally
- Calcium channel blocker added to beta blocker
- Nicorandil
- Perhexiline

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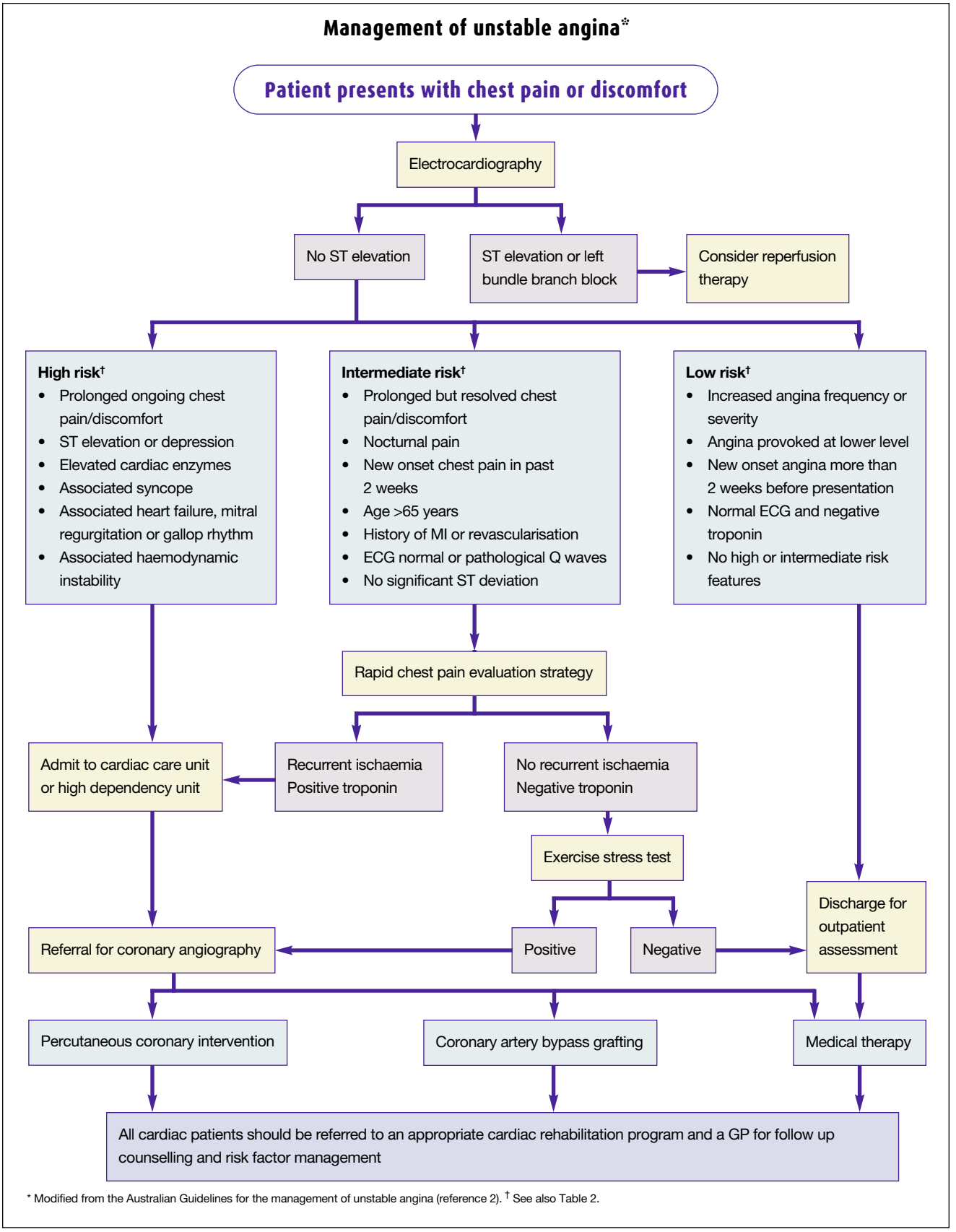

* Modified from the Australian Guidelines for the management of unstable angina (reference 2). † See also Table 2.

Perhexiline

Perhexiline (Pexsig) is thought to act by causing ischaemic tissues to shift from fatty acid to glucose metabolism. Its major use is in severe refractory angina that is unsuitable for revascularisation and does not settle on other drug therapy.

Interventional therapy

The Fragmin and fast Revascularisation during Instability in Coronary artery disease II trial (FRISC II) showed that early coronary angiography, after at least two days of treatment with dalteparin, followed by coronary intervention with PTCA or CABG, was of significant benefit in patients with unstable coronary artery disease and ECG changes or raised cardiac enzymes, when compared with a conservative treatment group.[13]

In this trial, 1222 of the 2457 patients entered were randomised to the invasive regimen. At 12 months, 78% of the invasive group had undergone revascularisation (44% PTCA with 62% receiving coronary stents, and 38% CABG). This group had a lower mortality (2.2% *v.* 3.9%), lower incidence of acute myocardial infarction (8.6% *v.* 11.6%) and lower readmissions (37% *v.* 57%), compared with a conservatively managed group. It is of interest that by 12 months of follow up, 52% of the conservative group had received coronary angiography with 43% of these proceeding to an interventional procedure.

Management in rural setting

Acute intervention for coronary disease patients is not usually immediately available in most rural settings. Management should initially be with the medical regimens outlined above, with high risk or poorly controlled patients being started on an intravenous infusion of tirofiban before their early transfer to an interventional centre.

Follow up

The management of patients after discharge should be shared by the GP and the cardiologist. The possible complications of coronary intervention – acute stent or graft closure, wound infection, pleural effusion, for example – require early detection and treatment, and should be looked for.

In addition, control of risk factors (such as hyperlipidaemia, cigarette smoking, hypertension, diabetes, obesity and sedentary lifestyle) through modification of lifestyle and pharmacological measures is important in reducing any ongoing symptoms and future cardiovascular events.

Conclusion

The management of unstable angina has undergone many changes recently, with management now directed by patient risk stratification. In high risk patients an aggressive approach is required with early investigation and revascularisation leading to reduced cardiac events and hospital readmissions. New drug therapy has helped in patient stabilisation, reducing cardiac events and reducing complications during coronary angioplasty and stenting procedures. MT

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