National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the management of acute coronary syndromes 2016

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These clinical guidelines have been developed to assist in managing patients presenting with chest pain suspected to be caused by an acute coronary syndrome (ACS) and those with confirmed ACS. The development of these guidelines has been informed by reviews of the literature dealing with key aspects of chest pain assessment and ACS care, as well as broad consultation with local opinion leaders, stakeholder groups and the public. The recommendations focus on the core clinical and system-based components of care most associated with improved clinical outcomes. As such, these guidelines should be read in conjunction with the *Acute coronary syndromes clinical care standard*, developed by the Australian Commission on Safety and Quality in Health Care,[1] and the *Australian acute coronary syndromes capability framework*, developed by the National Heart Foundation of Australia (NHFA).[2] Guidance regarding both the strength of evidence supporting the recommendations and their potential impact on outcomes is provided to assist in informing clinical practice.[3,4] Additional guidance regarding the timing and considerations informing the use of therapies and management strategies is given in the accompanying practice advice. A full version of the NHFA and Cardiac Society of Australia and New Zealand (CSANZ) *Australian clinical guidelines for the management of acute coronary syndromes 2016* is available at: http://heartfoundation.org.au/for-professionals/clinical-information/acute-coronary-syndromes.

Methods

The NHFA, in partnership with the CSANZ, has undertaken an update to the NHFA/CSANZ *Guidelines for the management of acute coronary syndromes 2006* and addenda of 2007 and 2011.[5-7] The updated guideline will provide a synthesis of current evidence-based guidance for health professionals caring for patients with ACS.

The ACS Guideline Development Working Group comprised an Executive and the four writing groups of which it had oversight, covering the topics of chest pain, ST segment elevation myocardial infarction (STEMI), non-ST segment elevation ACS (NSTEACS) and secondary prevention. In addition, a Reference Group

Abstract

Introduction: The modern care of suspected and confirmed acute coronary syndrome (ACS) is informed by an extensive and evolving evidence base. This clinical practice guideline focuses on key components of management associated with improved clinical outcomes for patients with chest pain or ACS. These are presented as recommendations that have been graded on both the strength of evidence and the likely absolute benefit versus harm. Additional considerations influencing the delivery of specific therapies and management strategies are presented as practice points.

Main recommendations: This guideline provides advice on the standardised assessment and management of patients with suspected ACS, including the implementation of clinical assessment pathways and subsequent functional and anatomical testing. It provides guidance on the:

- diagnosis and risk stratification of ACS;
- provision of acute reperfusion therapy and immediate post-fibrinolysis care for patients with ST segment elevation myocardial infarction;
- risk stratification informing the use of routine versus selective invasive management for patients with non-ST segment elevation ACS;
- administration of antithrombotic therapies in the acute setting and considerations affecting their long term use; and
- implementation of an individualised secondary prevention plan that includes both pharmacotherapies and cardiac rehabilitation.

Changes in management as a result of the guideline: This guideline has been designed to facilitate the systematic integration of the recommendations into a standardised approach to ACS care, while also allowing for contextual adaptation of the recommendations in response to the individual's needs and preferences. The provision of ACS care should be subject to continuous monitoring, feedback and improvement of quality and patient outcomes.

included representatives from stakeholder groups, potential endorsing organisations and regional experts. The Working Group comprised a broad mix of health professionals, including a

general practitioner, general physician, cardiac surgeon, consumer representative, pathologist, ambulance service representative, cardiologists, emergency physicians, exercise physiologists and cardiac nurses.

The Working Group consulted state-based cardiac clinical networks and the Reference Group on the scope determination for the updated guideline. Based on this consultation, the expert Working Group generated clinical questions to inform the literature search of evidence required for the guideline's development. The separate writing groups reviewed and graded the evidence, generated and graded recommendations, and produced draft sections for the four topic areas. The Executive group provided oversight for this process and approved the final document.

A draft of the guideline was open for a 30-day period of public consultation in April 2016 to capture stakeholder views and aid engagement with the guideline once completed. Attention has been paid to ensuring appropriate governance processes were in place, to ensure transparency, minimise bias, manage conflict of interest and limit other influences during guideline development.

Key evidence-based recommendations

Each recommendation is presented with a Grading of Recommendations Assessment, Development and Evaluation (GRADE) strength of recommendation (Appendix 1) and a National Health and Medical Research Council level of evidence (Level) (Appendix 2). Practice points (PPs) are also provided.

Assessment of possible cardiac causes of chest pain

- It is recommended that a patient with acute chest pain or other symptoms suggestive of an ACS receives a 12-lead electrocardiogram (ECG), and this ECG is assessed for signs of myocardial ischaemia by an ECG-experienced clinician within 10 minutes of first acute clinical contact.[8] *GRADE: Strong; Level: IIIC*
  - ▶ *PP: Oxygen supplementation.* The routine use of oxygen therapy among patients with a blood oxygen saturation (SaO_2) level > 93% is not recommended, but its use when

the SaO_2 is below this level is advocated, despite the absence of clinical data.[9,10] However, care should be exercised in patients with chronic obstructive pulmonary disease where the target SaO_2 level is to be 88−92%.

- ▶ *PP: Initial aspirin therapy.* In all patients with possible ACS and without contraindications, aspirin (300 mg orally, dissolved or chewed) should be given as soon as possible after presentation. Additional antiplatelet and anti-coagulation therapy, or other therapies such as β-blockers, should not be given to patients without a confirmed or probable diagnosis of ACS.

- A patient presenting with acute chest pain or other symptoms suggestive of an ACS should receive care guided by an evidence-based Suspected ACS Assessment Protocol (Suspected ACS-AP) that includes formal risk stratification.[11] *GRADE: Strong; Level: IA*
  - ▶ *PP: Selecting and implementing a Suspected ACS-AP.* For hospitals using sensitive or highly sensitive troponin assays, the ADAPT or modified ADAPT protocol, respectively, identifies low risk patients (< 1% major adverse cardiac events [MACE] at 30 days) on the basis of negative troponin test results at both 0 and 2 hours, a Thrombolysis in Myocardial Infarction (TIMI) risk score of 0 (ADAPT) or 0 or 1 (modified ADAPT), and no ischaemic changes on ECG at both 0 and 2 hours.[12,13]

- Using serial sampling, cardiac-specific troponin levels should be measured at hospital presentation and at clearly defined periods after presentation using a validated Suspected ACS-AP in patients with symptoms of possible ACS.[14] *GRADE: Strong; Level: IA*
  - ▶ *PP: Timing of troponin testing.* Most patients with an underlying diagnosis of acute myocardial infarction (AMI) have elevated troponin levels within 3−6 hours of symptom onset, although some assays may not show elevated levels for up to 12 hours (Box 1). Validated rapid rule-in and rule-out algorithms for AMI incorporated into Suspected ACS-APs and/or using highly sensitive troponin assays may reduce the serial testing time to 1−2 hours after presentation.[18,19,21,24,25] Incorporating sensitive or highly sensitive

1 Timing of troponin testing

Timing of sampling	Strategy*	Assays
0 hour (single sample)	Patients whose pain and symptoms resolved 12 hours prior to testing (cut points are the assay-specific 99th percentile	Both sensitive and highly sensitive (HS) assays
0 hour (single sample)	Patients with value < LoD of the specific assay (not > 99th percentile cut point) and symptom onset > 3 hours[†15-17]	HS assays
0 hour and 1 hour after presentation	Rule-in and rule-out AMI algorithms (cut points are assay-specific and not the 99th percentile)[18-20]	HS assays
0 and 2 hours after presentation	ADAPT protocol[13] Modified ADAPT protocol[12,21] (cut points are the assay-specific 99th percentile)	Sensitive assays HS assays
0 and ≥ 3 hours after presentation	Previous NHFA protocol[7] HEART Pathway[22,23] (cut points are the assay-specific 99th percentile)	HS assays Both sensitive and HS assays
0 and ≥ 6−12 hours after presentation	Rule-in and rule-out AMI algorithms[5] (cut points are the assay-specific 99th percentile)	Sensitive and point-of-care assays

ADAPT = 2-Hour Accelerated Diagnostic Protocol to Assess Patients with Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker. AMI = acute myocardial infarction. HEART = History, Electrocardiogram, Age, Risk factors and Troponin. LoD = limit of detection. NHFA = National Heart Foundation of Australia. * With concurrent clinical risk stratification. † Reports on the use and outcomes of the biomarker strategy in clinical practice are not currently available. ◆

troponin assay results into the ADAPT or modified ADAPT protocol, respectively, allows early (2 hours after emergency department presentation) risk stratification.[12,13]

- Non-invasive objective testing is recommended in intermediate risk patients, as defined by a validated Suspected ACS-AP, with normal serial troponin and ECG testing and who remain symptom free.[26] *GRADE: Weak; Level: IA*

  ▶ *PP: Timing of testing.* High risk patients require further objective testing during the index admission (Box 2). Intermediate risk patients may be safely accelerated for early inpatient testing or discharged for outpatient testing, ideally within 7 days but acceptable up to 14 days after presentation. Investigation before discharge from the emergency department is desirable among patients with characteristics associated with significant failure to re-attend for medical review, given the higher rates of MACE in such patients.[27]

- Patients in whom no further objective testing for coronary artery disease is recommended are those at low risk, as defined by a validated Suspected ACS-AP: age < 40 years, symptoms atypical for angina, in the absence of known coronary artery disease, with normal troponin and ECG testing and who remain symptom free.[26] *GRADE: Weak; Level: III-3C*

Diagnostic issues, risk stratification and acute management of ACS

- The routine use of validated risk stratification tools for ischaemic and bleeding events (eg, GRACE score for ischaemic risk and CRUSADE score for bleeding risk) may assist in patient-centric clinical decision making in regards to ACS care.[28-30] *GRADE: Weak; Level: IIIB*

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2 Risk classification for possible cardiac causes of chest pain

High risk	• Ongoing or recurrent chest discomfort despite initial treatment
	• Elevated cardiac troponin level
	• New ischaemic changes on electrocardiogram (ECG), such as persistent or dynamic ECG changes of ST segment depression ≥ 0.5 mm; transient ST segment elevation (≥ 0.5 mm) or new T wave inversion ≥ 2 mm in more than two contiguous leads; or ECG criteria consistent with Wellens syndrome
	• Diaphoresis
	• Haemodynamic compromise — systolic blood pressure < 90 mmHg, cool peripheries, Killip Class > I and/or new onset mitral regurgitation
	• Sustained ventricular tachycardia
	• Syncope
	• Known left ventricular systolic dysfunction (left ventricular ejection fraction $\leq 40\%$)
	• Prior acute myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting
Low risk	• Age < 40 years
	• Symptoms atypical for angina
	• Remain symptom free
	• Absence of known coronary artery disease
	• Normal troponin level
	• Normal ECG
Intermediate risk	• Neither high risk nor low risk criteria

- ▶ *PP: Choice of risk score.* For ischaemic risk, the GRACE risk score is superior to the TIMI risk score in terms of discriminating between high risk and intermediate or low risk patients.[28] However, estimating risk of death or recurrent myocardial infarction (MI) for an individual patient depends on local validation. For bleeding risk, the CRUSADE risk score is preferred, although it has limited validation in the Australian setting.[31]

Acute reperfusion and invasive management strategies for ACS

- For patients with STEMI presenting within 12 hours of symptom onset, and in the absence of advanced age, frailty and comorbidities that influence the individual's overall survival, emergency reperfusion therapy with either primary percutaneous coronary intervention (PCI) or fibrinolytic therapy is recommended.[32,33] *GRADE: Strong; Level: IA*

  ▶ *PP: ECG interpretation.* In situations where expertise in ECG interpretation may not be available, an electronic algorithm for ECG interpretation (coupled with review by an expert) can assist in diagnosing STEMI. Local or state care pathways should incorporate means for allowing expert ECG reading within 10 minutes of first contact, integrated with clinical decision making to enable timely reperfusion.

- Primary PCI is preferred for reperfusion therapy in patients with STEMI if it can be performed within 90 minutes of first medical contact; otherwise, fibrinolytic therapy is preferred for those without contraindications.[34-36] *GRADE: Strong; Level: IA*

  ▶ *PP: Strategies for reducing the time to reperfusion therapy.* Coordinated protocols with planned decision making that incorporates ambulance services and paramedics, first-responder primary care physicians, and emergency and cardiology departments are critical for achieving acceptable reperfusion times. Strategies need to be tailored to the local community and the distribution of emergency services. Strategies that effectively shorten the time to reperfusion include: developing hospital networks with pre-determined management pathways for reperfusion; pre-hospital ECG and single call catheter laboratory activation; pre-hospital fibrinolytic therapy administered by suitably trained clinicians (eg, paramedics); the bypassing, where appropriate, of non-PCI-capable hospitals; and bypassing the emergency department on arrival in PCI-capable centres. Furthermore, an established capability for timely expert consultation for complex clinical scenarios is highly desirable. In the context of a system-based approach to reperfusion, the capacity for continuous audit and feedback is also advocated.

- Among patients treated with fibrinolytic therapy who are not in a PCI-capable hospital, early or immediate transfer to a PCI-capable hospital for angiography, and PCI if indicated, within 24 hours is recommended.[37] *GRADE: Weak; Level: IIA*

- Among patients treated with fibrinolytic therapy, for those with $\leq 50\%$ ST recovery at 60–90 minutes and/or with haemodynamic instability, immediate transfer for angiography with a view to rescue angioplasty is recommended.[38] *GRADE: Strong; Level: IB*

  ▶ *PP: Hospital networks.* Systems of care should be developed to provide advice and enable, when appropriate, immediate or early transfer for angiography of patients treated with fibrinolytic therapy who are not in a PCI-capable hospital.

- Among high and very high risk patients with NSTEACS (except type 2 MI [secondary to ischaemia due to either

increased oxygen demand or decreased supply]), a strategy of angiography with coronary revascularisation (PCI or coronary artery bypass grafting [CABG]), where appropriate, is recommended.[39] *GRADE: Strong; Level: IA*

▶ *PP: Mode of revascularisation.* Patient comorbidities, fitness for major surgery and coronary anatomy are the main determinants. Urgent revascularisation with CABG may be indicated for patients with failed PCI, cardiogenic shock or mechanical defects resulting from MI (eg, septal, papillary muscle or free-wall rupture). A combined Heart Team approach may provide the best consensus decision about the care of an individual patient.

▶ *PP: Invasive management for type 2 MI.* Type 2 MI remains a challenging diagnosis, and no trials have examined the benefits of a routine invasive strategy in patients with type 2 MI. In the absence of any trial evidence, angiography with a view to revascularisation may be considered if there is ongoing ischaemia or haemodynamic compromise despite adequate treatment of the underlying acute medical problem that provoked the type 2 MI.

- Patients with NSTEACS who have no recurrent symptoms and no risk criteria are considered at low risk of ischaemic events and can be managed with a selective invasive strategy guided by provocative testing for inducible ischaemia.[39] *GRADE: Strong; Level: IA*

- Very high risk patients: Among patients with NSTEACS with very high risk criteria (ongoing ischaemia, haemodynamic compromise, arrhythmias, mechanical complications of MI, acute heart failure, recurrent dynamic or widespread ST segment and/or T wave changes on ECG; Box 3), an immediate invasive strategy is recommended (ie, within 2 hours of admission).[40] *GRADE: Strong; Level: IIC*

- High risk patients: In the absence of very high risk criteria, for patients with NSTEACS with high risk criteria (GRACE score >140, dynamic ST segment and/or T wave changes on ECG or rise and/or fall in troponin compatible with MI; Box 3), an early invasive strategy is recommended (ie, within 24 hours of admission).[40] *GRADE: Weak; Level: IC*

- Intermediate risk patients: In the absence of high risk criteria, for patients with NSTEACS with intermediate risk criteria (such as recurrent symptoms or substantial inducible ischaemia on provocative testing; Box 3), an invasive strategy is recommended (ie, within 72 hours of admission).[40-42] *GRADE: Weak; Level: IIC*

Pharmacology for ACS

- Aspirin 300 mg orally (dissolved or chewed) initially, followed by 100–150 mg/day, is recommended for all patients with ACS, in the absence of hypersensitivity.[43] *GRADE: Strong; Level: IA*

- Among patients with confirmed ACS at intermediate to very high risk of recurrent ischaemic events, use of a $P2Y_{12}$ inhibitor (ticagrelor 180 mg orally, then 90 mg twice a day; or prasugrel 60 mg orally, then 10 mg daily; or clopidogrel 300–600 mg orally, then 75 mg daily) is recommended in addition to aspirin (ticagrelor or prasugrel preferred; see below).[44-47] *GRADE: Strong; Level: IA*

  ▶ *PP: Choosing between $P2Y_{12}$ inhibitors.* Given their superior efficacy, ticagrelor and prasugrel are the preferred first-line $P2Y_{12}$ inhibitors. Use of ticagrelor is advised for a broad spectrum of patients with STEMI or NSTEACS who are at intermediate to high risk of an ischaemic event, in the absence of atrioventricular conduction disorders

3 Markers of increased risk of mortality and recurrent events among patients with confirmed acute coronary syndrome

Risk classification	Clinical characteristic
Very high	• Haemodynamic instability, heart failure, cardiogenic shock or mechanical complications of myocardial infarction (MI)
	• Life-threatening arrhythmias or cardiac arrest
	• Recurrent or ongoing ischaemia (ie, chest pain refractory to medical treatment) or recurrent dynamic ST segment and/or T wave changes, particularly with intermittent ST segment elevation, de Winter T wave changes or Wellens syndrome, or widespread ST segment elevation in two coronary territories
High	• Rise and/or fall in troponin level consistent with MI
	• Dynamic ST segment and/or T wave changes with or without symptoms
	• GRACE score >140
Intermediate	• Diabetes mellitus
	• Renal insufficiency (glomerular filtration rate < 60 mL/min/1.73 m^2)
	• Left ventricular ejection fraction ≤ 40%
	• Prior revascularisation: percutaneous coronary intervention or coronary artery bypass grafting
	• GRACE score >109 and < 140

GRACE = Global Registry of Acute Coronary Events. ◆

(second and third degree atrioventricular block) and asthma or chronic obstructive pulmonary disease. Prasugrel may be considered for patients who have not received a $P2Y_{12}$ antagonist and in whom PCI is planned, but it should not be used for patients >75 years of age, of low bodyweight (< 60 kg) or with a history of transient ischaemic attack or stroke. Use of either prasugrel or ticagrelor, rather than clopidogrel, is also recommended for patients who have experienced recurrent events while taking clopidogrel or who have experienced stent thrombosis. Clopidogrel is recommended for patients who cannot receive ticagrelor or prasugrel, as an adjunctive agent with fibrinolytic therapy or for those requiring oral anticoagulation (refer to relevant prescribing information documentation). Ticagrelor or clopidogrel should be commenced soon after diagnosis, but due consideration should be given to ischaemic and bleeding risks, the likelihood of need for CABG (more likely in patients with extensive ECG changes, ongoing ischaemia or haemodynamic instability) and the delay to angiography. Prasugrel should be commenced immediately after diagnosis among patients undergoing primary PCI for STEMI, or after the coronary anatomy is known among those undergoing urgent PCI. Initiation of prasugrel before coronary angiography outside the context of primary PCI is not recommended.

▶ *PP: Combination of $P2Y_{12}$ inhibition with long term anticoagulation.* Among patients with an indication for oral anticoagulation, a careful assessment of thrombotic and bleeding risks is required, using CHA_2DS_2-VASc and HAS-BLED scores, respectively. The following advice is based on consensus opinion. In patients with a strong indication for long term anticoagulation (ie, mechanical heart valves, atrial fibrillation with CHA_2DS_2-VASc score ≥ 2), the anticoagulant should be continued at a

reduced dose, and clopidogrel, rather than ticagrelor or prasugrel, should be used for these patients. The duration of triple therapy (ie, aspirin, clopidogrel and oral anticoagulation) should be determined by the bleeding risk.

- Intravenous glycoprotein IIb/IIIa inhibition in combination with heparin is recommended at the time of PCI among patients with high risk clinical and angiographic characteristics or for treating thrombotic complications among patients with ACS.[48] *GRADE: Strong; Level: IB*

- Either unfractionated heparin or enoxaparin is recommended in patients with ACS at intermediate to high risk of ischaemic events.[49,50] *GRADE: Strong; Level: IA*
  - ▶ *PP: Choosing between indirect thrombin inhibitors.* Enoxaparin may be preferred over unfractionated heparin as it does not require monitoring of partial thromboplastin time and is simpler to administer. Swapping between enoxaparin and unfractionated heparin has been shown to increase bleeding risk and is not recommended.

- Bivalirudin (0.75 mg/kg intravenously with 1.75 mg/kg/h infusion) may be considered as an alternative to glycoprotein IIb/IIIa inhibition and heparin among patients with ACS undergoing PCI with clinical features associated with an increased risk of bleeding events.[51] *GRADE: Weak; Level: IIB*

Discharge management and secondary prevention

- Aspirin (100–150 mg/day) should be continued indefinitely unless it is not tolerated or an indication for anticoagulation becomes apparent.[43] *GRADE: Strong; Level: IA*

- Clopidogrel should be prescribed if aspirin is contraindicated or not tolerated. *GRADE: Strong; Level: IA*

- Dual antiplatelet therapy with aspirin and a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) should be prescribed for up to 12 months in patients with ACS, regardless of whether coronary revascularisation was performed. The use of prasugrel for up to 12 months should be confined to patients receiving PCI. *GRADE: Strong; Level: IA*

- Consider continuation of dual antiplatelet therapy beyond 12 months if ischaemic risks outweigh the bleeding risk of $P2Y_{12}$ inhibitor therapy; conversely, consider discontinuation if bleeding risk outweighs ischaemic risks.[52] *GRADE: Weak; Level: IIC*

- Initiate and continue indefinitely, the highest tolerated dose of an HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitor (statin) for a patient following hospitalisation

with ACS, unless contraindicated or there is a history of intolerance.[53] *GRADE: Strong; Level: IA*
  - ▶ *PP: Target cholesterol levels.* There is additional benefit from progressive lowering of cholesterol levels, with no apparent lower limit. Within the context of an individualised care plan, a target low density lipoprotein cholesterol level of less than 1.8 mmol/L is suggested in the first instance.

- Initiate treatment with vasodilatory β-blockers in patients with reduced left ventricular systolic function (left ventricular ejection fraction ≤ 40%) unless contraindicated.[54] *GRADE: Strong; Level: IIA*

- Initiate and continue angiotensin-converting enzyme inhibitors (or angiotensin receptor blockers) in patients with evidence of heart failure, left ventricular systolic dysfunction, diabetes, anterior MI or co-existent hypertension.[55] *GRADE: Strong; Level: IA*

- Attendance at cardiac rehabilitation or undertaking a structured secondary prevention service is recommended for all patients hospitalised with ACS.[56,57] *GRADE: Strong; Level: IA*
  - ▶ *PP: Individualisation of cardiac rehabilitation or secondary prevention service referral.* A wide variety of prevention programs improve health outcomes in patients with coronary disease. After discharge from hospital, patients with ACS and, where appropriate, their companion(s) should be referred to an individualised preventive intervention according to their personal preference and values and the available resources. Services can be based in the hospital, primary care, the local community or the home.

System considerations

- Continuous audit and feedback systems, integrated with work routines and patient flows, are strongly advocated to support quality assurance initiatives and provide data confirming continued, cost-efficient improvement in patient outcomes as a result of new innovations in care.

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