Guideline Addendum

2011 Addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand Guidelines for the Management of Acute Coronary Syndromes (ACS) 2006

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About This Addendum

This addendum summarises clinical trial evidence published since 2007 that is relevant to the recommendations contained in the Heart Foundation's *Guidelines for the management of acute coronary syndromes 2006* [1] (2006 Guidelines) and *2007 addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand Guidelines for the management of acute coronary syndromes 2006* [2] (2007 Addendum). These recommendations are directed at the management of patients with spontaneous acute coronary syndromes, rather than those occurring as a result of other conditions (e.g. anaemia or thyrotoxicosis) where management may be directed at the underlying cause.

Grades of recommendation and levels of evidence are indicated according to current National Health and Medical Research Council classifications (Tables 1 and 2) [3]. In addition, consensus recommendations have been made where there is insufficient evidence on which to base a grading.

When applying this information, clinicians should consider the context and circumstances of the individual patient and the clinical setting.

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Investigations: Serum Troponin Measurement (2006 Guidelines Pages S12–S13)

Important Recent Findings

EARLY DETECTION OF MYOCARDIAL INFARCTION. New improved assays of cardiac troponins T (TnT) and I (TnI) show acceptable analytical precision at levels 10- to 100-fold lower than conventional assays. The superior performance of these "high sensitivity" assays for early detection of myocardial infarction (MI) has been confirmed in large clinical trials [4–6].

A study of 1818 consecutive patients with chest pain reported that a single test at presentation to the emergency department (ED) was highly accurate for the diagnosis of MI (area under the receiver-operating-characteristic curve [AUC] 0.96) when using a sensitive TnI assays, compared with conventional assays (AUC 0.85) [5].

A study in patients with a confirmed diagnosis of non-ST elevation myocardial infarction (NSTEMI) demonstrated that serial sampling using a high sensitivity TnT assay enabled possible earlier diagnosis. Amongst patients with a negative test on admission using conventional fourth-generation TnT testing, two-thirds tested positive on the high sensitivity test. Compared with the conventional assay, the high sensitivity assay identified 20% more patients with a final diagnosis of NSTEMI [7].

SENSITIVITY AND SPECIFICITY. The new high sensitivity assays achieve increased sensitivity in early diagnosis at the cost of reduced specificity [5,6,8,9]. The cumulative sensitivity of a sensitive TnI for the diagnosis of acute MI, using a

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Table 1. *Summary of Recommendations.*

Recommendation	Grade	Level
Investigations: serum troponin measurement		
Where available, high sensitivity troponin assays should be used in preference to conventional assays.	N/A	N/A
When using high sensitivity troponin assay, a test should be interpreted as positive if level is ≥99th centile for reference population OR there is a change of >50% above an initial baseline level. A positive finding should be followed up by a search for an alternative plausible diagnosis and/or cardiac consultation if ACS is suspected.	Consensus	N/A
At 3 hours after presentation (with at least one assay performed >6 hours from symptom onset), a test using a high sensitivity troponin assay should be interpreted as negative if the level is <99th percentile AND change from baseline is <50%. A negative test in this circumstance may be used in an 'early rule-out ACS' strategy to enable earlier functional or anatomic testing for symptomatic coronary artery disease.	C	III
If the local pathology laboratory cannot provide troponin results within 60 min, point-of-care testing should be performed.	N/A	N/A
Choice of reperfusion therapy for STEMI		
Consider early routine angiography and revascularisation amongst patients receiving fibrinolysis, regardless of the success of pharmacologic reperfusion.	A	I
Antiplatelet therapies should be continued for 12 months after the insertion of drug-eluting stents.	A	II
The use of mechanical thrombectomy techniques to reduce thrombus burden during primary percutaneous coronary intervention (PCI) should be considered.	A	I
Antithrombotic therapy for STEMI		
Amongst patients with STEMI undergoing primary PCI, the use of bivalirudin can be considered as an alternative to heparin and GP IIb/IIIa inhibitors.	B	II
Amongst patients undergoing primary PCI for reperfusion for STEMI or revascularisation for ACS, a high-dose clopidogrel regimen (600 mg oral bolus and 150 mg daily for 7 days, then 75 mg/day for at least 12 months) should be considered.	B	II
In patients undergoing PCI, the use of a potent oral antiplatelet agent (prasugrel and ticagrelor) should be considered as an alternative to clopidogrel for subgroups at high risk of recurrent ischaemic events (e.g. those with diabetes, stent thrombosis, recurrent events on clopidogrel or a high burden of disease on angiography). Careful assessment of bleeding risk should be undertaken before using these agents.	B	II
Antithrombotic therapy for NSTEACS		
For all patients with high-risk NSTEACS, consider methods to reduce bleeding risk:	A	I
• Titrate antithrombotic agents to optimal dose for weight and renal function.	A	I
• Avoid upstream GP IIb/IIIa inhibitors unless there is recurrent ischaemia on standard medical therapy.	B	II
• Consider radial access in preference to femoral access for PCI, but be mindful that this may be used as a conduit for surgery (CABG).	B	III
• During PCI, avoid right heart catheterisation and intra-aortic balloon pulsation unless indicated, and avoid prolonged procedure times.	C	III
For all patients with high-risk NSTEACS, assess bleeding risk individually according to the number and severity of bleeding risk factors.	A	II
Use a standard management strategy for patients at low risk of bleeding:		
• Choose the most effective antithrombotic regimen (e.g. prasugrel or ticagrelor)	A	I
• Use fast-acting agents or multiple agents, as required, to control ischaemia rapidly.	B	II
Use a 'priority low-bleeding' strategy in patients at high risk of bleeding:	B	II
• Use antithrombotic agents with a lower bleeding risk, e.g.:		
– clopidogrel in preference to prasugrel		
– (in context of a non-invasive strategy) fondaparinux in preference to enoxaparin		
– (in context of an invasive strategy) bivalirudin in preference to enoxaparin.		
• Minimise the number of agents used.		
• When additional agents are needed, consider substituting rather than adding them.		
• Consider shorter-acting or reversible agents, e.g. bivalirudin.		
• Avoid the use of GP IIb/IIIa inhibitors, if possible.		
Bleeding risk in ACS		
The following risk factors should be considered when assessing bleeding risk and when choosing anti-thrombotic therapies in patients with ACS:	B	II
• age >75 years		
• female sex		
• history of bleeding		
• history of stroke or TIA		
• creatinine clearance rate <60 mL/min		
• diabetes		
• heart failure		
• tachycardia		
• blood pressure <120 mmHg or hypertension >180 mmHg		

Table 1 (*Continued*).

Recommendation	Grade	Level
• peripheral vascular disease • anaemia • concomitant use of a GP IIb/IIIa inhibitor • administration of enoxaparin 48 hours prior to intervention • switching between UF heparin and enoxaparin • procedural factors associated with increased risk (femoral artery versus radial artery access, prolonged procedure, intra-aortic balloon pulsation, right heart catheterisation). • low body weight <60 kg		
Oxygen therapy for patients with ACS		
The routine use of supplemental oxygen is not recommended.	C	I
Oxygen therapy is indicated for patients with hypoxia (oxygen saturation <93%) and those with evidence of shock, to correct tissue hypoxia. In the absence of hypoxia, the benefit of oxygen therapy is uncertain, and in some cases oxygen therapy may be harmful.	Consensus	N/A
System factors		
System-based approaches to deliver timely reperfusion should be undertaken at local level. Establishment of clinical networks and efficient protocols to maximise the proportion of patients receiving timely reperfusion should be considered.	B	III-1
Routine audit should be integrated into all clinical services that provide care to patients with ACS.	B	III
In the absence of ready access to primary PCI services, systems should be developed to train local general practitioners and other health workers to initiate fibrinolysis in patients with STEMI, to maintain practitioners' skills, and to ensure practitioners are supported by ready access to expert cardiology consultation.	N/A	N/A

Table 2. *Grades of Recommendation [3].*[a]

A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution
N/A	Not applicable – recommendation cannot be graded

[a] See Appendix A for levels of evidence hierarchy.

cut-off value of 99th centile (0.07 μg/L), has been reported as 93% at 30 min after presentation, 98% at 2 hours, and 100% at 3 hours, with a specificity of 57% at 2 hours and 54% at 3 hours [8]. Another retrospective study found that acceptable accuracy for the diagnosis of acute MI was achieved with a sensitive TnI test (positive test defined as >99th centile = 0.04 μg/L) using serial specimens at least 3 hours apart or one specimen at least 6 hours from onset of symptoms [9].

These data suggest that, when using a sensitive TnI assays, results from either two specimen sets at least 3 hours apart (with one at least 6 hours from pain onset), or one specimen at least 6 hours after onset for patients who present late, are sufficient to provide high accuracy for ruling out MI.

It should also be noted that troponin elevation has also been reported in a variety of non-ischaemic conditions (Table 3) [10]. Therefore the use of a 99th centile cut-off value will not only identify patients with coronary heart disease, but also patients in whom the aetiology of cardiac injury is unclear [11]. Troponin results should be interpreted within the context of the entire clinical presentation with consideration of the diagnostic possibilities listed in Table 3.

INTERPRETING SERIAL TEST RESULTS. The National Academy of Clinical Biochemistry Laboratory Medicine recommends that a >20% increase from baseline troponin suggests evolving MI, whilst a 20% decrease suggests resolving MI [13]. Accordingly, recent consensus guidelines [13–15] recommend that, in patients who present with ischaemic

Table 3. *Elevations of Troponin in the Absence of Overt Ischaemic Heart Disease [12].*

- Cardiac contusion, or other trauma including surgery, ablation, pacing, etc.
- Congestive heart failure—acute and chronic
- Aortic dissection
- Aortic valve disease
- Hypertrophic cardiomyopathy
- Tachy- or bradyarrhythmias, or heart block
- Apical ballooning syndrome
- Rhabdomyolysis with cardiac injury
- Pulmonary embolism, severe pulmonary hypertension
- Renal failure
- Acute neurological disease, including stroke or subarachnoid haemorrhage
- Infiltrative diseases, e.g. amyloidosis, haemochromatosis, sarcoidosis, and scleroderma
- Inflammatory diseases, e.g. myocarditis or myocardial extension of endo-/pericarditis
- Drug toxicity or toxins
- Critically ill patients, especially with respiratory failure or sepsis
- Burns, especially if affecting >30% of body surface area
- Extreme exertion

symptoms or electrocardiogram (ECG) changes, the diagnosis of MI requires both an elevation of troponin levels above the 99th centile and a >20% change (rise and/or fall) in troponin level when using older troponin assays.

However, a recent study in healthy individuals demonstrated intra-individual variation of 46% between samples taken hours or weeks apart [16]. Therefore, the minimum change in troponin levels that represents a clinically meaningful finding may actually be greater than the 20% cited in current guidelines. Hence, clear documentation of the type of troponin assay being used is necessary.

Diagnostic thresholds have not yet been defined according to outcome data and there are currently no data clearly demonstrating the amount of change between serial assays that accurately identifies MI and balances sensitivity and specificity. Nevertheless, a rising troponin level on serial testing suggests that evolving MI or other significant pathology cannot be excluded and further investigations may be required. Confirmation of the diagnosis of MI will often require troponin interpretation in the context of entire clinical presentation and additional cardiac tests. The finding of stable troponin concentrations (e.g. no change during a period of more than 24 hours) suggests that the presence of troponin is due to chronic disease such as renal failure, heart failure, sepsis or myocarditis. These guidelines will be updated when further information regarding the link between serial troponin testing and outcomes are established.

RECOMMENDED PROTOCOL FOR TROPONIN TESTING USING HIGH SENSITIVITY ASSAYS IN "RULING-OUT" ACS. All patients with a suspected ACS should undergo troponin testing on arrival at ED to 'rule in' ACS within the differential diagnosis (Fig. 1):

- For a patient with a positive troponin result or a change in troponin levels over time, neither ACS nor other significant pathology (e.g. pulmonary embolus, aortic dissection, and sepsis, see Table 3) can be excluded. These patients are at higher risk of subsequent events. A positive result should be considered within the entire clinical context (history, examination, ECG findings and other investigations). Further investigations directed at all plausible clinical diagnoses should be considered and, if ACS is thought to be the likely cause, these patients may require cardiology assessment.
- All patients with a negative result should undergo repeat testing 3–4 hours later.

The testing interval to 'rule out' MI may be reduced to 3 hours, provided that one sample is taken at least 6 hours after symptom onset:

- Patients with a negative result at 3 hours after presentation and at least 6 hours after the onset of pain should be considered for early assessment by non-invasive anatomic or functional testing, as determined by local availability.
- For patients presenting more than 6 hours after pain onset, a single high sensitivity troponin assay is sufficient to rule out myocardial infarction.

Implications of the Findings

Previous recommendations

The 2006 Guidelines advised that serum troponin levels be measured on admission to the ED. This recommendation still applies.

The 2006 Guidelines recommended that, if the initial troponin test is negative, it should be repeated at least 8 hours after the last episode of pain or other symptoms of coronary insufficiency. (When used in this way, troponin assays have a high sensitivity for detecting MI, but levels may be normal in other presentations of ACS.) This recommendation still applies when using standard-sensitivity troponin assays.

New recommendations

1. Where available, high sensitivity troponin assays should be used in preference to conventional assays. [Grade of recommendation N/A]
2. When using high sensitivity troponin assays for the identification of patients at increased risk (see *Recommended protocol*):
   - A test should be interpreted as positive if level is ≥99th centile for reference population OR there is a change of >50% above an initial baseline level. A positive finding identifies patients at increased risk, but does not provide definitive evidence of MI. A positive troponin result should be followed up by a search for an alternative plausible diagnosis and/or cardiac consultation if ACS is suspected in the context of the clinical presentation. [Consensus recommendation]
   - At 3 hours after presentation, a test should be interpreted as negative if level is <99th percentile AND change from baseline is <50% (with at least one of these assays having been performed >6 hours from symptom onset). A negative test in this circumstance may be used in an 'early rule-out ACS' strategy to enable earlier functional or anatomic testing for symptomatic coronary artery disease. [Grade C recommendation; Evidence level III]
3. If the local pathology laboratory cannot provide troponin results within 60 min, point-of-care testing should be performed. [Grade of recommendation N/A]

High sensitivity troponin assays have an *increased sensitivity* for the detection of "myonecrosis", but a *reduced specificity* for the diagnosis of "MI". A positive result (≥99th centile for reference population OR where there is a change of >50% above an initial baseline level) should be interpreted in the context of the entire clinical presentation and does not necessarily represent an indication for coronary angiography. In addition to the alternative diagnoses presented in Table 3, the management MI secondary to other conditions (e.g. anaemia, thyrotoxi-

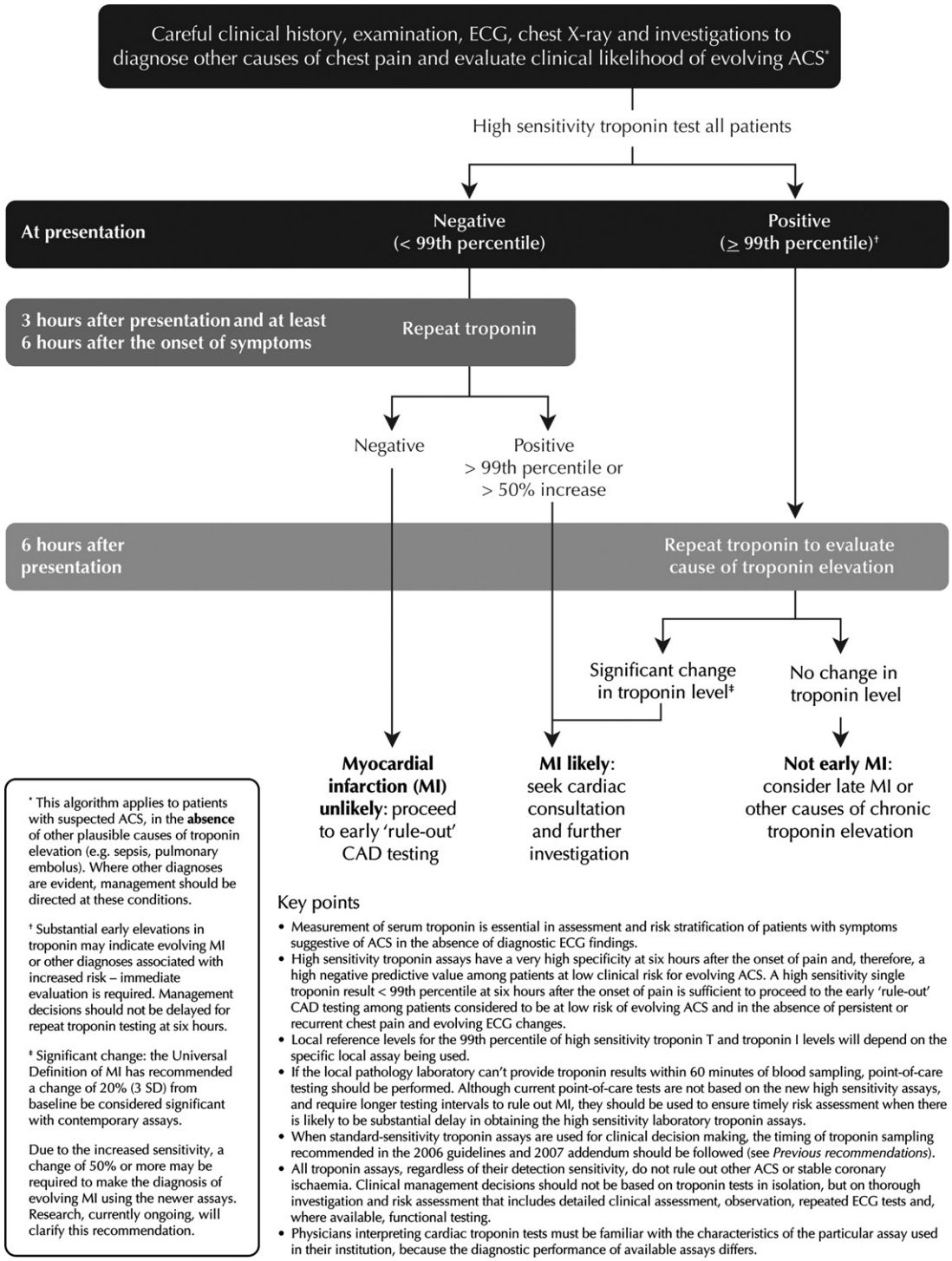

Figure 1. *Algorithm for incorporating a high sensitivity troponin into the work-up of patients with suspected acute coronary syndromes (ACS).*

cosis, and sepsis) should be primarily directed at those conditions.

The finding of troponin concentrations that remain stable over time suggests that the presence of troponin is due to chronic disease. Acute exacerbations of chronic disease that result in elevated troponin levels can mimic an MI release pattern [16].

Choice of Reperfusion Therapy for STEMI (2006 Guidelines Pages S14–S20)

Important Recent Findings

REPERFUSION STRATEGY. Accumulating evidence supports reduction in delays to primary percutaneous coronary intervention (PCI) for patients with ST-elevation MI

(STEMI) through ambulance triage and early activation of the catheterisation laboratory. Several recent studies support the implementation of a pharmaco-invasive strategy for patients presenting to centres without primary PCI capacity. In patients with STEMI and high risk features including extensive elevation, or Killip class ≥2, treatment with fibrinolysis, followed by routine early coronary angiography and PCI with intra-procedural glycoprotein (GP) IIb/IIIa inhibition, was associated with reductions in the combined endpoint of recurrent MI and recurrent ischaemia and the combined endpoint of death and recurrent MI, but not mortality alone, compared with standard treatment in the NORDICSTEMI,[1] CARESS-AMI[2] and TRANSFER-AMI[3] studies [17–20]. Overall, no increase in major bleeding or stroke was seen.

Emerging data suggest superior outcomes for primary PCI compared with fibrinolysis amongst the very elderly. In the relatively small TRIANA[4] study in patients with STEMI aged more than 80 years in whom reperfusion was considered appropriate, primary PCI was associated with a lower rate of the combined endpoint of death, MI and stroke, but not mortality alone, compared with fibrinolysis [21].

Implications of the Findings

Previous recommendations

The 2006 Guidelines indicated that undertaking immediate PCI after full-dose fibrinolysis, regardless of reperfusion status (also known as facilitated PCI) could not be recommended at the time of writing.

New recommendations

1. Consider early routine angiography and revascularisation amongst patients receiving fibrinolysis, regardless of the success of pharmacologic reperfusion. [Grade A recommendation, Evidence level I]
2. Antiplatelet therapies should be continued for 12 months for all stented patients. [Grade A recommendation, Evidence level II]
3. The use of mechanical thrombectomy techniques to reduce thrombus burden during primary PCI should be considered. [Grade A recommendation, Evidence level I]

MODIFICATIONS TO PRIMARY PCI TECHNIQUE. Data from the HORIZONS-AMI[5] randomised trial and large Swedish Coronary Angiography and Angioplasty Registry (SCAAR) do not confirm that the use of drug-eluting stents is associated with an increased risk of late clinical events within the context of primary PCI for STEMI [22,23].

Accumulating evidence supports the use of mechanical thrombectomy techniques prior to balloon inflation and stent placement in patients undergoing primary PCI. A recent meta-analysis of eleven trials comparing standard PCI with or without thrombectomy found that those receiving thrombectomy experienced a significantly lower rate of death and recurrent MI [24].

Antithrombotic Therapy for STEMI (2006 Guidelines Page S14, 2007 Addendum Pages 302–303)

Important Recent Findings

BIVALIRUDIN. The HORIZONS-AMI study in patients with STEMI undergoing PCI found that anticoagulation with bivalirudin was associated with a reduction in major bleeding events, compared with heparin plus GP IIb/IIIa inhibition [25]. A reduction in 30-day mortality was also seen in the bivalirudin group compared with the group receiving heparin plus GP IIb/IIIa inhibition (2.1% versus 3.1%, $P = 0.048$) [25].

However, a small increase in early (24 hours) stent thrombosis was observed in the bivalirudin group [25], indicating the need for early initiation of high-dose antiplatelet therapy and highlighting a potential role for more potent oral agents (see below). These data reinforce the need for thorough consideration of bleeding risk when considering pharmacotherapy options amongst patients undergoing primary PCI.

EARLY ANTITHROMBOTIC THERAPY. Amongst patients undergoing cardiac catheterisation procedures, there is accumulating evidence that those who commence GP IIb/IIIa inhibition prior to transfer to the catheterisation laboratory show improved angiographic outcomes at the time of the procedure. In the On-TIME 2[6] study in patients with STEMI undergoing primary PCI, early antithrombotic therapy was also associated with reductions in all-cause mortality at 12 month follow-up [26].

CARDIOGENIC SHOCK AND CARDIAC ARREST. In the PRAGUE-7[7] study, the administration of GP IIb/IIIa inhibition was of little benefit in patients with cardiogenic shock [27]. Similarly, amongst patients in cardiac arrest, thrombolytic therapy is not associated with improved outcomes [28]. However, amongst patients with resuscitated cardiac arrest, where there is evidence of ST-elevation or new bundle branch block, emergent reperfusion should be considered [28].

[1] Norwegian Study on District Treatment of ST-elevation Myocardial Infarction.
[2] Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction.
[3] Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction.
[4] Thrombolysis Versus Primary Angioplasty for AMI in Elderly Patients.
[5] Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction.
[6] Ongoing Tirofiban In Myocardial Infarction Evaluation 2.
[7] Routine Upfront Abciximab Versus Standard Peri-Procedural Therapy in Patients Undergoing Percutaneous Coronary Intervention for Cardiogenic Shock.

HIGH-DOSE CLOPIDOGREL. The CURRENT-OASIS 7[8] study in patients with ACS reported that high-dose clopidogrel (600 mg oral bolus and 150 mg/day for 7 days, then 75 mg/day) was associated with a reduction in ischaemic events in the subgroup who underwent PCI [29]. These benefits were not observed amongst those patients receiving conservative therapy [29]. In the non-randomised HORIZONS-AMI study in patients with STEMI undergoing primary PCI, a 600 mg loading dose of clopidogrel was associated with an approximately 50% reduction in the rate of stent thrombosis, compared with a 300 mg clopidogrel loading dose [30].

PRASUGREL AND TICAGRELOR. In the TRITON-TIMI 38[9] study in patients with STEMI undergoing primary PCI, antiplatelet treatment with prasugrel (a rapid-onset antagonist of platelet adenosine diphosphate $P2Y_{12}$ receptors) was associated with a reduction in the combined endpoint of cardiovascular death, myocardial infarction or stroke at 30-day and 15-month follow-up [31]. Benefits were apparent regardless of the use of GP IIb/IIIa inhibitors. The rate of bleeding events was not increased in the prasugrel treatment group at 30 days. Similarly, the PLATO[10] study reported that ticagrelor (a reversible oral $P2Y_{12}$ inhibitor) was superior to clopidogrel in patients admitted to hospital with ACS with or without ST elevation [32].

These data suggest that the use of prasugrel or ticagrelor should be considered for high-risk subgroups including patients with diabetes, stent thrombosis, recurrent events on clopidogrel or a high burden of disease on angiography. However, subgroup analysis of trial data suggests that the long-term use of prasugrel or ticagrelor should be considered carefully in patients at increased risk of bleeding (e.g. those aged >75 years, patients with prior stroke or transient ischaemic attack [TIA] and those with body weight <60 kg) as seen with prasugrel treated patients in the TRITON TIMI-38 study) [32,33].

Antithrombotic Therapy for NSTEACS (2006 Guidelines Page S22, 2007 Addendum Page 303)

Important Recent Findings

FONDAPARINUX. In the large OASIS-5[11] clinical trial in patients with high-risk non-ST-segment-elevation ACS (NSTEACS), fondaparinux significantly reduced the rates of major bleeding and the composite endpoint of death, myocardial infarction, stroke and major bleeding, compared with enoxaparin [34]. However, further analysis of these results [35] revealed that the benefits of fondaparinux over enoxaparin were restricted to the subgroup patients with the lowest quartile of renal function, suggesting that excess bleeding associated with enoxaparin in this group may have led to this difference in outcome.

Implications of the Findings

Previous recommendations

The 2006 Guidelines recommended that:

- antithrombin therapy with unfractionated (UF) heparin should be used in conjunction with PCI and fibrinolysis for patients with STEMI.
- it is reasonable to use abciximab with primary PCI,
- glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors should not be used with full or reduced doses of fibrinolytic therapy.

The 2007 Addendum recommended that enoxaparin and fondaparinux were appropriate antithrombin agents for use in patients with STEMI.

New recommendations

1. Amongst patients with STEMI undergoing primary PCI, the use of bivalirudin can be considered as an alternative to heparin and GP IIb/IIIa inhibitors. [Grade B recommendation; Evidence level II]
2. Amongst patients undergoing primary PCI for reperfusion for STEMI or revascularisation for ACS, a high-dose clopidogrel regimen (600 mg oral bolus and 150 mg daily for 7 days, then 75 mg/day for at least 12 months) should be considered. [Grade B recommendation, Evidence level II]
3. In patients undergoing PCI, the use of an oral antiplatelet agent (prasugrel and ticagrelor) should be considered as an alternative to clopidogrel for subgroups at high risk of recurrent ischaemic events (e.g. those with diabetes, stent thrombosis, recurrent events on clopidogrel or a high burden of disease on angiography). Careful assessment of bleeding risk should be undertaken before using these agents. [Grade B recommendation; Evidence level II]

EPTIFIBATIDE. In the large EARLY ACS[12] clinical trial in patients with high-risk NSTEACS, routine early treatment with eptifibatide did not improve overall efficacy, but was associated with increased rates of major bleeding and transfusion [36].

BIVALIRUDIN. In the large ACUITY[13] clinical trial in patients with ACS, bivalirudin reduced rates of major bleeding, compared with heparin or the combination of bivalirudin plus a GP IIb/IIIa inhibitor [37]. In the large ISAR-REACT 3[14] clinical trial in patients with stable or unstable angina undergoing PCI [38], bivalirudin reduced the rate of major bleeding, compared with UF heparin.

[8] Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions.
[9] Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis In Myocardial Infarction.
[10] Platelet Inhibition and Patient Outcomes.
[11] Organization to Assess Strategies in Acute Ischaemic Syndromes.
[12] Early Glycoprotein IIb/IIIa Inhibition in Non-ST-segment Elevation Acute Coronary Syndrome.
[13] Acute Catheterization and Urgent Intervention Triage strategy.
[14] Intracoronary Stenting and Antithrombotic Regimen—Rapid Early Action for Coronary Treatment.

PRASUGREL AND TICAGRELOR. The Triton-TIMI 38 study reported that, compared with clopidogrel, prasugrel was associated with a reduction in the combined endpoint of cardiovascular death, MI or stroke in patients with ACS scheduled for PCI, but at the cost of an increase in the rate of major bleeding [33]. Similarly, in the PLATO trial in patients admitted to hospital with ACS with or without ST elevation, ticagrelor was associated with a reduction in the composite endpoint of cardiovascular death, MI or stroke at 12 months, compared with clopidogrel [32]. However, the ticagrelor group showed higher rates of major bleeding not related to the coronary artery bypass graft procedure, which included cases of fatal intracranial bleeding [32].[15]

ENOXAPARIN. The SYNERGY[16] study reported that, compared with UF heparin, enoxaparin was associated with an increased rate of thrombolysis in myocardial infarction (TIMI) major bleeding amongst patients with high-risk NSTEACS [39].

Cross-over between enoxaparin and UF heparin was associated with increased bleeding in the SYNERGY study [39]. Crossover from heparin or enoxaparin to bivalirudin was associated with lower rates of bleeding than uninterrupted treatment with combined heparin and GP IIb/IIIa inhibitor in the ACUITY study [40].

DOSING ERRORS. Data from the CRUSADE[17] study demonstrated that dosing errors with antithrombotic agents are most common in the elderly, women and patients with chronic kidney disease. Failure to correct for weight and renal function may account for 15% of cases of major bleeding in patients with NSTEACS [41].

Implications of the Findings

Previous recommendations

The 2006 Guidelines recommended use of heparin or subcutaneous enoxaparin until angiography, or for 48–72 hours, for those with high-risk NSTEACS. The 2007 addendum indicated that fondaparinux and/or bivalirudin (both of which were then unlicensed for upstream therapy for NSTEACS), may be preferable alternatives to standard therapy with UF heparin or low-molecular-weight heparin (LMWH) with a GP IIb/IIIa inhibitor for patients with high-risk NSTEACS, particularly in patients with an increased risk of bleeding.

New recommendations

A new paradigm for the management of patients with high-risk NSTEACS is now recommended. Management decisions must take into consideration the balance between ischaemic and bleeding risk for the individual patient.

1. For all patients with high-risk NSTEACS, consider methods to reduce bleeding risk. [Grade A recommendation, Evidence level I]
   - Titrate antithrombotic agents to optimal dose for weight and renal function. [Grade A recommendation, Evidence level I]
   - Avoid upstream GP IIb/IIIa inhibitors unless there is recurrent ischaemia on standard medical therapy. [Grade B recommendation, Evidence level II]
   - Consider radial access in preference to femoral access for PCI, but be mindful that this may be used as a conduit for surgery (CABG). [Grade B recommendation, Evidence level III]
   - During PCI, avoid right heart catheterisation and intra-aortic balloon pulsation unless indicated, and avoid prolonged procedure times. [Grade C recommendation, Evidence level III]
2. For all patients with high-risk NSTEACS, assess bleeding risk individually according to the number and severity of bleeding risk factors (see *Bleeding risk in ACS*). [Grade A recommendation, Evidence level II]
3. Assign a management strategy according to assessed individual bleeding risk:

   Use a 'standard' strategy for patients at low risk of bleeding:
   - Choose the most effective anti-platelet regimen (e.g. prasugrel or ticagrelor). [Grade A recommendation, Evidence level I], and use fast-acting agents or multiple agents, as required, to control ischaemia rapidly. [Grade B recommendation, Evidence level II]

Use a 'priority low-bleeding' strategy in patients at high risk of bleeding:

- Use antithrombotic agents with a lower bleeding risk, e.g.:
  - clopidogrel in preference to prasugrel. [Grade B recommendation, Evidence level II]
  - (in the context of a non-invasive strategy) fondaparinux in preference to enoxaparin. [Grade B recommendation, Evidence level II]
  - (in the context of an invasive strategy) bivalirudin in preference to enoxaparin. [Grade B recommendation, Evidence level II]
- Minimise the number of agents used. [Grade B recommendation, Evidence level II]
- When additional agents are needed, consider substituting rather than adding them. [Grade B recommendation, Evidence level II]

[15] Use of long-acting potent antiplatelet agents (clopiodgrel, prasugrel and possibly ticagrelor) before the coronary anatomy has been defined should be weighed against the possible need for urgent CABG. Prediction of NSTEACS patients who will likely require urgent CABG is difficult, and strongly influenced by local practices.

[16] Superior Yield of the New strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa inhibitors.

[17] Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines.

(*Continued*)

- Consider shorter-acting or reversible agents, e.g. bivalirudin. [Grade B recommendation, Evidence level II]
- Avoid the use of GP IIb/IIIa inhibitors, if possible. [Grade B recommendation, Evidence level II]

Bleeding Risk in ACS (2006 Guidelines Pages S14, S16, S18–19)

Important Recent Findings

BLEEDING AND PROGNOSIS. Reducing bleeding has been shown to improve outcomes for patients with ACS and reduce costs. Major bleeding occurs in approximately 4.8% of patients with STEMI, 4.7% of patients with NSTEMI and 2.3% of patients with unstable angina [42]. It is associated with increased in-hospital mortality (estimated rates of 7.0–22.8% in patients with STEMI, 5.3–15.3% in patients with NSTEMI and 3.0–16.1% in patients with unstable angina). Major bleeding [43,44] and transfusion [45] are both strong predictors of mortality in ACS patients and are associated with an increase in risk that is comparable to recurrent myocardial infarction.

FACTORS ASSOCIATED WITH BLEEDING RISK. Older age, female sex, renal insufficiency, history of bleeding, right heart catheterisation and use of GPIIb/IIIa inhibitors were identified as independent risk factors for major bleeding in patients with ACS in the large Global Registry of Acute Coronary Events (GRACE) database [42]. Anaemia, creatinine clearance <60 mL/min, high ischaemic risk and hypertension were predictors of major bleeding in patients with ACS undergoing early invasive management in the ACUITY study [44]. An estimated 33% of patients with ACS have creatinine clearance <60 mL/min [46].

Access via the radial artery during PCI has been shown to reduce the rate of severe bleeding, compared with femoral artery access [47,48].

ASSESSMENT OF INDIVIDUAL BLEEDING RISK. An individual's risk of bleeding is correlated with the number of risk factors present. A greater weighting may be attributed to certain risk factors (e.g. recent history of bleeding, severe anaemia, or creatinine clearance <20 mL/min). Bleeding risk scores are evolving:

- A risk score for predicting major peri-procedural bleeding after PCI via the femoral approach, based on data from the REPLACE-2[18] study, includes age, sex, esti-

Table 4. *Integer-Based Risk Score for Non–CABG-Related Major Bleeding Within 30 Days of Patient Presentation With Acute Coronary Syndrome [51].*

Gender	Add to score	Total Score	Non-CABG major bleeding within 30 days (%)
Male	0	0	0.9
Female	8	5	1.6
Age (years)		10	2.8
< 50	0	15	4.7
50-59	3	20	7.9
60-69	6	25	12.9
70-79	9	*30*	20.4
≥ 80	12	35	30.7
Serum creatinine (mg/dl)		40	43.5
< 1.0	0		
1.0-	2		
1.2-	3		
1.4-	5		
1.6-	6		
1.8-	8		
≥ 2.0	10		
White blood cell count (giga/l)			
< 10	0		
10-	2		
12-	3		
14-	5		
16-	6		
18-	8		
≥ 20	10		
Anaemia			
No	0		
Yes	6		
Presentation			
STEMI	+ 6		
NSTEMI – raised biomarkers	+ 2		
NSTEMI – normal biomarkers	0		
Antithrombotic medications			
Heparin plus a GPI	0		
Bivalirudin monotherapy	-5		

*If patient is on bivalirudin alone rather than heparin plus glycoprotein IIb/IIIa inhibitor (GPI), the total score should be reduced by 5.

Table 5. *GRACE risk score for acute coronary syndromes (0–258) [12].*

	Points	Total points	Probability of in-hospital death (%)
Age (years)			
< 40	0	≤ 60	≤ 0.2
40–49	18	70	0.3
50–59	36	80	0.4
60–69	55	90	0.6
70–79	73	100	0.8
≥ 80	91	110	1.1
Heart rate (beats per min)		120	1.6
< 70	0	130	2.1
70–89	7	140	2.9
90–109	13	150	3.9
110–149	23	160	5.4
150–199	36	170	7.3
> 200	46	180	9.8
Systolic blood pressure (mm Hg)			
< 80	63	190	13
80–99	58	200	18
100–119	47	210	23
120–139	37	220	29
140–159	26	230	36
160–199	11	240	44
> 200	0	≥ 250	≥ 52
Creatinine (μmol/L)			
0–34	2		
35–70	5		
71–105	8		
106–140	11		
141–176	14		
177–353	23		
≥ 354	31		
Killip class			
Class I	0		
Class II	21		
Class III	43		
Class IV	64		
Other risk factors			
Cardiac arrest at admission	43		
Elevated cardiac markers	15		
ST segment deviation	30		

mated glomerular filtration rate (eGFR), pre-existing anaemia, and use of LMWH within 48 hours prior to PCI [49].

- A risk score for predicting bleeding in patients with NSTEACS, based on independent risk factors identified in the CRUSADE registry data, includes creatinine clearance rate, anaemia, female sex, tachycardia, hypotension or severe hypertension, heart failure, diabetes and peripheral vascular disease [50].

The use of clinical risk scores for both recurrent ischaemic events and bleeding events may assist in the individualisation of pharmacotherapies amongst patients with additional co-morbidities. Details of the GRACE risk score for recurrent ischaemic events and risk score for bleeding events derived from recent ACS trials are presented in Tables 4 and 5.

[18] Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events.

Oxygen Therapy for Patients with ACS (2006 Guidelines Pages S7, S11–12)

Important recent findings

Recent analyses have raised questions about the role of routine oxygen therapy within the first 24 hours of treatment for acute MI. A recent Cochrane meta-analysis [52] examining this question identified three trials with a total of 387 patients in whom 14 deaths occurred. The relative risk of death for those receiving oxygen therapy was 2.88 (95% CI 0.88–9.39) by intention-to-treat analysis and 3.03 (95% CI 0.93–9.83) amongst patients with confirmed acute MI. Whilst these findings suggest increased hazard, the analyses lacked adequate power to address the risks and benefits of oxygen therapy in acute MI. There is currently insufficient evidence to formulate clear recommendations about oxygen therapy [52]. Definitive trials are needed to answer this question.

There is a lack of evidence to support the routine use of oxygen therapy in patients presenting with potential or confirmed ACS. However, there is some evidence suggesting it may be harmful.

Implications of the Findings

Previous recommendations

The 2006 Guidelines specify the following contraindications to fibrinolysis based on bleeding risk:

- full-dose GP IIb/IIIa inhibitors with fibrinolytic therapy, particularly in the elderly
- active bleeding or bleeding diathesis (excluding menses)
- significant closed head or facial trauma within 3 months
- suspected aortic dissection (including new neurological symptoms)
- current use of anticoagulants (risk of bleeding is positively correlated with international normalised ratio)
- non-compressible vascular punctures
- recent major surgery (<3 weeks)
- traumatic or prolonged (>10 min) cardiopulmonary resuscitation
- recent (within 4 weeks) internal bleeding (for example, gastrointestinal or urinary tract haemorrhage)
- active peptic ulcer.

These contraindications still apply in addition to new recommendations.

New recommendations

1. The following risk factors should be considered when assessing bleeding risk and when choosing anti-thrombotic therapies in patients with ACS: [Grade B recommendation, Evidence level II]
   - age >75 years
   - female sex
   - history of bleeding
   - history of stroke or TIA
   - creatinine clearance rate <60 mL/min
   - diabetes
   - heart failure
   - tachycardia
   - blood pressure <120 mmHg or >180 mmHg
   - peripheral vascular disease
   - anaemia
   - concomitant use of a GP IIb/IIIa inhibitor
   - administration of enoxaparin 48 hours prior to intervention
   - switching between UF heparin and enoxaparin
   - procedural factors associated with increased risk (femoral artery versus radial artery access, prolonged procedure, intra-aortic balloon pulsation, right heart catheterisation).

Implications of the Findings

Previous recommendation

The 2006 Guidelines recommended administration of oxygen in transit and on arrival to hospital for patients with suspected ACS. This recommendation has been superseded.

New recommendation

1. The routine use of supplemental oxygen is not recommended. [Grade C recommendation, Evidence level I]
2. Oxygen therapy is indicated for patients with hypoxia (oxygen saturation <93%) and those with evidence of shock, to correct tissue hypoxia. In the absence of hypoxia, the benefit of oxygen therapy is uncertain, and in some cases oxygen therapy may be harmful. [Consensus recommendation]

System Factors (2006 Guidelines Page S9)

Important Recent Findings

Reduction of the delay between onset of symptoms and reperfusion is increasingly recognised as an important clinical goal, and various strategies for achieving this have been recommended:

- 12-lead EGC performed in the ambulance during transit was shown to facilitate pre-hospital diagnosis [53,54]. This approach enables patients to be triaged and directed to PCI centres as appropriate.
- The CAPTIM[19] study demonstrated that, where it is not feasible to direct patients to centres with PCI capability immediately, pre-hospital fibrinolysis may improve 5-year mortality rates [55]. Recent Australian consensus recommendations support the initiation of thrombolysis by appropriately trained general practitioners and other healthcare workers in remote settings where PCI is unavailable [56].
- Within hospitals that provide a primary PCI service, system adjustments such as emergency department or pre-hospital-initiated single-call activation of the catheterisation laboratory, coupled with systems of audit and rapid-cycle feedback, have been associated with improved performance and reductions in recurrent ischaemic events and late mortality [57]. Strategies associated with reduced door to balloon times are presented in Table 6.
- Robust clinical networks that link hospital services with capacity for cardiac catheterisation and early invasive management to those without this capacity, and which enable timely cardiac consultation, are necessary to ensure equitable delivery of sustained reperfusion, early revascularisation and appropriate secondary prevention to the majority of patients [56].

[19] Comparison of Primary Angioplasty and Pre-hospital fibrinolysis In Acute Myocardial Infarction.

Table 6. *Adjusted Associations Between Hospital Strategies and Door-to-Balloon Times [58]*.*

Strategy	Door-to-Balloon Time (95% CI) (min)	*P* value†	Wald *P* Value‡
Catheterisation laboratory is activated by emergency medicine physician			0.01
No			
Yes	−8.2 (−14.3 to −2.0)	0.01	
Process for activating catheterisation team			0.01
After communicating with the emergency department, interventional cardiologist activates catheterisation laboratory by calling staff or a central page operator			
Emergency department makes at least two calls: one to the interventional cardiologist and another to a central page operator, who pages catheterisation laboratory staff	−6.8 (−12.5 to −1.0)	0.03	
Emergency department makes a single call to a central page operator, who then pages interventional cardiologist and catheterisation laboratory staff	−13.8 (−21.2 to −6.4)	0.001	
No standard approach	13.2 (−37.8 to 64.2)	0.66	
Other	−5.0 (−14.1 to 4.0)	0.28	
Process after emergency medical service transmits ECG results			0.004
Emergency department waits for patient to arrive at the hospital to determine whether catheterisation laboratory should be activated			
Emergency department contacts cardiologist whilst the patient is en route to determine whether catheterisation laboratory should be activated	−8.9 (−17.8 to 0)	0.06	
Emergency department activates catheterisation laboratory whilst the patient is still en route to the hospital	−15.4 (−24.2 to −6.6)[a]	0.001	
No set protocol or variable protocol	−23.2 (−35.3 to −11.1)[b]	0.001	
Not applicable because ECG data not transmitted to emergency department	−6.6 (−15.2 to 2.1)	0.14	
Not applicable because ECG never performed en route	−4.3 (−12.0 to 3.3)	0.27	
Unknown or no response	−5.6 (−13.3 to 2.2)	0.17	
Expected interval between page and arrival of staff in catheterisation laboratory			0.01
≤20 min			
21–30 min	3.5 (−4.6 to 11.6)[c]	0.40	
>30 min	19.3 (6.0 to 32.7)	0.002	
No expected time	8.8 (−0.7 to 18.3)	0.06	
An attending cardiologist is always at the hospital			0.01
No			
Yes	−14.6 (−25.7 to −3.6)	0.01	
Hospital gives real-time feedback to staff in emergency department and catheterisation laboratory			0.001
No			
Yes	−8.6 (−13.6 to −3.6)	0.001	

[a] $P = 0.01$ for the comparison with the door-to-balloon time at hospitals reporting that electrocardiography was never performed en route by emergency medical services.

[b] $P = 0.01$ for the comparison with the door-to-balloon time at hospitals reporting that emergency medical services never called in or transmitted electrocardiographic data. Hospitals that reported having no set protocol or a variable protocol could have used a variety of strategies, including activation of the catheterisation laboratory before the patient arrived, for expediting the door-to-balloon time.

[c] $P = 0.003$ for the comparison with the door-to-balloon time at hospitals with an expected interval of more than 30 min.

* All variables are centred at their mean value; therefore, the changes in minutes are relative to those of hospitals with an "average" score on all other items. CI denotes confidence interval, and ECG electrocardiography.

† The reference category is the first listed response to each question.

‡ *P* values were calculated with the use of the Wald chi-square test.

Implications of the Findings
Timely reperfusion remains a key treatment objective in the management of STEMI.
Previous recommendations
The 2006 Guidelines stated that local approaches to reperfusion depend on the specific local resources available for assessment, transfer and delivery of care.
New recommendations

1. System-based approaches to deliver timely reperfusion should be undertaken at local level. Establishment of clinical networks and efficient protocols to maximise the proportion of patients receiving timely reperfusion should be considered. [Grade B recommendation; Evidence level III-1]
2. Routine audit should be integrated into all clinical services that provide care to patients with ACS. [Grade B recommendation; Evidence level III].
3. In the absence of ready access to primary PCI services, systems should be developed to train local general practitioners and other health workers to initiate fibrinolysis in patients with STEMI, to maintain practitioners' skills, and to ensure practitioners are supported by ready access to expert cardiology consultation. [Recommendation grade N/A]

Measures of performance such as door-to-balloon time, door-to-needle time and the prescription of secondary prevention therapies have been established internationally and locally.

Conflicts of interest

Derek Chew has received travel assistance, speaker fees or been on the advisory board for Astra Zeneca Australia, Eli-Lilly Australia and Sanofi Aventis Australia. Con Aroney has received travel assistance from Boehringer Ingelheim. Philip Aylward has received research honoraria, research grants, travel assistance or been on advisory boards for Boehringer Ingelheim, Astra Zeneca, Eli-Lilly, CSL, Merck Sharp & Dohme, Pfizer, Sanofi Aventis. Philip Tideman has received speakers honoraria from Roche Diagnostics Australia. Harvey White has received research grants from Sanofi Aventis, Eli-Lilly, The Medicines Company, National Institutes of Health, Pfizer, Roche, Johnson & Johnson, Schering Plough, Merck Sharp & Dohme, Astra Zeneca, Daiichi Sankyo Pharma Development, Bristol-Myers Squibb and consulting fees from Regado Biosciences. Anne-Maree Kelly is a member of advisory boards to Astra Zeneca and Merck Sharp & Dohme and has received travel assistance from Radiometer Pty Ltd, is the Senior Clinical Advisor for the Emergency Care Improvement and Innovation Clinical Network (Department of Health Victoria), is on the editorial boards of *Emergency Medicine Australasia*, *Annals of Emergency Medicine and Hong Kong Journal of Emergency Medicine* and conducts research in acute cardiology and biomarkers.

Appendix A.

A1. *NHMRC Evidence Hierarchy.*[a]

Level	Intervention	Diagnostic Accuracy	Prognosis	Aetiology	Screening Intervention
I	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, amongst consecutive persons with a defined clinical presentation	A prospective cohort study	A prospective cohort study	A randomised controlled trial
III-1	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, amongst non-consecutive persons with a defined clinical presentation	All or none	All or none	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: • Non-randomised, experimental trial • Cohort study • Case–control study • Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: • Non-randomised, experimental trial • Cohort study • Case–control study
III-3	A comparative study without concurrent controls: • Historical control study • Two or more single arm study • Interrupted time series without a parallel control group	Diagnostic case–control study	A retrospective cohort study	A case–control study	A comparative study without concurrent controls: • Historical control study • Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

[a] For all references and explanatory notes, see Ref. [3].

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