Heart, Lung and Circulation (2016) **25,** 895–951
1443-9506/04/$36.00
http://dx.doi.org/10.1016/j.hlc.2016.06.789

POSITION STATEMENT

National Heart Foundation of Australia & Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Management of Acute Coronary Syndromes 2016

Contents

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Executive Summary

These clinical guidelines have been developed to assist in the management of patients presenting with chest pain suspected to be due to an acute coronary syndrome (ACS) and those with confirmed ACS. These guidelines should be read in conjunction with the ACS Clinical Care Standards developed by the Australian Commission for Safety and Quality in Health Care (ACSQHC) [1] and the *Australian acute coronary syndromes capability framework* developed by the Heart Foundation [2]. Additional guidance around the timing and use of therapies is detailed in the accompanying practice advice.

Key Evidence-Based Recommendations

Recommendation	GRADE strength of recommendation	NHMRC Level of Evidence (LOE)
Initial assessment of chest pain		
It is recommended that a patient with acute chest pain or other symptoms suggestive of an ACS receives a 12-lead ECG and this ECG is assessed for signs of myocardial ischaemia by an ECG-experienced clinician within 10 minutes of first acute clinical contact.	Strong	IIIC
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.	Strong	IA
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.	Strong	IA
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.	Weak	IA
Patients in whom no further objective testing for coronary artery disease (CAD) 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 CAD, with normal troponin and ECG testing, and who remain symptom-free.	Weak	III-3C
Diagnostic considerations and risk stratification of ACS		
The routine use of validated risk stratification tools for ischaemic and bleeding events (e.g. GRACE score for ischaemic risk or CRUSADE score for bleeding risk) may assist in patient-centric clinical decision-making in regards to ACS care.	Weak	IIIB
Acute reperfusion and invasive management strategies in ACS		
For patients with ST elevation myocardial infarction (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.	Strong	IA
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 contra-indications.	Strong	IA
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.	Weak	IIA

(Continued).

Recommendation	GRADE strength of recommendation	NHMRC Level of Evidence (LOE)
Among patients treated with fibrinolytic therapy, for those with ≤50% ST recovery at 60–90 minutes, and/or with haemodynamic instability, immediate transfer for angiography with a view to rescue angioplasty is recommended.	Strong	IB
Among high- and very high-risk patients with non-ST elevation acute coronary syndromes (NSTEACS) (except Type 2 MI), a strategy of angiography with coronary revascularisation (PCI or coronary artery bypass grafts) where appropriate is recommended.	Strong	IA
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.	Strong	IA
Timing of invasive management for NSTEACS		
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), an immediate invasive strategy is recommended (i.e. within 2 hours of admission).	Strong	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) an early invasive strategy is recommended (i.e. within 24 hours of admission).	Weak	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), an invasive strategy is recommended (i.e. within 72 hours of admission).	Weak	IIC
Pharmacology for ACS		
Aspirin 300 mg orally initially (dissolved or chewed) followed by 100–150 mg/day is recommended for all patients with ACS in the absence of hypersensitivity.	Strong	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 75mg per day) is recommended in addition to aspirin. (Ticagrelor or prasugrel preferred: see practice advice)	Strong	IA
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.	Strong	IB

(Continued).

Recommendation	GRADE strength of recommendation	NHMRC Level of Evidence (LOE)
Either unfractionated heparin or enoxaparin is recommended in patients with ACS at intermediate to high risk of ischaemic events.	Strong	IA
Bivalirudin (0.75 mg/kg IV with 1.75 mg/kg/hr 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.	Weak	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.	Strong	IA
Clopidogrel should be prescribed if aspirin is contraindicated or not tolerated.	Strong	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.	Strong	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.	Weak	IIC
Initiate and continue indefinitely, the highest tolerated dose of HMG-CoA reductase inhibitors (statins) for a patient following hospitalisation with ACS unless contraindicated or there is a history of intolerance.	Strong	IA
Initiate treatment with vasodilatory beta blockers in patients with reduced left ventricular (LV) systolic function (LV ejection fraction [EF] $\leq$40%) unless contraindicated.	Strong	IIA
Initiate and continue angiotensin converting enzyme (ACE) inhibitors (or angiotensin receptor blockers [ARBs]) in patients with evidence of heart failure, LV systolic dysfunction, diabetes, anterior myocardial infarction or co-existent hypertension.	Strong	IA
Attendance at cardiac rehabilitation or undertaking a structured secondary prevention service is recommended for all patients hospitalised with ACS.	Strong	IA

Note: Refer to Appendix 4 for details on the National Health and Medical Research Council (NHMRC) guideline development methodology, including grades of evidence, and Appendix 5 for details on the GRADE methodology.

1. Preamble

1.1. Incidence

Acute coronary syndromes (ACS) – myocardial infarction (MI) and unstable angina (UA) – are the result of unstable atheromatous plaques or endothelial disruption with associated transient or permanent thrombotic occlusion of the coronary vascular tree leading to myocardial ischaemia and infarction. As a result of the improved sensitivity of troponin assays, incidence of unstable angina is decreasing with a proportionate increase in the incidence of MI. In 2012, the Australian Institute of Health and Welfare estimated there were 68,200 ACS events [3]. Chest pain and other symptoms suggestive of possible ACS are common presenting complaints in the emergency department (ED) [4]. It is estimated that over 500,000 patients present in Australia each year with chest pain, but more than 80% of all patients investigated for ACS will not have this diagnosis confirmed [5]. In unselected patients presenting with acute chest pain to the ED in the Australian setting, the prevalence of different diagnostic groups are: 2-5% ST elevation MI (STEMI), 5-10% Non-STEMI (NSTEMI), 5-10% UA, 15-20% other cardiac conditions and 50-70% non-cardiac diseases [5–7]. The costs and burden of the diagnostic process to patients, clinicians and the healthcare system are significant.

1.2. Contemporary Outcomes of ACS and Chest Pain in Australia

Patient level estimates of overall 30-day outcomes and 12-month mortality rates within Australian contemporary practice, as ascertained by recent clinical audits, are provided as a reference for estimating the absolute benefits for various guideline recommended therapies and strategies (Table 1) in the 'average' patient. In deriving estimates of the absolute reduction or increase in events as a result of specific treatments, the relative effects for each treatment seen in trials is applied to the estimated baseline absolute event rates seen in audits. This absolute change in events is then used to calculate the number needed to treat to benefit (NNTB) (e.g. reducing recurrent MI) and the number needed to treat to harm (NNTH) (e.g. treatment-related bleeding or adverse events). These figures should be considered an approximation as clinical audits comprise patients who have received varying intensities of different interventions, as opposed to clinical trials where, apart from the specific intervention under study, all other forms of care are provided equally. When considering the use of evidence-based recommendations in individual patients, patient-specific disease and treatment risks, and therefore potential benefits and harms from therapies, should be weighed. The relative increase in both risks associated with key clinical and demographic characteristics within the Australian and New Zealand clinical experience is provided in Table 2.

1.3. The Process of Developing the 2016 ACS Guidelines

This clinical guideline for the management of ACS seeks to provide guidance regarding the clinical care of patients presenting with suspected or confirmed ACS. It is intended to replace the National Heart Foundation of Australia (NHFA)/Cardiac Society of Australia and New Zealand (CSANZ) ACS guideline published in 2006, 2008 and 2011[8–10]. The methodology used in the development of this guideline was guided by the methodological expertise of working group members [11].

Table 1 Kaplan-Meier event rates for ACS diagnosis adjusted for age from SNAPSHOT ACS

	STEMI	NSTEMI	Unstable angina	Chest pain
Death or MI by 30 days	12.7%	6.8%	1.2%	0.7%
In hospital major bleeding	2.4%	1.4%	1.0%	0.2%
Death by 12 months	9.8%	6.0%	1.7%	2.9%
Death or MI by 12 months	17.7%	15.1%	5.1%	4.9%
Death/MI/stroke by 12 months	18.6%	16.2%	7.0%	5.9%

Table 2 Relative increase in ischaemic and bleeding events with key clinical characteristics from SNAPSHOT ACS

	Relative increase in in-hospital MACE OR (95% CI)	Relative increase in in-hospital bleeding events OR (95% CI)
Age >75 years vs age ≤75 years	1.69 (1.15–2.45)	1.36 (0.58–3.00)
Female gender vs male gender	1.19 (0.83–1.72)	0.91 (0.40–1.97)
Diabetes vs non-diabetes	1.53 (1.05–2.21)	1.60 (0.73–3.40)
CKD Stage 3-5 vs CKD Stage 1-2	2.81 (1.96–4.04)	1.91 (0.89–4.03)

CKD=chronic kidney disease; CI=confidence interval; OR=odds ratio; MACE=Major adverse cardiac events

Initiation phase

- In mid-2014, officers of the NHFA and a small group of senior cardiologists representing the CSANZ, together with a methodologist, formed an ad hoc group to initiate the process of developing the 2016 guideline.
- This group approached the Cardiac Clinical Networks around Australia seeking feedback regarding the content and development process for the guideline.
- In December 2014, the ad hoc group, under a formal partnership between NHFA and CSANZ, and acting on advice from the previous expert panel responsible for prior editions of the guideline, sought representation from key stakeholder organisations for experts in ACS management to contribute to the process of guideline development.
- Among those canvassed as recognised clinical experts in chest pain and ACS management, proposed contributors where offered roles in either a reference group, which had the role of critical review of the entire guideline content, or work groups focussing on guideline writing related to specific topics.

Reference group

- This group comprised nominated representatives of identified key stakeholder organisations with national relevance in the provision of ACS care in Australia.
- The roles of the group were to review and provide input into the scope of the guidelines, the questions being submitted for literature review, draft guideline content and recommendations, and issues of implementation.

Guideline work groups

- Work groups were established for each of four topics: chest pain assessment, STEMI, non-ST segment elevation ACS (NSTEACS) and secondary prevention. For each work group, among all those who agreed to join the group, a primary author and senior advisor were appointed by group consensus on the basis of expertise and previous experience in guideline development.
- Each work group was then supplemented with members with recognised expertise from stakeholder groups and the clinical community.
- Members of each work group met on several occasions to discuss the content of each of the four sections of the guideline.

Executive group

- The primary author and senior advisor from each of the four workgroups and representatives from the NHFA formed an executive group with overall responsibility for the progression, content and consistency of the guideline, and for resolving disputes within or between work groups relating to guideline content and recommendations or conflicts of interest.
- The executive group had several meetings throughout 2015 and 2016, to discuss and refine the full content of the draft guidelines, with particular focus on the wording and grading of final recommendations.
- The executive group had the authority for final approval of guideline content and recommendations.

Literature reviews

- Informed by stakeholder consultation, each of the work groups proposed sentinel questions, presented in PICO format (population, intervention, comparator and outcome), for external literature review. These questions were reviewed and refined by the reference group. The questions proposed for literature review are provided in the appendix.
- The literature reviewer was appointed through an open tender process. The literature review sought published studies from 2010 to 2015. The process of literature review was commenced in the second quarter of 2015 and completed in the fourth quarter of 2015. Evidence summaries were reviewed and signed off by the work groups and, where deemed appropriate, were supplemented with additional studies published after the literature search dates.

Finalisation phase

- In December 2015, the full first draft of the guideline was given to members of the reference group for detailed comments. These comments were received and responses drafted in February 2016.
- A public consultation period of 30 days was conducted in April 2016.
- Final approval and submission for publication was undertaken in June 2016.

1.4. Conflicts of Interest Process

Conflicts of interest were considered within a framework of both the relationship (direct or indirect) of the participating individual to any third party with interest in the topic under consideration within the guideline development process, and the nature (financial and non-financial) of the potential conflict. All members of the work groups and reference group were asked to declare all potential conflicts of interest and these declarations were updated every six months and at each meeting. Individuals with pecuniary or academic conflicts of interest deemed to be high were excluded from the drafting of specific recommendations. All other conflicts of interest were managed by the work group chair or senior advisor, under guidance from the executive group. The executive group was responsible for managing conflicts of interest. A summary of the conflicts of interest and executive group responses is provided in the online appendix and a full description of the governance process for the development of this guideline will be available on the NHFA website.

1.5. Development of Recommendations

In developing this document, we sought to provide practical guidance for contemporary ACS care in Australia derived from the extensive evidence base regarding the clinical effectiveness of different interventions and treatment strategies. In addition to reviews of published trials and systematic reviews, guideline content was informed by other international clinical guidelines, the *Acute Coronary Syndrome Clinical Care Standard* and local clinical expertise. In formulating recommendations, we focussed on clinical actions likely to be associated with the largest impact on patient-important outcomes. The guidelines are presented in the format described below.

The key 'Recommendations' are presented up-front for easy identification. In making these recommendations, we chose to provide a strength of recommendation (strong or weak) according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (12) (Refer to Appendix 5) alongside the National Health and Medical Research Council (NHMRC) level of evidence scheme [13] (Refer to Appendix 4). The executive group considered that providing a clear dichotomous statement regarding the strength of the recommendation – strong versus weak - would benefit clinicians seeking to prioritise use of interventions in clinical practice, develop systems designed to provide more consistent care, or formulate quality indicators for reviewing clinical performance. Each of the final recommendations was independently reviewed and refined by the work groups and the reference group, with final review and endorsement by the executive group. The definition of consensus was >80% agreement of all members of the executive group.

The 'Rationale' section provides a very brief summary of the key evidence. In this section, treatment effects are presented in relative terms, i.e. odds ratios [OR], risk ratios [RR] or hazard ratios [HR] (with 95% confidence intervals). Hence an OR of 0.90 represents a 10% relative reduction in the event. We have confined the reporting of treatment effects to those that were significant to a p-value of <0.05, with the exception of mortality outcomes where relevant to the weighing of the evidence.

To assist in the translation of these treatment effects into clinical decision-making, we have attempted to provide, wherever possible, estimates of the absolute changes in intervention-specific outcomes such as ischaemic episodes or care-related adverse events for the 'average' patient, in the section 'Benefits and harms'. This approach has been used to assist clinicians in their discussions with patients by quantifying the likely absolute benefits or risks associated with each guideline recommendation.

In formulating recommendations, we were mindful of their implications for use of resources although, unfortunately, there is a lack of robust cost-effectiveness analyses for almost all ACS interventions within the Australian context. Commentary regarding the key economic implications or other relevant system factors are included in the 'Resources and other considerations' section where appropriate.

Aspects of care associated with a very limited evidence base and reliant on consensus opinion, or where the impact of interventions on clinical outcomes was considered to be modest, are highlighted in the 'Practice advice' sections of the guideline. While medication dosing is generally provided, clinicians are advised to refer to additional resources such as the Australian Medicines Handbook for relevant contraindications, precautions, drug interactions and adverse effects.

The writing groups were aware that much of the evidence has focussed on 'hard' clinical events such as mortality, recurrent MI and stroke. As a consequence, the recommendations and practice advice are strongly influenced by this literature, which has been used to generate estimates of treatment effect within the benefits and harms commentaries. However, within clinical practice, it is recognised that these endpoints are not universally valued as the highest priority by patients when compared with other outcomes such as quality of life. It is also recognised that the evidence base for ACS care is very limited in regards to older patients with substantial multi-morbidity, which precludes specific recommendations being made for this patient group for most ACS interventions. In such circumstances, users of these guidelines must rely on their own clinical judgment and a shared decision-making process involving individual patients that recognises their values and preferences. Furthermore, clinical decisions should take into account the cultural and linguistic diversity of Australia's community, in particular the Aboriginal and Torres Strait Islander community. Practice advice sections include relevant comments wherever published research has specifically focussed on such patients.

2. Assessment of Possible Cardiac Chest Pain

The single most important consideration in the assessment of patients presenting with chest pain to an emergency medical setting is to identify all patients with ACS or another life-threatening condition. The inappropriate discharge of patients with acute MI (AMI) and unstable angina (UA) from the emergency department (ED) is associated with a substantial increase in mortality compared with admitted patients [14] [15] [16]. Thus, the sensitivity and negative predictive value (NPV) of Suspected ACS Assessment Protocols (Suspected ACS-AP) for the exclusion of ACS is paramount. It is equally important to use rapid and efficient assessment protocols that maximise specificity and positive predictive value (PPV) for ACS in reducing unnecessary investigations and minimising delays in the decision to discharge or admit from the ED.

Patients with ACS may present with a variety of typical (e.g. chest pain) and atypical (e.g. fatigue) symptoms (Refer to warning signs of a heart attack http://heartfoundation.org.au/your-heart/heart-attack-warning-signs). The most frequent symptoms of ischaemia other than chest discomfort include shoulder, arm, jaw and upper abdominal pain; shortness of breath; nausea; vomiting and sweating (diaphoresis).

While there are many causes for chest pain and other symptoms of possible AMI, the recommendations in this section of the guidelines relate to patients with symptoms suggestive of a coronary origin and in whom a diagnosis of an ACS (AMI or UA) has to be considered. It is beyond the scope of these recommendations to provide detailed assessment, investigation and management strategies for all conditions causing chest pain.

2.1. Initial Evaluation

Chest pain assessment is a time critical, hierarchical diagnostic process based upon the history of the presenting complaint, serial electrocardiographs (ECGs), serial biomarkers for myocardial necrosis and an assessment of the patient's risk of having an ACS. The chest pain diagnostic process can be represented by a stepped series of clinical questions:

1. Does this patient have a ST elevation MI (STEMI)? (Rule-in STEMI)
2. What alternative life-threatening or other high-risk conditions (e.g. aortic dissection, pulmonary embolus) need to be considered in the differential diagnosis, especially in the presence of cardiac biomarker elevation?
3. Does this patient have evidence of non-ST-elevation ACS (NSTEACS)? (Rule-in NSTEMI/UA)
4. Does the patient have symptomatic obstructive coronary artery disease (CAD)? (Rule-in angina)
5. Can patients at low likelihood of major adverse cardiac events (MACE) be identified with a high degree of certainty (>99%)? (Rule-out high-risk patients)
6. Does the patient understand what to do in the event of future episodes of chest pain or other symptoms after discharge?

2.1.1. Outpatient Presentation

Initial clinical assessment including history, examination, ECG and single troponin testing are unable to exclude a diagnosis of ACS by themselves. For this reason, patients who present to primary care physicians or to clinicians in other outpatient settings with chest pain (within 24 hours) and suspected ACS should be referred as soon as possible to the ED or a facility capable of definitive risk stratification and diagnosis of ACS. Patients presenting with high-risk features such as ongoing chest pain, dyspnoea, syncope/presyncope or palpitations should be referred immediately to the ED. For these patients, the goals of initial management include establishing the diagnosis with an ECG if available, and ensuring immediate access to cardiac defibrillation where possible. For this reason, patients should not drive themselves to the ED and transport by emergency medical services is recommended. Referral to ED should not depend on troponin testing. Care should be initiated where possible and includes administering aspirin and sublingual GTN in the absence of contraindications (i.e. avoid IM injections) (See 2.3.1.1-2.3.1.2).

2.1.2. Emergency Department Presentation

Patients with suspected ACS must be evaluated rapidly to identify patients with life-threatening non-ACS causes for their acute presentation, quantify risk for ACS and promptly institute appropriate management. Evidence-based clinical pathways that guide assessment and management of patients presenting with acute chest pain or other symptoms suggestive of an ACS should be used. The Australasian Triage Scale recommendation for patients presenting to the ED with chest pain is to commence assessment within 10 minutes of presentation (i.e. Category 2 priority). Historical features may alter estimates of pre-test probability for ACS, but no feature or combination of features alone rules out ACS in the absence of further investigations. Consideration should be given to patient cohorts in whom atypical presentations of ACS are more frequently encountered (e.g. people with diabetes, women, older patients, those with mental-illness, those from culturally and linguistically diverse (CALD) populations, and Aboriginal and Torres Strait Islander peoples).

2.1.3. Initial ECG and Assessment

Recommendation: It is recommended that a patient with acute chest pain or other symptoms suggestive of an ACS receives a 12-lead ECG and this ECG is assessed for signs of myocardial ischaemia by an ECG-experienced clinician within 10 minutes of first acute clinical contact. (NHMRC Level of Evidence (LOE): IIIC; GRADE strength of recommendation: Strong).

Rationale: This initial assessment is to rapidly identify patients with an acute STEMI, for whom emergency reperfusion is clinically appropriate, and who require immediate activation of a defined STEMI pathway. (Refer to Section 3.1.1). Initial assessment may also disclose patients with a high

probability of NSTEMI or UA who require admission, further confirmatory investigation and appropriate management [17] (Refer to Section 3.1.2 and 3.2). There is limited evidence exploring optimum timing of ECG acquisition and interpretation.

Benefits and harms: Approximately 2–5% of all patients with possible cardiac chest pain have a STEMI, for whom delays in identification and initiation of optimum treatment incur significant morbidity and mortality (Refer to Section 3.1.1).

Resources and other considerations: Training in ECG acquisition is required for all health services. Interpretation should be performed by an experienced clinician. Computer-assisted interpretation of the ECG may increase diagnostic accuracy, particularly for STEMI, among clinicians less experienced in reading ECGs. In some settings (e.g. rural and remote areas), ECG interpretation may be supported by linking local clinicians with experienced clinicians via one or other telemedicine modalities (fax/telephone, digital ECG network, video consultation) within a clinical network [18,19].

Practice Advice

2.1.3.1. Serial ECGs should be taken every 10-15 minutes until the patient is pain-free and compared in sequence and, where possible, with pre-existing ECGs.

2.1.3.2. Blood samples for biomarkers (cardiac troponin being preferred) should be drawn on presentation (Refer to Section 2.5).

2.1.3.3. A chest X-ray is recommended in the assessment for cardiac enlargement and identification of other non-coronary causes of chest pain where the diagnosis is yet to be established, though the utility of this investigation may be limited. If a recent chest X-ray is available for review, repeat radiological investigation may not be required.

2.2. Differential Diagnosis

The differential diagnosis of patients with chest pain is broad and includes non-ACS conditions that may be associated with ECG changes and normal or elevated troponin values (Table 3 and Refer to Section 3.1.3: Type 2 AMIs). In the absence of ECG evidence consistent with STEMI, potentially treatable, life-threatening conditions that should always be considered in the differential diagnosis of chest pain include aortic dissection, pulmonary embolism and tension pneumothorax. Non-life-threatening causes for chest pain that should be considered include gastro-oesophageal pathology, pleuritis and other pulmonary disease, muscular and skeletal causes including costochondritis, and herpes zoster. In addition, patients with myocardial oxygen supply–demand mismatch due to non-atherosclerotic and non-coronary conditions (e.g. Type 2 MI, Refer to Section 3.1.3) may also present with chest pain but who require a different management pathway to patients with type 1 MI (i.e. plaque rupture).

2.3. Initial Clinical Management

Practice Advice

2.3.1.1. Oxygen Supplementation. There are no randomised comparisons of the routine use of oxygen therapy versus room air that demonstrate improvements in clinical outcomes in patients with suspected or confirmed ACS. A randomised comparison has suggested an increase in infarct size with routine supplemental oxygen among patients who are not hypoxic [20]. The routine use of oxygen therapy among patients with a blood oxygen saturation (SaO_2) >93% is not recommended, but its use when the SaO_2 is below this level is advocated despite the absence of clinical data [21–24]. However care should be exercised in patients with chronic obstructive airways disease where the target SaO_2 is to be 88-92%.

2.3.1.2. Initial pharmacotherapy. In the presence of ongoing chest pain, nitro-glycerine (GTN) sublingual tablet (0.3-0.6 mg) or spray (0.4-0.8 mg) should be administered every 5 minutes for up to three doses if no contraindications exist (such as hypotension). If the symptoms are unrelieved, assessment for the need for intravenous (IV) GTN and/or alternative therapy should be made. In the absence of contraindications, it is reasonable to administer titrated morphine

Table 3 Differential diagnosis of causes of chest pain

Ischaemic cardiovascular causes	• ACS (e.g. acute myocardial infarction, unstable angina) • Stable angina • Severe aortic stenosis • Tachyarrhythmia (atrial or ventricular)
Non-ischaemic cardiovascular causes of chest pain	• Aortic dissection (tear between the layers of the wall of the aorta) and expanding aortic aneurysm • Pulmonary embolism • Pericarditis and myocarditis • Gastrointestinal causes (e.g. gastro-oesophageal reflux, oesophageal spasm, peptic ulcer, pancreatitis, biliary disease)
Non-cardiovascular causes	• Musculoskeletal causes (e.g. costochondritis, cervical radiculopathy, fibrositis) • Pulmonary (e.g. pneumonia, pleuritis, pneumothorax) • Other aetiologies (e.g. sickle cell crisis, herpes zoster)

Table 4 Risk Scores: TIMI score [28] (Chest pain section), GRACE Score [29] and CRUSADE score [115] (ACS risk stratification section)

Clinical risk scores						
	TIMI Risk Score for NSTEACS (points 0–7)		**GRACE Risk Score (points 2–306)**		**CRUSADE Risk Score (points 0–96)**	
Purpose	Ischaemic risk and ruling out ACS		Ischaemic risk		Bleeding risk	
Components	Age ≥ 65	1	Age	0–91	Haematocrit %	0–9
	Aspirin use in the last 7 days	1	Heart rate	0–46	Heart rate	0–11
	⩾2 angina episodes within last 24 hrs	1	Systolic BP	0–63	Systolic BP	0–63
	ST changes of at least 0.5 mm in contiguous leads	1	Creatinine	2–31	eGFR	0–36
	Elevated serum cardiac biomarkers	1	Cardiac arrest at admission	43	Female	8
	Known CAD (coronary stenosis ⩾50%)	1	ST segment deviation	30	Heart failure	7
			Elevated cardiac markers	15	Diabetes	6
	At least 3 risk factors for CAD, such as: - Hypertension >140/90 or on anti-hypertensives - Current cigarette smoker - Low HDL cholesterol (< 40 mg/dL) - Diabetes mellitus - Family history of premature CAD	1	Killip class	0–64	Peripheral vascular disease	6
Score interpretation	% risk at 14 days of all-cause mortality, new or recurrent MI, or severe recurrent ischaemia requiring urgent revascularisation • 0–1=4.7% risk • 2=8.3% risk • 3=13.2% risk • 4=19.9% risk • 5=26.2% risk • 6–7=at least 40.9% risk Derived from clinical trial patients		% risk by 6 months for all-cause mortality • 60–100 = ∼3% risk • 100–140 = ∼8.0% risk • 140–180 = ∼20% risk • >180 = >40% risk Derived from international registry of ACS patients		% risk of in-hospital major bleeding • <20 = ∼3% risk • 20–30 = ∼6% risk • 30–40 = ∼10% risk • >40 = >15% risk Derived from US-based registry of ACS patients	
Reference	Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, et al. The TIMI Risk Score for Unstable Angina/Non-ST Elevation MI, JAMA, 2000; 284:335–42		Fox KAA, Dabbous OH, Goldberg RJ, et al. Prediction of risk of death and myocardial, infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE), BMJ, 2006:333:1091.		Subherwal S, Bach RG, Chen AY, et al. Baseline Risk of Major Bleeding in Non-ST-Segment-Elevation Myocardial Infarction: The CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) Bleeding Score. Circulation. 2009; 119:1873–82	
Implementation	Easily implemented in paper format but web-based tools also available (Reference: TIMI Risk Score Calculator for UA/NSTEMI. http://www.timi.org/index.php?page=calculators)		Implementation is more easily undertaken using electronic platforms (Reference: https://www.outcomes-umassmed.org/grace/acs_risk/acs_risk_content.html)		Implementation is more easily undertaken using electronic platforms (Reference: http://www.crusadebleedingscore.org)	

ACS, acute coronary syndromes: BP, blood pressure; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; MI, myocardial infarction

or fentanyl intravenously (not pethidine) for ongoing chest discomfort at any time during the initial management (note: morphine administration has been shown to slow absorption of oral medications including ticagrelor). Non-steroidal anti-inflammatory medications should not be given due to the increased risk of MACE [25,26] in patients subsequently shown to have ACS.

2.3.1.3. 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.

2.3.1.4. Other Anti-Thrombotic Therapies. Additional anti-platelet and anticoagulation therapy or other therapies such as beta blockers should not be given to patients without a confirmed or probable diagnosis of ACS.

2.4. Risk Scores and Clinical Assessment Protocols

The process of risk stratification is to assist in estimating the probability of ACS and ACS-related morbidity and mortality. In patients presenting acutely with chest pain this process aids evaluation, treatment (drug therapies or an early invasive therapeutic approach) and disposition (cardiac care unit, monitored environment, short stay units or discharge). The process of risk stratification reduces unnecessary investigations and therapies and decreases avoidable inpatient admissions among low-risk patients [27] while identifying higher risk patients requiring longer periods of observation or further investigation before discharge.

Risk scores usually incorporate elements of history, examination findings, ECGs and biomarker values [28–32]. No risk score in isolation identifies patients at low risk for ACS who can be safely discharged without further investigation (Refer to Table 5). Suspected ACS Assessment Protocols (Suspected ACS-AP), sometimes called accelerated diagnostic protocols (ADPs), integrate risk scores and define a process of assessment that includes recommendations for biomarker testing intervals for patients with possible cardiac symptoms.

2.4.1. Use of Clinical Assessment Protocol

Recommendation: 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 that includes formal risk stratification. (NHMRC Level of Evidence (LOE): IA; GRADE strength of recommendation: Strong).

Rationale: A single meta-analysis, two randomised controlled trials (RCTs) and a large number of prospective observational trials have been published describing risk scores and Suspected ACS-APs. Risk scores include those originally derived from cohorts with ACS (TIMI [33,34,35,36,37], GRACE [38–40]) and newer tools derived from cohorts with undifferentiated chest pain (HEART [41], EDACS [31], MACS [32] rules). Formal risk stratification allows quantification of risk of MACE in patients with chest pain up to 30 days after presentation. However, if used alone, these scores lack the ability to define a low-risk population suitable for limited assessment and early discharge from ED. For example, the NPV for MACE for low-risk patients using the HEART score is 96-98% (i.e. up to 4% missed MACE rate) [30,37,41,42].

Some risk scores have been incorporated into defined Suspected ACS-APs (ADAPT [43], modified-ADAPT [36], HEART pathway [44], EDACS-ADP [31]). Several Suspected ACS-APs facilitate the early disposition of patients identified as low risk for 30-day MACE. The pathways with consistently high NPV (>99%) for MACE in validation studies, and which allow identification of patients safe for early discharge, include the ADAPT (using sensitive troponin assays), modified-ADAPT (using highly sensitive troponin assays) rules [36,43], and the HEART pathway [45]. The EDACS-ADP [31], MACS rule [32], and North American chest pain rule [46] currently have limited validation to support widespread use. Risk scores such as the TIMI score, GRACE score and HEART score cannot rule-out ACS in primary care or hospital-based settings. Suspected ACS-APs have not been assessed in a primary care setting [47]. The estimates of benefits and harms listed below are based on these Suspected ACS-APs (Table 5).

Benefits and harms: Formal risk assessment of patients with symptoms of possible ACS supports quantification of MACE risk within 30 days of assessment, may reduce misdiagnosis and inappropriate discharge from ED of patients with ACS from 2-8% to less than 1%, and increase absolute rates of early discharge of low-risk patients from ED by up to 20-40% [43,48,49]. Use of Suspected ACS-APs can assist in identifying low-risk patients (up to 40% of all patients presenting to ED with chest pain) for whom early discharge from ED may be appropriate.

Resources and other considerations: Use of formal risk scores and Suspected ACS-APs in assessing patients with chest pain should be documented and may be aided by the use of electronic decision aids. Suggested pathways/protocols and methods for monitoring their effectiveness are provided in Figures 1–3. Such documentation may inform local audit and quality improvement processes aimed at optimising appropriateness of care. Accelerated management and disposition of patients as a result of formal risk scoring integrated with Suspected ACS-APs could be highly cost-effective.

Practice Advice

2.4.1.1. Implementing a Suspected ACS-AP. In choosing among different Suspected ACS-APs, for hospitals using sensitive or highly sensitive troponin assays, the ADAPT or modified-ADAPT protocol, respectively identifies low-risk patients (<1% MACE at 30 days) on the basis of negative troponin measurement at both 0 and 2 hours, TIMI score of 0 (ADAPT) or TIMI score of 0 and 1 (Modified-ADAPT), and no ischaemic changes on ECG at both 0 and 2 hours. Suggested implementation of an ADP is presented in the Figures 1–3.

Table 5 Performance of various risk scores and Clinical Assessment Protocols in the management of suspected ACS#

Tool ^	Sens	Spec	NPV	PPV	LR	Proportion in risk group	References
High risk Risk Score (*Positive Likelihood ratios*)							
HFA – high risk	78 - 100	8 – 72	98	23	2.2-2.7	33-59%	[6,36,200]
TIMI 5-7	22	96.4	92	39	6.8	1-5%	[7,36]
GRACE ≥100	69	76	96	24	2.9	28%	[36]
HEART score 7-10					13		[30,37,201,202]
Low risk Risk Score (*Negative Likelihood ratios*)							
TIMI 0-1	89 - 98	13 - 56	96 - 99	12 - 20	0.19	23 – 51%	[30,36,200,203,204]
HEART score	58- 100	32 - 85	96-99	4-34	0.05-0.15	28 -34%	[30,41,42,205,206]
HFA - Low	100	1	100	10	0.4	1-17%	[7,36]
GRACE ≤50	99	27	100	13	0.04	24%	[36]
GRACE FFE score	93-100	35-68	100		0.4		[39,207]
MACS rule	98		99		0.09		[32,208]
Low risk Suspected ACS-APs (*Negative Likelihood ratios*)							
ADAPT ADP*	100	23	100	19	0.014	20%	[43,108]
Modified ADAPT ADP*	99	47-49	100	26-28	0.17	39-42%	[49,209]
HEART Pathway^^	99-100		99-100		0.04	20-82%	[45,48]
EDACS-ADP*	99- 100	50-59			0.011	42 - 51	[31]
NACPR (age cut-off 50)	100	20.9	100		0	18%	[46]
TRUST ADP	99	43	100	14	0.029	40%	[210]
TRAPID	97	75	99	44	0.044	17%	[86]

Note: All values are rounded to nearest whole number

#Table was modified from Fanaroff AC, et al. ''Does This Patient With Chest Pain Have Acute Coronary Syndrome?: The Rational Clinical Examination Systematic Review.'' JAMA. 2015;314(18):1955-65. [211]

^ **Abbreviations and acronyms:**

PPV: positive predictive value;

NPV: negative predictive value;

Sens: sensitivity;

Spec: specificity;

HEART: History, Electrocardiogram, Age, Risk Factors, Troponin;

HFA/CSANZ:The Heart Foundation of Australia and Cardiac Society of Australia and New Zealand (2006 guideline);

ADAPT: 2-Hour Accelerated Diagnostic Protocol to Assess Patients With Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker;

EDACS: Emergency Department Assessment of Chest pain Score;

NACPR: North American Chest Pain Rule;

ADP: Accelerated Diagnostic Protocol;

FFE: Freedom From Event;

LR: Likelihood Ratio;

TIMI: Thrombolysis in Myocardial Infarction.

Endpoints differ with some studies reporting MACE or cardiac events at 30 days*. Others report events to 6 weeks^^.

2.4.1.2. Local Validation of Suspected ACS-AP. Some centres may choose to assess and implement an alternate strategy to the recommended Suspected ACS-AP for the assessment of ED patients with possible ACS. The performance of any pathway for suspected ACS depends on the incidence of ACS within the local ED population and the subpopulation among whom the pathway is applied. Validation of an alternate locally implemented Suspected ACS-AP, including the assessment of 30-day mortality and representation with confirmed ACS in all patients presenting with chest pain, is recommended (Refer to Section 7).

2.4.1.3. Identification of Patients at High Risk for a Cardiac Cause of Chest Pain. The clinical characteristics of patients at high risk for a cardiac cause of chest pain (including ACS and other cardiac diagnoses) are described in Table 6. More than 25% of patients with these high-risk features will have a confirmed diagnosis of ACS and should be referred for inpatient investigation [5]. Several recognised high-risk groups of patients are underrepresented in current trials, including patients over the age of 85 years, patients with renal disease, HIV, familial hypertriglyceridaemia, rheumatoid arthritis or mental health disorders, and certain ethnic

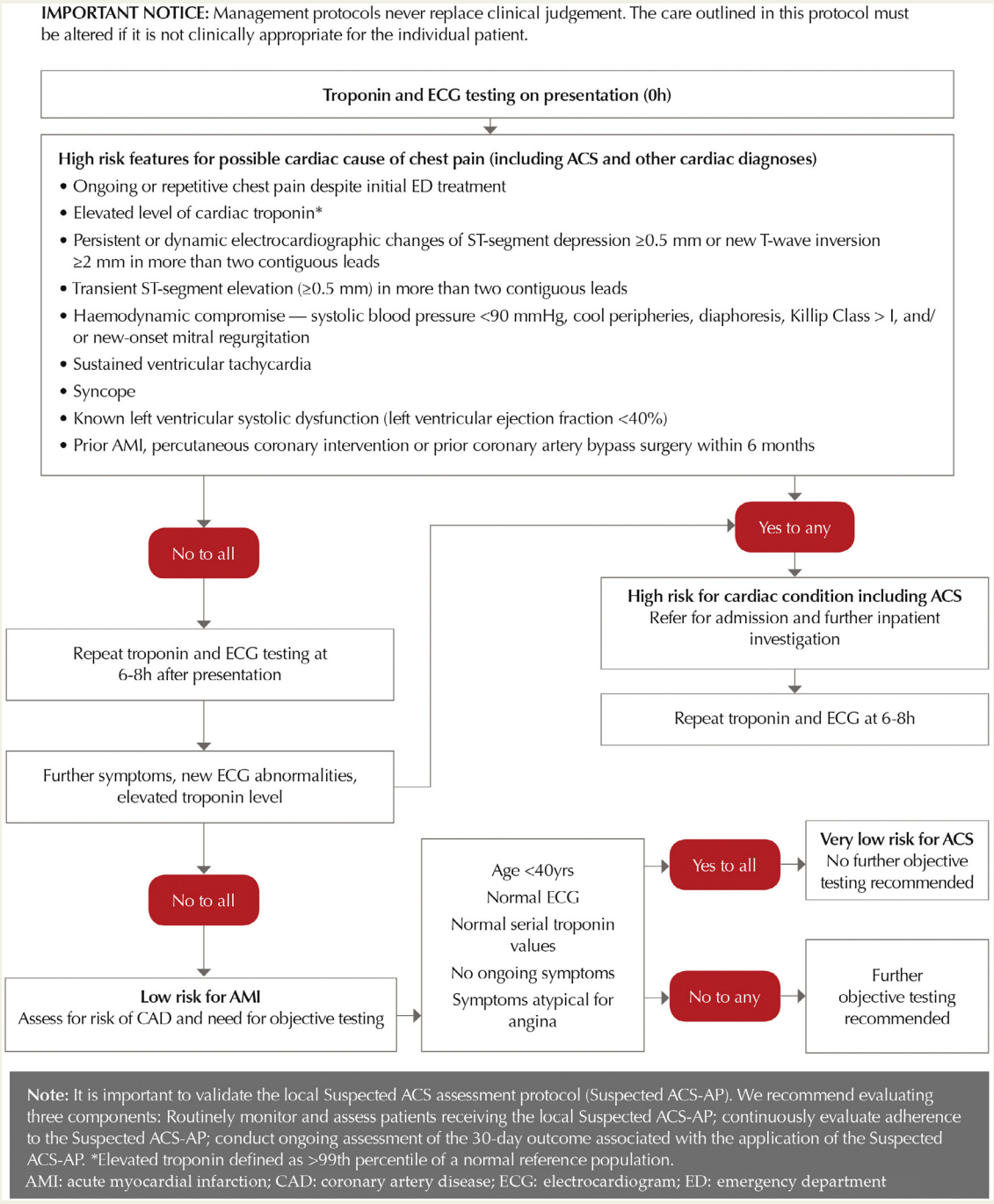

Figure 1 Example of Assessment Protocol for suspected ACS using point-of-care assays.

groups. It is also recognised that women and the elderly may present more commonly than men with atypical symptoms. A higher index of suspicion of ACS should be exercised when assessing risk in such situations.

2.4.1.4. Identification of Patients at Low Risk for a Cardiac Cause of Chest Pain. A central consideration in determining which Suspected ACS-APs are most appropriate for clinical use is the miss rate (false negative rate) for MACE that is acceptable to both patients and clinicians. One study has defined the miss rate for MACE for ED physicians as <1% at 30 days following ED presentation [50]. Little is known about patient expectations. Shared decision-making tools have reduced rates of exercise testing and hospital admission in patients with undifferentiated chest pain [51,52].

2.5. Biomarkers

Cardiac troponins are the most sensitive and specific biomarker for myocardial injury and necrosis. Both troponin I and T subtypes are cardio-specific. Troponin levels become elevated in the blood stream within 1-3 hours after AMI and

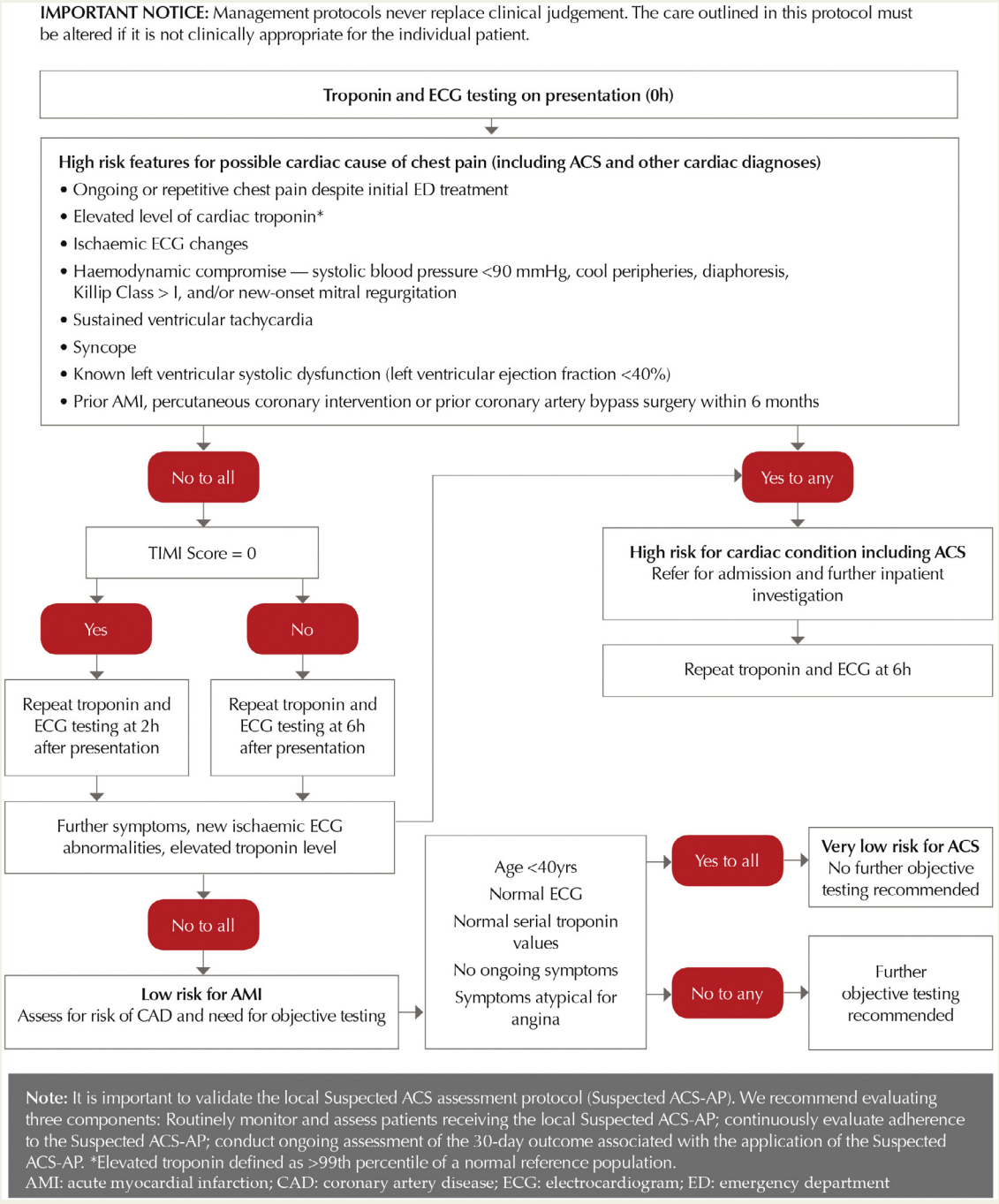

Figure 2 Example of Assessment Protocol for suspected ACS using a sensitive lab-based assay.

may remain elevated for up to 14 days. The rise and/or fall of troponin with at least one value greater than the 99th percentile is a key criterion for diagnosis of MI according to the 2012 Third Universal Definition of MI [53]. For the vast majority of patients being investigated for possible AMI, a rising pattern is suggestive of AMI. In patients who present late following AMI, troponin elevations may have peaked, and in this context a fall in troponin is significant.

Five clinical presentations of MI have been defined on the basis of pathological, clinical, and prognostic factors (Refer to Section 3.1.2 and Table 7). In the clinical setting of patients with chest pain and identification of possible AMI, Type 1 MI (spontaneous MI related to atherosclerotic plaque rupture, with ulceration fissuring, erosion or dissection) is the focus of treatment strategies. Increasingly sensitive assays (highly sensitive troponin assays) have reduced the time interval before an elevated troponin value can be detected in the setting of AMI, and may increase the diagnostic rate of NSTEMIs [54–56]. In addition, highly sensitive troponin assays have reduced the time interval over which a clinically significant change in serial troponin levels can be reliably detected.

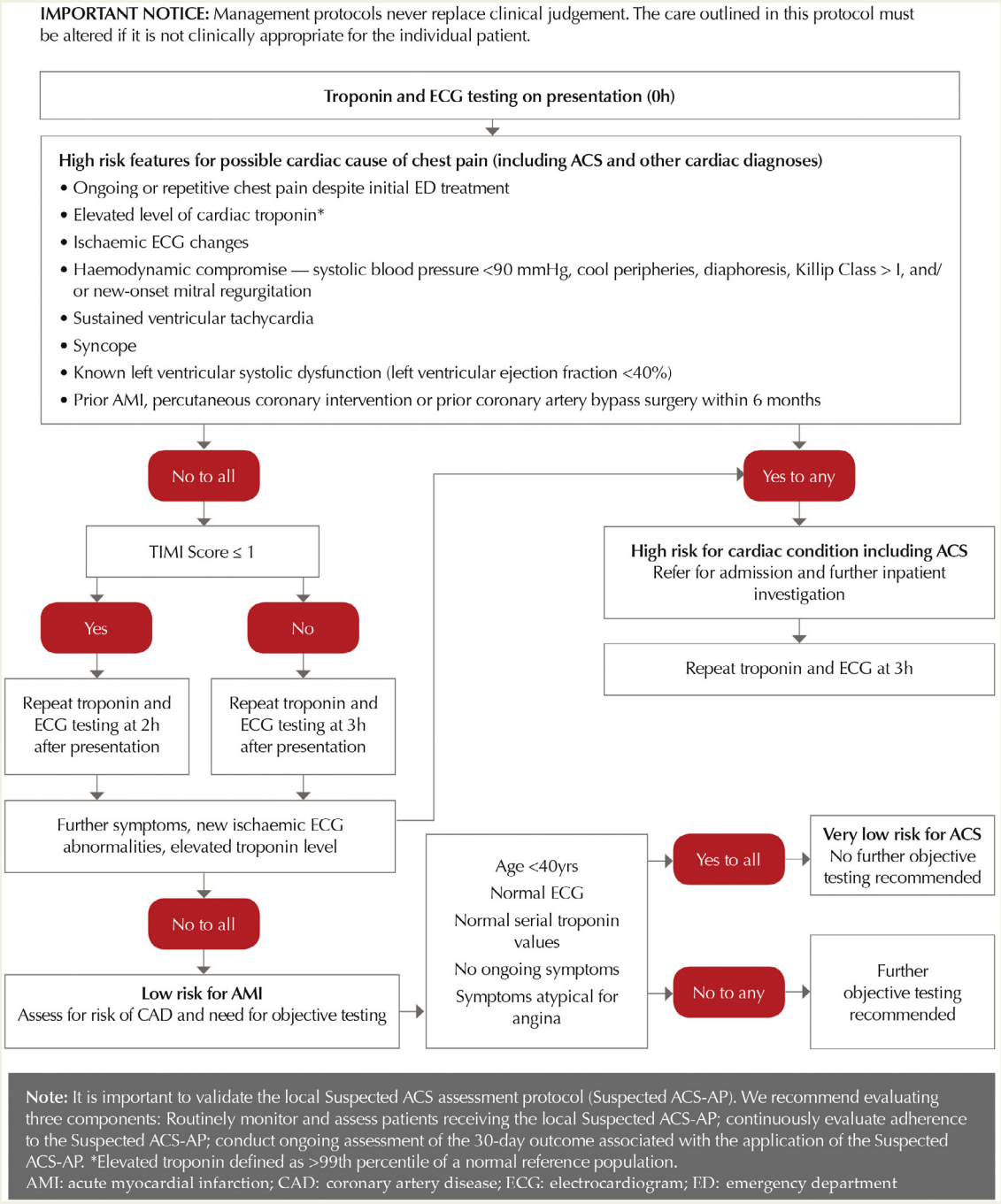

Figure 3 Example of Assessment Protocol for suspected ACS using a highly sensitive lab-based assay.

2.5.1. Troponin Testing

Recommendation: 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 [57–60]. (NHMRC Level of Evidence (LOE): 1A; GRADE strength of recommendation: Strong).

Rationale: Newer, more sensitive troponin assays can detect increasingly lower concentrations of troponin in the setting of myocardial necrosis, thus allowing earlier detection of patients with AMI. In addition, Suspected ACS-APs have been derived using both sensitive and highly sensitive troponin assays that support the early rule-in and rule-out of AMI when applied as per protocol. Serial measurement of cardiac-specific troponin levels is necessary to accommodate differences in time of presentation and to identify instances of acutely or chronically elevated troponin attributable to factors other than ACS. While the quality of evidence is moderately high, consideration must be given to the varying

Table 6 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 ECG changes (such as persistent or dynamic electrocardiographic 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 <40%) • Prior AMI, percutaneous coronary intervention, or prior CABG
Low risk	• age <40 years • symptoms atypical for angina • remain symptom-free • absence of known CAD • normal troponin level • normal ECG
Intermediate risk	• Neither high-risk nor low-risk criteria.

ECG: electrocardiogram
CAD: coronary artery disease
CABG: coronary artery bypass grafting

Table 7 Universal classification of myocardial infarction [53]

Classification	Descriptor
Type 1: Spontaneous MI	Spontaneous MI related to atherosclerotic plaque rupture, ulceration, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis.
Type 2: MI secondary to an ischaemic imbalance	Myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/bradyarrhythmias, anaemia, respiratory failure, hypotension, and hypertension with or without LVH.
Type 3: MI resulting in death when biomarker values are unavailable	Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or when cardiac biomarkers were not collected.
Type 4a: MI related to percutaneous coronary intervention (PCI)	MI associated with PCI (refer to reference for specific criteria)
Type 4b: MI related to stent thrombosis	MI associated with stent thrombosis (refer to reference for specific criteria)
Type 5: MI related to coronary artery bypass grafting (CABG)	MI associated with CABG (refer to reference for specific criteria)

CAD: coronary artery disease
LVH: left ventricular hypertrophy
LBBB: left bundle branch block

analytical characteristics and performance of different troponin assays.

Benefits and harms: The effects of routinely implementing troponin testing within a validated Suspected ACS-AP on the rate of missed MI and early mortality are difficult to quantify due to study heterogeneity and varying levels of expertise within current practice [27,61].

Resources and other considerations: Biomarker-based strategies for the rule-in and rule-out of AMI have variable accuracy. Biomarker elevation portending a clinical diagnosis of AMI may not occur in a small proportion of patients until 8–12 hours after pain onset [62]. Our understanding about timing of sampling with newer assays and differences between assays is evolving [63,64]. Clinically usable strategies must maintain safety, with missed MI rates ≤1% (NPV ≥ 99%). Clinicians must understand the analytical and performance characteristics of the local assay in use and the specific Suspected ACS-APs used in their setting which incorporate that assay. Of importance, quantitative comparisons cannot be made between troponin I and troponin T, or between point-of-care (POC) devices and laboratory based immunoassays.

Practice Advice

2.5.1.1. Definition of Elevation and Biomarker Evidence of AMI. An elevated troponin value indicating myocardial necrosis is one greater than the 99th percentile (upper reference level) for a specific assay [53]. For the diagnosis of AMI, serial samples are required to determine a rise and/or fall in values. The optimum change value for identification of AMI is usually assay specific and depends on the degree of initial elevation (if present), the time interval between consecutive samples, the time of pain onset and the possible presence of non-ACS causes of elevated troponin (Refer to Section 3.1.2). Absolute changes in nanograms per litre using highly sensitive troponin assays have better diagnostic accuracy for AMI than relative change values [65–67]. In patients with a high clinical suspicion of ACS, troponin values below or close to the 99th percentile, changes of ≥ 2–3 standard deviations of variation around the initial value, depending on the assay, should prompt additional testing, as this is unlikely to reflect normal biological variability [53] [65]. Laboratory reports should indicate whether clinically significant changes in troponin values of a specific assay have occurred. It should be noted that non-ACS causes of chest discomfort may also result in a rise and fall in serial troponin levels (e.g. pulmonary embolus, myocarditis and extreme exercise: See Table 8). False positive results due to analytical issues may be detected by using an alternate assay.

2.5.1.2. Assays. Nomenclature used for describing assay types may cause misunderstandings of assay capabilities and performance that could lead to incorrect use of early assessment strategies. The majority of cardiac troponin assays are performed on automated platforms within centralised laboratories using sensitive or highly sensitive assays. Without access to central laboratories or automated assay platforms, POC assays are also in use and those with highest sensitivity for detecting troponin are recommended [68]. The analytical characteristics of assays as reported by the manufacturers are available at <www.ifcc.org/media/276661/IFCC%20Troponin%20Tables%20ng_L%20DRAFT%20Update%20NOVEMBER%202014.pdf>

Table 8 Causes of troponin elevation*

Cardiac contusion, or other trauma including surgery, ablation, pacing, frequent defibrillator shocks
Congestive heart failure — acute and chronic
Coronary vasculitis, e.g. SLE, Kawasaki syndrome
Aortic dissection
Aortic valve disease
Hypertrophic cardiomyopathy
Tachy- or bradyarrhythmias, or heart block
Stress cardiomyopathy (Takotsubo cardiomyopathy)
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 e.g. anthracyclines, CO poisoning
Critically ill patients, especially with respiratory failure or sepsis
Hypoxia
Burns, especially if affecting > 30% of body surface area
Extreme exertion
False positives: Cross reacting heterophile antibodies

*Life–threatening, non-coronary conditions highlighted in bold

Highly sensitive assays are those with total imprecision (coefficient of variation) at the 99th percentile value ≤10% and the ability to measure troponin concentrations below the 99th percentile that are above the assay's limit of detection in at least 50% (and ideally >95%) of healthy individuals [67,69]. All other troponin assays are labelled *sensitive* or *contemporary assays*.

POC assays currently have lower analytical sensitivity for detecting troponin, with no currently commercially available assay meeting high sensitivity criteria [70] [71,72] [69,73]. The shorter turnaround times for POC assays may aid further management for patients with elevated values detected on early (within 2 hours of presentation) or late (>12 hours) sampling. In addition, serial sampling over 6–12 hours after presentation may be used for the rule-out of AMI, while early repeat testing (1-3 hours) in patients with initial troponin elevation may be useful for documenting a rise/fall in troponin for ruling in MI. Strategies to use POC assay results in isolation of an evidence-based Suspected ACS-AP in early rule-out for AMI are insufficiently sensitive and cannot be supported at this time. Decisions based on POC testing are not recommended if laboratory troponin test results are available within one hour of request.

Patients with suspected or proven ACS, in whom transfer to another site is necessary, should have blood samples, stored at 4° C, accompany them for repeat analysis using the troponin assay used at that site.

2.5.1.3. Timing of Testing. The majority of patients with an underlying diagnosis of AMI have elevated troponin values within 3-6 hours of symptom onset, although some assays may not show elevated values for up to 12 hours [54,74] (Table 9). Despite improvements in troponin assay sensitivity and use of Suspected ACS-APs, an initial troponin value from a blood sample taken on ED presentation that is below the 99th percentile of a sensitive or highly sensitive assay cannot be used by itself for the rule-out of AMI [75,76]. Whether an initial value below the limit of detection for a highly sensitive assay rules out AMI is yet to be established in prospective studies that i) clearly delineate the time interval between pain onset and collection of initial troponin [77–84], and ii) report on the outcomes of this strategy utilised in clinical care.

The time of symptom onset, even if reliable, does not define the time point of coronary occlusion. Early rule-out biomarker strategies must incorporate serial samples that detect

Table 9 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 assays
0 hour (single sample)	Patients with value <LoD of the specific assay (**not** >99th percentile cut point) and symptom onset >3 hours[^] [78,87,88]	Highly sensitive assays
0 and 1 hours after presentation	Rule-in and rule-out AMI algorithms [83,89,90] (cut points are assay-specific and not the 99th percentile)	Highly sensitive assay
0 and 2 hours after presentation	ADAPT protocol [43] Modified ADAPT protocol [49,57] (cut points are the assay-specific 99th percentile)	Sensitive assays Highly sensitive assays
0 and ≥3 hours after presentation	Previous NHF protocol [9] HEART pathway, [45,48] (cut points are the assay-specific 99th percentile)	Highly sensitive assays Both sensitive and highly sensitive-assays
0 and ≥6-12 hours after presentation	Rule-in and rule-out AMI algorithms [10] (cut points are the assay-specific 99th percentile)	Sensitive and point-of-care assays

LOD = limit of detection
AMI = Acute myocardial infarction
ADAPT = 2-Hour Accelerated Diagnostic Protocol to Assess Patients With Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker
NHF = National Heart Foundation of Australia
HEART = History, Electrocardiogram, Age, Risk Factors, Troponin
[#] With concurrent clinical risk stratification
[^] Reports on the use and outcomes of the biomarker strategy in clinical practice are not currently available

a rising/falling pattern, timed from the initial sample taken at ED presentation. Possible exceptions to this are patients who are symptom-free for 12 hours prior to assessment, or present >3 hours after symptom-onset with values less than the limit of detection (LoD) using a highly sensitive troponin assay. Additional troponin testing should be performed in patients with ongoing or recurrent symptoms of ischaemia.

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 one to two hours after presentation [57,83–86]. Incorporation of sensitive or highly sensitive troponin assay results into the ADAPT- and modified ADAPT-ADP respectively allows early (two hours after ED presentation) risk stratification [43,49] (see Figures 2 and 3).

2.5.1.4. Cut Points for the Determination of an Abnormal Troponin Value. While the universal definition of myocardial infarction defines an elevated troponin value of greater than the 99th percentile as abnormal, novel strategies often report values in alternate troponin concentrations [78,83,87–90]. Some strategies have been assessed in multiple large cohorts and the results are reassuring in regards to safety for the exclusion of AMI when the specific parameters are met. Further research reporting the outcomes in clinical practice of utilisation of such strategies are needed. The evidence for the use of sex-specific reference ranges for high sensitivity assays is evolving [91]. For females, the sex-specific cut point identifies patients at greater long-term risk of adverse events [56,92,93]. Further research is needed to clarify the optimum strategy for both males and females.

2.5.1.5. Other Biomarkers Beyond Troponin. Creatine kinase myocardial enzyme (CK and CK-MB) and myoglobin are not useful for the initial diagnosis of ACS where there is access to troponin testing

2.5.1.6. Observation and Continuous ECG Monitoring. Patients in whom symptoms have resolved, initial ECG shows no ischaemic changes (including the absence of left bundle branch block (LBBB)) and initial troponin value is within normal reference range can be observed in an ED observation unit or chest pain unit, and do not require continuous ECG monitoring. Reinstitution of ECG monitoring should be considered for patients with subsequent elevation of troponin on serial testing.

2.6. Further Diagnostic Testing

The aims of further diagnostic testing in patients with resolved symptoms, non-ischaemic ECGs and normal serial troponin values are to diagnose significant underlying CAD and provide prognostic information. Increasingly, the utility of such testing is questioned in patients at low risk for an evolving ACS as defined by Suspected ACS-APs, which includes those with atypical symptoms, no or very few vascular risk factors, no arrhythmias or clinical features suggestive of arrhythmia and no prior heart disease. Evidence suggests that such patients are at negligible risk of MACE and further testing is not warranted [94–96] and may actually be harmful.

In patients defined as having intermediate risk, such as those with more typical pain and/or multiple risk factors, further testing may be safely performed during admission or shortly after discharge. Patients at high risk, in whom one in three will prove to have ACS, and who include those with classical crescendo angina symptoms and/or prior history of CAD, should be investigated early, as an inpatient, and managed empirically as having ACS.

Various studies have shown that a normal exercise ECG (based on achieving more than 85% predicted maximum heart rate), dobutamine or dipyridamole stress echocardiogram or coronary computerised tomography angiography (CTCA) has high NPV for ischaemia and is associated with excellent patient outcomes [97–100]. Several high quality systematic reviews and one high quality RCT for CTCA [61,99,101–105] attest to its diagnostic accuracy for CAD in patients with suspected ACS. Although both stress imaging and CTCA have greater diagnostic accuracy [106], exercise ECG is a widely available, low-cost method which, in patients with an interpretable ECG and who can exercise, can identify patients at low risk for MACE [100]. However, the quality of evidence for all objective testing strategies is inconsistent and limited to the period prior to the advent of highly sensitive troponin assays. If clinical suspicion is high despite meeting clinical criteria for very low risk, patients should continue to be evaluated according to local protocols for intermediate- or high-risk patients.

2.6.1. Selection of Patients for Further Diagnostic Testing

(a) Recommendation: 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 (NHMRC Level of Evidence (LOE): IA; GRADE strength of recommendation: Weak).

(b) Recommendation: Patients in whom no further objective testing for CAD 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 CAD, with normal troponin and ECG testing and who remain symptom free (NHMRC Level of Evidence (LOE): III-3C; GRADE strength of recommendation: Weak).

Rationale: A small but significant proportion (<4%) of patients presenting with possible cardiac chest pain in whom biomarker and ECGs are normal have UA and underlying CAD [5]. Important diagnostic and prognostic information is derived from objective testing which may guide further diagnostic procedures and support therapeutic interventions to alter short- and long-term coronary risk.

Benefits and harms: The benefit of diagnosing UA is to allow the timely instigation of therapy to improve prognosis. The

harms include needless downstream interventions (including invasive strategies and each with their own risks) and provocation of patient anxiety in response to an incorrect or highly unlikely diagnosis of coronary-related pain. Appropriate identification of pre-test risk is required to optimally balance the benefits and harms.

Resources and other considerations: Considerable healthcare resources may be consumed by the inappropriate use of testing procedures in patients with low pre-test probability of ACS. The aim of improving short- and long-term outcomes in patients with UA must be balanced against the cost effectiveness of downstream interventions [5]. Conversely, constraints on the availability and expertise of local investigative facilities in regional and smaller community hospital settings can hamper appropriate evaluation of patients at higher risk in the absence of service networks which link these locales with expert advice.

Practice Advice

2.6.1.1. Test Selection – Functional Versus Anatomical. The choice of objective test is based on patient criteria (ECG interpretability, ability to exercise), diagnostic accuracy, local expertise and available technologies, and risks and costs associated with specific investigations, including equipment, radiation and contrast risks. Treadmill exercise testing is useful in patients without contraindications and able to exercise, due to widespread access, simplicity, low risk, low cost and understanding of its utility in prognostication by clinicians; however its overall benefit is not clearly defined. Studies available prior to the availability of troponin assays showed NPV of 97-99% for AMI and death [100]. Anatomical investigations including CTCA and functional imaging tests such as stress echocardiography are sensitive for the diagnosis of CAD. While there is evidence that stress echocardiography and CTCA are superior to exercise stress testing [61,99,107], access to these modalities is limited in many ED settings and the overall incremental benefit is not proven. Whether CTCA can be used, as part of a Suspected ACS-AP, to identify a subset of low-risk patients with normal coronary arteries who do not need delayed troponin testing is under active investigation [61,99,107], although cost, access, resource implications and risk of radiation exposure to large numbers of low risk patients may counterbalance any benefits.

Note: Clinical scenarios where ECG-only exercise testing may be inappropriate or provide sub-optimal diagnostic accuracy: bundle branch block; left ventricular hypertrophy (LVH) on voltage criteria or previous LV imaging; digoxin therapy; mitral valve prolapse; severe valvular disease; pre-excitation syndromes; severe cardiomyopathy; pacemaker in situ; women <50 years; anaemia (Hb <90 g/dL); uncorrected electrolyte abnormalities; inability to exercise to achieve maximum predicted heart rate; concomitant beta blocker therapy.

2.6.1.2. Timing of Testing. High-risk patients require further objective testing during the index admission. Intermediate risk patients may be safely accelerated for early inpatient testing or discharged for outpatient testing ideally within 7 days, although acceptable up to 14 days after presentation. Investigation prior to discharge from the ED 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 [100]. Low risk patients may not require any further investigation (Refer to Section 2.6.1.3) [43,49,108].

In patients without high-risk features and with negative biomarker and ECG testing, and who remain symptom-free, the risk of an ACS event within 30 days is <4%. A high clinical suspicion is needed in identifying patients who are at high risk for serious adverse events but who have initial normal troponin and ECG testing (e.g. classical crescendo angina symptoms, such as increasing episodes of ischaemic symptoms with less exercise or lasting longer). For a proportion of non-high-risk patients, well-defined accelerated strategies may allow early inpatient testing or delayed outpatient testing up to 30 days after presentation [43,49,108].

2.6.1.3. Criteria for Patients Requiring no Further Testing. The criteria used to define low-risk patients in whom further investigation may not be warranted has varied in studies, and criteria we have defined may be contested [94–96]. If clinical suspicion is high (e.g. patients of Aboriginal and Torres Strait Islander decent) despite meeting clinical low-risk criteria, patients should continue to be evaluated according to local protocols for intermediate or high-risk patients.

2.7. Representation With Symptoms

Patients who represent to ED with possible symptoms of NSTEACS within 30 days and who have not already undergone objective testing may warrant consideration of exercise testing, stress echocardiography, nuclear perfusion scanning or CTCA, as well as a detailed re-appraisal for alternate diagnoses. If representation has occurred after prior negative exercise testing, use of investigations with greater sensitivity and specificity should be considered.

2.8. Discharge Advice

On discharge from ED, patients who have been assessed for possible cardiac chest pain should receive a management plan which includes information about their likelihood of ACS, advice about representation with recurrent symptoms, hospital follow-up arrangements regarding subsequent testing and timing of the test (if required), and review by their local general practitioner (GP) for risk factor modification. Consideration should be given to discharge with aspirin and GTN as required.

3. Diagnostic Considerations and Risk Stratification of Acute Coronary Syndromes

The following sections pertain to those patients where ACS is the working or confirmed diagnosis.

3.1. Diagnostic Considerations

3.1.1. ST-segment Elevation Myocardial Infarction (STEMI)

ST-segment elevation on the 12-lead ECG suggests an acute epicardial coronary occlusion as a cause for the clinical presentation. The diagnostic criteria are a clinical history of typical chest discomfort or pain of ≥20 minutes duration (which may have resolved by the time of presentation) and ECG criteria with persistent (>20 minutes) ST segment elevation in ≥2 contiguous leads of:

- ≥2.5 mm ST elevation in leads V_{2-3} in men under 40 years, or
- ≥2.0 mm ST elevation in leads V_{2-3} in men over 40 years, or
- ≥1.5 mm ST elevation in V_{2-3} in women, or
- ≥1.0 mm in other leads
- or development of new onset left bundle-branch block (LBBB) [109].

In patients with LBBB, the modified Sgarbossa Criteria is useful in identifying MI: ST elevation ≥1 mm concordant with QRS (5 points); ST depression ≥ 1 mm in lead V1-V3 (3 points); ST elevation ≥ 5 mm discordant with QRS (2 points) (i.e. >3 points associated with 98% MI, but score of 0 does not rule out STEMI). It should be noted that occlusion of the left circumflex artery may not be associated with any ST segment changes on the standard 12-lead ECG, and pursuing the diagnosis with posterior lead placement may be useful, while ST segment depression in V1-3 and abnormal R waves in V1 may also indicate posterior infarction.

The differential diagnosis for ST segment elevation includes pericarditis (which is distinguished by more global ST segment elevation [often concave] across most ECG leads, often accompanied by PR depression in lead II), stress cardiomyopathy (i.e. Takotsubo cardiomyopathy) which is often difficult to differentiate without coronary angiography, and Brugada Syndrome.

In situations where expertise in ECG interpretation may not be available, an electronic algorithm for ECG interpretation (coupled with remote review by an expert) can assist in diagnosing STEMI. Local/state care pathways should incorporate means for allowing expert ECG reading within 10 minutes of first contact, integrated with clinical decision-making around timely reperfusion. The diagnosis of STEMI and therefore the decision to initiate reperfusion therapy, does not depend on results of serial ECGs or troponin testing, or chest X-ray, although these may assist in prognostication and determining the extent of myocardial injury.

3.1.2. Non-ST-Elevation Acute Coronary Syndromes (NSTEACS)

The diagnosis of NSTEACS is often more challenging than STEMI, as is the differentiation of NSTEMI from UA. In such cases, implementation of the criteria for MI contained within the Third Universal Definition of MI should be considered rather than relying on investigational evidence of cardiac injury alone (i.e. troponin elevation) [53] (Refer to Table 7). Also to be considered are alternative, and sometimes life-threatening, non-ACS diagnoses in patients with atypical features but who demonstrate elevated cardiac biomarkers. Similarly, among patients with biomarker elevation without a culprit coronary lesion identified on coronary angiography, a broad differential diagnosis including Takotsubo cardiomyopathy, myocarditis, coronary embolism, pulmonary embolus and coronary spasm should be considered. (See Table 8)

3.1.3. Type 1 Versus Type 2 Myocardial Infarction

Among those patients with confirmed MI, applying the diagnostic classification in Table 7 may help inform the choice of potential treatment pathways for ACS. Importantly, though often clinically challenging, Type 1 MI (i.e. plaque rupture) must be differentiated from Type 2 MI (oxygen supply-demand imbalance) in the context of another concurrent acute illness (e.g. pneumonia or tachyarrhythmia), and which often presents as NSTEMI. Evidence-based recommendations regarding the use of ACS interventions for patients with Type 2 MI cannot currently be made. In such circumstances, clinical assessment should be guided by pre-event likelihood of prognostically significant CAD and increased risk of recurrent cardiac events and mortality proportional to the degree of injury, while also weighing the potential impact of non-cardiac competing risks [110], including treatment-related harm [111].

3.2. Risk Stratification for Patients with Confirmed ACS

When clinician intuition of ongoing ischaemic risk is compared directly with risk estimation using risk scores such as the Global Registry of Acute Cardiac Events (GRACE) and the Thrombolysis In Myocardial Infarction (TIMI) scores, the latter show better discrimination and calibration than the former [28,29,112] (Table 4). For late mortality and recurrent MI, the GRACE risk score appears to perform better than the TIMI risk score [113] and may thus be preferred for clinical decision-making and communication with patients and families. Similarly, risk scores for bleeding risk exist, such as those derived from the CRUSADE and ACUITY cohort studies, with CRUSADE being most discriminatory [114,115]. Stratification of ischaemic and bleeding risks may be useful for guiding initiation of antithrombotic therapies, use and timing of early invasive management, and transfer to larger institutions when access to expertise or invasive facilities are not locally available. For both ischaemic and bleeding risk

Table 10 Markers of increased risk of mortality and recurrent events among patients with confirmed ACS

Risk classification	Clinical characteristic
Very High	• Haemodynamic instability, heart failure, cardiogenic shock or mechanical complications of MI • Life-threatening arrhythmias or cardiac arrest • Recurrent or ongoing ischaemia (i.e. 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<60mL/min/1.73m^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

scores, prospective evidence that their routine use improves care or outcomes is not currently available. Clinical features associated with the risk of mortality and recurrent ischaemic events are described in Table 10.

3.2.1. Integrating Stratification of Ischaemic and Bleeding Risk into Clinical Decision-Making

Recommendation: The routine use of validated risk stratification tools for ischaemic and bleeding events (e.g. GRACE score for ischaemic risk or CRUSADE score for bleeding risk) may assist in patient-centric clinical decision-making in regards to ACS care. (NHMRC Level of Evidence (LOE): IIIB; GRADE strength of recommendation: Weak).

Rationale: Several studies of ACS practice have demonstrated a mismatch between physician assessment of ischaemic and bleeding risks and those derived from validated risk models [113,116,117]. Over and under estimation of these risks may contribute to the misapplication of evidence-based guideline recommendations that are poorly aligned with individual patient choice or clinical need [118,119]. In particular, better estimation of bleeding risks may significantly impact the choice between invasive and non-invasive management [115] [114]. Nevertheless, it should be noted that many of these tools have not been validated within Aboriginal and Torres Strait Islander populations and the higher risk profile of these patients should be recognised. As yet, there are no prospective randomised trials comparing clinical judgement and use of risk scores against clinical judgment alone in deciding the use of diagnostic and therapeutic interventions and assessing downstream effects on clinical outcomes.

Benefits and harms: For the endpoint of mortality or recurrent ischaemic events, no estimates of effect can be currently provided. The likelihood of an increase in adverse outcomes or the over/under use of therapies is thought to be low, but remains unproven.

Resources and other considerations: The routine use of risk tools may provide modest improvements in individualising care decisions, and may be more relevant to rural settings where clinical experience may be limited and where decisions regarding transfer to other institutions and its timing are more frequently encountered. Incorporation of routine risk scoring into local protocols with the aid of electronic risk calculators (web/mobile apps) may assist development of patient-specific clinical care plans and evaluation of the appropriateness of care within local audit and quality assurance efforts.

Practice Advice

3.2.1.1. Choice of Risk Score. For ischaemic risk, the GRACE risk score is superior to the TIMI risk score in terms of discriminating between high- and intermediate- or low-risk patients. However, estimating risk of recurrent MI or death for an individual patient depends on local validation [113]. In regards to bleeding risk scores, the CRUSADE risk score is preferred, although it has limited validation in the Australian setting.

4. Acute Reperfusion and Invasive Management Strategies in Acute Coronary Syndromes

In patients with confirmed STEMI, the immediate priority is initiation of an emergency reperfusion strategy to improve short- and long-term survival and cardiac function.

4.1. Reperfusion for STEMI

4.1.1. Eligibility for Reperfusion

Recommendation: For patients with STEMI presenting within 12 hours of symptom onset, and in the absence of advanced age, frailty and co-morbidities that influence the individual's overall survival, emergency reperfusion therapy with either primary percutaneous coronary intervention (PCI) or fibrinolytic therapy is recommended. (NHMRC level of evidence (LOE) 1A; GRADE strength of recommendation: Strong).

Rationale: The aim of reperfusion therapy is the timely restoration of coronary flow and myocardial perfusion which limits the extent of MI and reduces mortality by minimising the total ischaemic time (i.e. symptom onset to reperfusion) (Refer to Section 4.1.2). Within current practice, the options for reperfusion are primary PCI or fibrinolytic therapy. Fibrinolytic therapy, compared with control groups, reduces overall mortality at 35 days with a relative risk of 0.82 (95% CI 0.77-0.87) based on data from nine trials involving 58,600 patients [120]. This benefit was greater among those patients with anterior MI, and those presenting earlier after symptom onset. The impact on mortality through myocardial salvage is greatest in the first hour after symptom onset and diminishes with time, virtually dissipated by 12 hours [121]. An analysis of 22 randomised trials (n=50246) demonstrated an attenuation of the mortality benefit with fibrinolysis of 1.6 lives per 1,000 patients per hour delay. Within analyses of primary PCI, this loss of benefit with delay persists, although the attenuation is less prominent. In the absence of large-scale studies comparing primary PCI with conservative management, evidence of efficacy is drawn from studies comparing this strategy with in-hospital fibrinolysis.

Benefits and harm: Refer to Section 4.1.2.

Practice Advice

4.1.1.1. Confirming the Diagnosis of STEMI/LBBB: The Diagnostic Criteria are Described in Section 3.1.1. In situations where expertise in ECG interpretation may not be available, an electronic algorithm for ECG interpretation (coupled with remote review by an expert) can assist in diagnosing STEMI. Local 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.

4.1.1.2. Patients With Advanced Age and Multiple Co-Morbidities. While age is not a contraindication to reperfusion therapy, decisions regarding reperfusion should include the patient's and their family's or carer's values and preferences, and the relative benefits and harms of each reperfusion strategy (Refer to Section 4.1.2).

4.1.1.3. Patients With Resolved Chest Pain or ECG Changes. The benefit of reperfusion is not dependent on the presence of ongoing chest pain and it should be provided to patients with persistent (>20 minutes) ST elevation/LBBB within 12 hours, despite resolution of chest pain.

4.1.1.4. Patients With Ongoing Chest Pain and ECG Criteria Presenting After 12 Hours. Persistent ischaemic chest pain or haemodynamic compromise beyond 12 hours after symptom onset suggests ongoing ischaemia and potential for myocardial salvage and reperfusion for these patients should be considered. Given the lower efficacy and persistent bleeding risks associated with fibrinolysis among patients presenting late, reperfusion with primary PCI in this setting is preferred (Refer to Section 4.1.2.1).

4.1.1.5. Patients with Out-of-Hospital Cardiac Arrest. In patients with a shockable rhythm and spontaneous return of circulation associated with persistent ST elevation on the ECG, reperfusion therapy either with primary PCI or fibrinolytic therapy, is recommended. In patients with ST segment depression, emergency angiography and revascularisation, if indicated, should be considered.

4.1.2. Choice of Reperfusion Strategy

Recommendation: 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 contra-indications. (NHMRC level of evidence (LOE) 1A; GRADE strength of recommendation: Strong).

Rationale: The choice of reperfusion strategy requires consideration of time from symptom onset to first medical contact, extent of ischaemic myocardium, presence of haemodynamic compromise, bleeding risk from fibrinolytic therapy and expected delays in providing PCI, including transfer times to PCI-capable hospitals. Meta-analyses of comparative trials show primary PCI to be superior to fibrinolytic therapy in reducing mortality, recurrent MI and stroke. Compared to fibrinolysis, primary PCI provides an additional benefit of 1.5–2 lives saved per 100 patients treated [122] based on a 2003 analysis of 23 trials involving 7,739 patients. Further reductions in rates of recurrent MI and stroke were also seen. Importantly, these trials predate coronary artery stenting and contemporary peri-procedural antithrombotic therapy. For patients presenting to non-PCI-capable centres, withholding fibrinolysis and transferring in a timely manner to a PCI-capable hospital for primary PCI, compared to on-site fibrinolysis, was associated with a reduction in mortality (5.6% vs 6.8%, p<0.02), re-infarction (2.1% vs 4.7%; p<0.001) and stroke (0.7% vs 1.7%, p=0.0005) by 30 days in a meta-analysis of 11 trials (n=5741) [123]. Hence, compared with in-hospital fibrinolysis, primary

PCI may provide further reductions in 30-day mortality (0.73 [95% CI 0.62-0.86]) with additional benefits in reducing recurrent MI (OR 0.35 [95% CI 0.27-0.45] and stroke risk (OR 0.46 [95% CI 0.30-0.72]) [122].

However, the benefits of PCI over fibrinolysis depend on context. An observational analysis from the National Registry of MI in the United States demonstrated the relative benefit of primary PCI over fibrinolysis was lost after a delay to PCI of 121 minutes [124]. In addition, many trials of primary PCI (with and without transfer) did not include early angiography in the fibrinolytic arms. Data from three relatively small trials [125,126] [127] comparing primary PCI with fibrinolytic therapy as part of a 'pharmaco-invasive' strategy using more contemporary antiplatelet therapy and higher rates [~30%] of rescue PCI and early routine angiography (6-24 hours) among ~3,000 patients showed no difference in mortality. Furthermore, very early administration of fibrinolysis in the pre-hospital setting (i.e. pre-hospital fibrinolysis) may confer superior outcomes to PCI, especially among patients presenting within two hours of symptom onset [128].

Benefits and harms: Estimates of the absolute reduction in mortality by 30 days with fibrinolysis is 4% (NNTB 25) with a further 1.5-2% reduction associated with primary PCI (NNTB 50-63). This relative benefit is diminished with pre-hospital fibrinolysis and when delay to PCI is >2 hours. Fibrinolysis is associated with a 2% risk of stroke (NNTH 50) [122]. Compared with fibrinolysis, primary PCI is associated with a 1% lower risk of stroke (NNTB 100).

Practice Advice

4.1.2.1. Clinical Circumstances where the Administration of Fibrinolytic Therapy (Assuming 'Door-to-Needle' Time ≤30 Minutes) Should be Considered the Default Reperfusion Strategy

- Patients presenting to ED or suitably trained pre-hospital paramedic teams within 60 minutes of symptom onset.
- Patients presenting within 60-120 minutes after symptom onset in whom the expected delay to first device time is >90 minutes.
- Unacceptable delays in cardiac catheter laboratory activation for primary PCI.
- Patient factors likely to impede successful performance of primary PCI: e.g. severe contrast allergy or poor vascular access.

4.1.2.2. Contra-Indications to Administration of Fibrinolytic Therapy (Consider Expert Consultation)

- BP>180/110 mmHg
- Recent trauma/surgery
- Gastrointestinal or genitourinary bleeding within previous 2–4 weeks
- Stroke/TIA within 12 months
- Prior Intracranial haemorrhage at any time
- Current anticoagulation or bleeding diathesis (relative contraindication with warfarin)

4.1.2.3. Clinical Circumstances where Primary PCI may be the Preferred Reperfusion Strategy due to Reduced Efficacy or Increased Bleeding Risk with Fibrinolytic Therapy

- Longer patient delay from symptom onset (2-4 hours), primary PCI is preferred if delay between first medical contact and first device time is expected to be <120 minutes.
- Late presentation after symptom onset (>4 hours), primary PCI is preferred due to lower efficacy with fibrinolytic therapy.
- Patients with haemodynamic compromise or cardiogenic shock, with the option of urgent coronary artery bypass grafting (CABG).
- Increased bleeding risk: among the elderly, patients with significant co-morbidity.

4.1.2.4. 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, emergency and cardiology departments are critical for achieving acceptable reperfusion times. While strategies need to be tailored to the local community and their 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 fibrinolysis by suitably trained clinicians (e.g. paramedics), the bypassing, where appropriate, of non-PCI capable hospitals; and bypassing the ED on arrival in PCI 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 recommended.

4.1.3. Practical Considerations Regarding Administration of Fibrinolytic Therapy

4.1.3.1. Choice of Fibrinolytic

Currently available fibrinolytics include: tenecteplase (weight adjusted [30-50 mg] IV bolus); reteplase 10 units IV followed by 10 units IV, 30 minutes later; alteplase (weight adjusted accelerated bolus and infusion regimen); and streptokinase 1.5 million units IV infusion over 30–60 minutes. (Note that streptokinase is associated with a higher rate of hypotension and intracerebral haemorrhage and, due to a high prevalence of streptococcal antibodies, should not be used for Aboriginal and Torres Strait Islander patients). A fibrinolytic agent that can be given as a bolus dose such as tenecteplase is advisable for ease of administration, especially in the pre-hospital setting. In patients aged ≥75 years, administration of half the standard dose of tenecteplase should be considered in reducing risk of intracranial bleeding [127].

4.1.3.2. Adjunctive Pharmacotherapy

- *Antithrombin therapy:* Enoxaparin is recommended over unfractionated heparin (refer to Section 5.3.1.2) [129].

- *Antiplatelet therapy:* For fibrinolytic-treated patients, clopidogrel (300 mg loading dose and 75 mg per day) is recommended at the time of fibrinolytic therapy. Currently, the safety and efficacy of ticagrelor or prasugrel has not been studied in conjunction with fibrinolysis (i.e. within 24 hours of fibrinolytic therapy).

4.1.4. Technical Aspects of Primary PCI

4.1.4.1. Mode of Arterial Access

Radial access is preferred over femoral access, largely due to reduced local bleeding, unless there are compelling reasons to use femoral access (such as imminent deployment of an intra-aortic balloon pump (IABP) [130] [131].

4.1.4.2. Peri-Procedural Pharmacotherapy

Unfractionated heparin (UFH) or enoxaparin is indicated in patients undergoing primary PCI. Similarly, substantial data supports the use of glycoprotein IIb/IIIa inhibitors, or alternatively, bivalirudin in primary PCI (refer to Section 5).

4.1.4.3. Aspiration Thrombectomy of Infarct-Related Artery (IRA)

Meta-analysis of several studies of this procedure has shown no reduction in mortality and a small increased risk of stroke with the routine use of thrombo-aspiration of the IRA [132]. Thrombus aspiration can be considered when large thrombus burden impairs achievement of a satisfactory PCI result.

4.1.4.4. IABP for Ongoing Cardiogenic Shock

Routine IABP use in cardiogenic shock complicating STEMI treated by primary PCI has not been shown to reduce 30-day or 6-month mortality and should be avoided.

4.1.4.5. Complete Revascularisation at the Time of Primary PCI

In several small studies, complete revascularisation of all stenosed coronary arteries in patients with multi-vessel disease at the time of primary PCI, rather than IRA stenosis alone, may lessen onset of recurrent ischaemia, although the number of objective late cardiovascular events in these trials was small [133,134].

4.2. Ongoing Management of Fibrinolytic-Treated Patients

4.2.1. Transfer and Subsequent Angiography Post Fibrinolysis

(a) Recommendation: 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. (NHMRC level of evidence (LOE) IIA; GRADE strength of recommendation: Weak).

(b) Recommendation: Among patients treated with fibrinolytic therapy, for those with ≤50% ST recovery at 60–90 minutes, and/or with haemodynamic instability, immediate transfer for angiography with a view to rescue angioplasty is recommended. (NHMRC level of evidence (LOE) 1B; GRADE strength of recommendation: Strong).

Rationale: Among patients receiving fibrinolysis but who were not in a PCI-capable hospital, immediate or early transfer for angiography, and PCI if indicated, within 24 hours after fibrinolytic therapy is associated with reduced ischaemic events [135] [136]. In a meta-analysis of seven trials of 2,961 patients, no difference in mortality was observed. There was a relative risk reduction in recurrent MI and recurrent ischaemia, (OR 0.55, 95% CI 0.36-0.82) and (OR 0.25, 95%, CI 0.13-0.49). The benefit in recurrent MI persisted to 6-12 months, with no increase in bleeding or stroke risk. However, the benefits may be confounded by ascertainment bias among those having early angiography/PCI [137].

Among fibrinolytic-treated patients who do not achieve 50% reduction in ST segment elevation at 60–90 minutes after commencement of fibrinolytic therapy, and/or have persistent haemodynamic instability, immediate transfer for angiography with a view to rescue angioplasty is associated with a non-significant reduction in mortality (RR 0.69 [95% CI 0.46-1.05), but a significant reduction in re-infarction (RR 0.58 [95% CI 0.35-0.97) [138]. However, stroke was increased five-fold (RR 4.98, 95% CI 1.10-22.5), albeit in an era with predominant femoral access and a significant proportion of patients receiving streptokinase.

Benefits and harms: For the endpoint of recurrent MI, routine early transfer and angiography for patients receiving effective fibrinolysis is estimated to provide a 2.8% absolute reduction in recurrent MI by 6-12 months (NNTB 35) without any increase in bleeding events.

Current data for rescue PCI demonstrates a reduction in recurrent MI but no significant reduction in mortality. Local estimates of re-infarction rates among patients with failed reperfusion are uncertain. While no estimates of absolute benefit are provided, event rates in untreated patients are high.

Resources and other considerations: Systems of care should be developed to achieve these transfer timelines (refer to Figure 4) [139]. Urgent consultation and transfer to centres with higher clinical expertise and interventional facilities should be considered. Systems of care should be developed to provide advice and enable, when appropriate, immediate or early transfer for angiography among fibrinolytic-treated patients who are not in a PCI-capable hospital.

Practice Advice

4.2.1.1. Detection of Failed Reperfusion. Among fibrinolytic-treated patients, failed reperfusion is defined as ≤50% ST recovery on an ECG performed at 60-90 minutes. Also ongoing haemodynamic instability, and ongoing ischaemic chest pain are indications for immediate angiography

4.3. Early Invasive Management for NSTEACS

The routine provision of early coronary angiography with subsequent revascularisation (i.e. PCI or CABG as indicated)

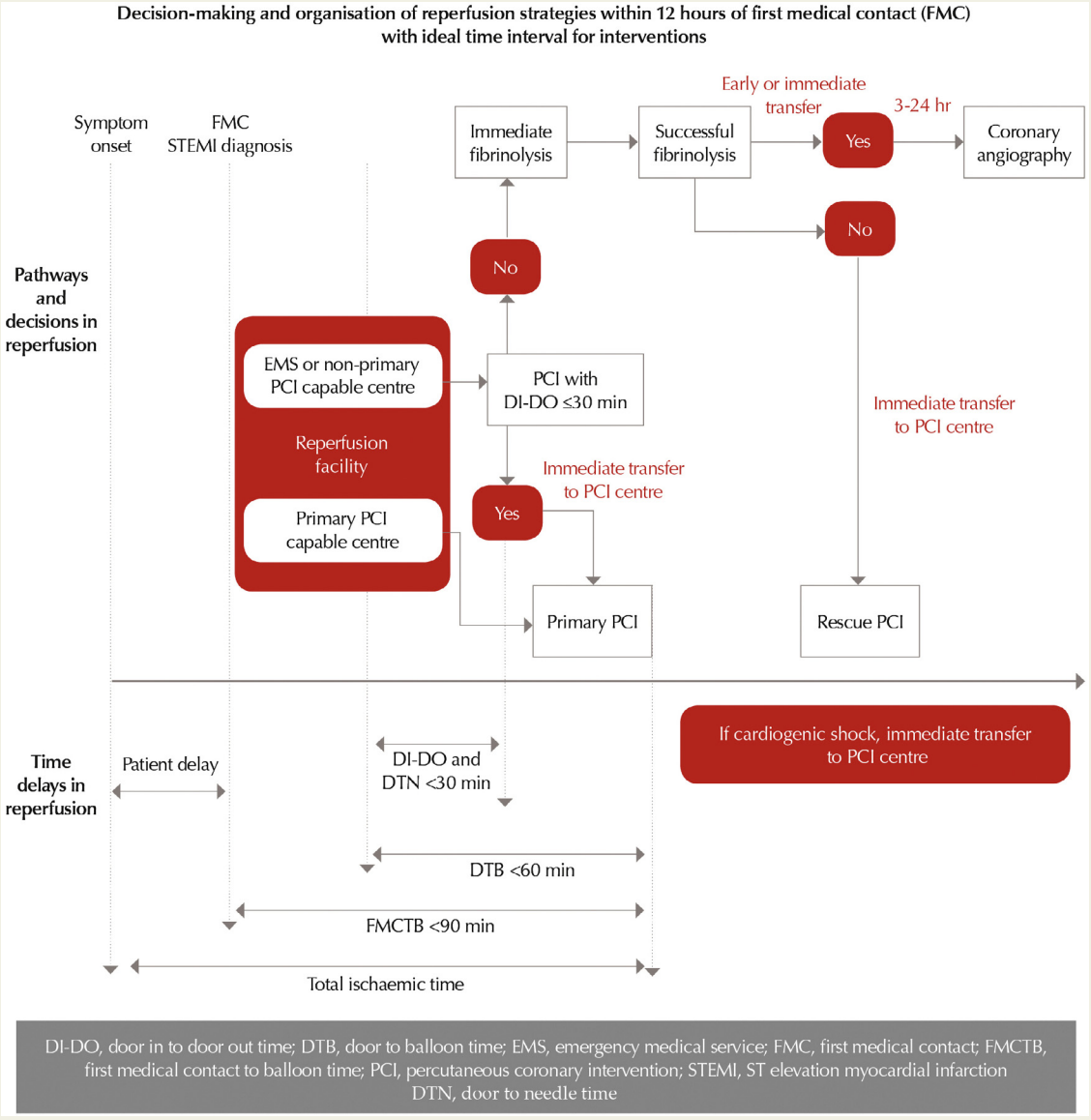

Figure 4 Decision-making and timing considerations in reperfusion for STEMI. (Adapted from [212].)

has been studied in several randomised clinical trials, observational studies and systematic reviews spanning two decades in the context of evolving patient selection criteria, adjunctive pharmacotherapies, and interventional practices. Overall, a net benefit in terms of reduction in late composite endpoints of death, recurrent MI and re-hospitalisation for ischaemia have been observed. However, no reduction in mortality alone has been observed. Patient preferences and goals of therapy, ischaemic and bleeding risk, impacts of other major co-morbidities, and the patient burden of travel from rural and remote settings to tertiary centres all need to be considered in decision-making. The following recommendations allow for latitude according to individual patient circumstances.

4.3.1. Routine Versus Selective Invasive Management for NSTEACS

(a) Recommendation: Among high- and very high-risk patients with NSTEACS (except Type 2 MI), a strategy of angiography with coronary revascularisation (PCI or CABG) where appropriate is recommended. (NHMRC Level of Evidence (LOE): IA; GRADE strength of recommendation: Strong).

(b) Recommendation: 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 (NHMRC Level of Evidence (LOE): IA, GRADE strength of recommendation: Strong).

Rationale: Several meta-analyses and systematic reviews have examined invasive management of NSTEACS [140–142]. In a Cochrane review of five randomised trials (7,818 participants) performed in the modern stent era, all-cause mortality during initial hospitalisation was associated with a non-significant early hazard with an invasive strategy (RR 1.59, 95% CI 0.96-2.64) with no difference seen on longer-term follow-up (RR 0.90, 95% CI 0.78-1.08). Rates of recurrent MI assessed at 6-12 months (five trials) and 3-5 years (three trials) were significantly decreased by an invasive strategy (RR 0.73, 95% CI 0.62-0.86; and RR 0.78, 95% CI 0.67-0.92 respectively). The incidence of early (< 4 months) and intermediate (6-12 months) refractory angina were also significantly decreased by an invasive strategy (RR 0.47, 95% CI 0.32-0.68; and RR 0.67, 95% CI 0.55-0.83 respectively), as were rates of early and intermediate re-hospitalisation for recurrent ACS (RR 0.60, 95% CI 0.41-0.88; and RR 0.67, 95% CI 0.61-0.74 respectively). The invasive strategy was associated with a two-fold increase in risk of peri-procedural MI (as variably defined) and an increase in risk of bleeding (RR 1.71, 95% CI 1.27-2.31) with no increased risk of stroke [143].

In another meta-analysis, a routine invasive strategy reduced the composite end-point of death and MI although this benefit was confined to biomarker-positive patients (OR 0.68, 95% CI 0.56-0.82) [144]. An individual patient data meta-analysis of three randomised trials with long-term follow-up out to five years reported a lower risk of cardiovascular death or MI in favour of a routine invasive strategy (14.7% vs 17.9%; HR 0.81, 95% CI 0.71-0.93), with benefit increasing according to patient risk (absolute risk reduction of 2.0%, 3.8% and 11.1% among low-, intermediate- and high-risk patients respectively) [142]. The most comprehensive meta-analysis includes 9,400 patients randomised in nine trials conducted from 1999 to 2012 [143]. Overall, the composite endpoint of death or recurrent MI was lower with routine early invasive management compared with selective invasive management (OR 0.85, 95% CI 0.76-0.95, I^2=50.4%). For the individual component end-points, greatest benefits are observed for recurrent MI (OR 0.75, 95% CI 0.66-0.87, p<0.0001) and re-hospitalisation for ischaemia (OR 0.71, 95% CI 0.55-0.90). No reductions were seen in overall mortality (OR 0.95, 95% CI 0.83-1.09). The high level of between-study heterogeneity in these meta-analyses reflect differences in adjunctive pharmacology, patient risk profiles and rates of invasive management between routine and selective arms.

Benefits and harms: When considering a routine early invasive approach, the relative benefits and harms should be weighed within the context of patient preferences and co-morbidities and competing clinical risks. A routine invasive approach to the management of NSTEACS patients is estimated to reduce the absolute rates of the combined end-point of death, recurrent MI and cardiovascular re-hospitalisation at 12 months by approximately 4.9% (NNTB 22), though the majority of this benefit is in non-fatal events.

Resources and Other Considerations:

Cost-effectiveness: The cost-effectiveness of this approach in those with substantial co-morbidities or in the setting of rural or remote patients has not been studied.

Concomitant therapies: Implementation of an early invasive strategy requires optimal use of concurrent parenteral anticoagulation (e.g. unfractionated heparin (UFH), enoxaparin, bivalirudin) (refer to Section 5.3). Aspirin is advocated in all patients with no allergy to this agent. Initiation of a $P2Y_{12}$ inhibitor (i.e. clopidogrel and ticagrelor) at the time of diagnosis is supported by evidence while benefits of initiation prior to coronary angiography in patients undergoing an early invasive approach remain uncertain (refer to Section 5.2.2.2).

Procedural considerations: The use of radial access for coronary angiography should be considered, particularly where bleeding risk is increased. The mode of revascularisation (i.e. PCI vs CABG) should consider anatomical disease burden, as well as clinical characteristics and patient preferences that may be best served with a heart team approach. The use of drug-eluting stents versus bare metal stenting depends on lesion and patient characteristics, including the need for long-term oral anticoagulation. Emerging data suggest benefits in reducing non-fatal MI associated with more complete revascularisation (i.e. the revascularisation of non-culprit coronary lesions) within the first 48 hours of presentation, but definitive evidence about effects on mortality are awaited. The value of fractional flow reserve (FFR)-guided PCI, or of complete revascularisation in the setting of FFR-guided PCI, has not been subject to randomised trials and hence no recommendations are possible currently.

Practice Advice

4.3.1.1. Mode of Revascularisation. Overall, patients suffering NSTEACS require CABG in approximately 10% of cases. The factors to be considered in deciding between PCI and CABG in NSTEACS do not differ from those among patients presenting electively. Patient comorbidities, fitness for major surgery, and coronary anatomy are the main determinants. Urgent revascularisation with CABG may be indicated for failed PCI, cardiogenic shock and mechanical defects resulting from MI (e.g. septal, papillary muscle, or free-wall rupture). Operative outcomes in emergency settings are inferior to those of elective cases, and timing needs to take the antiplatelet strategy into account. A combined heart team approach may provide the best consensus decision about the care of each individual patient.

4.3.1.2. The Elderly Patient. Chronological age, in isolation, should not determine eligibility for routine invasive strategy. Meta-analyses indicate older patients experience more events and derive greater absolute reductions in recurrent ischaemic events from the routine invasive approach, although few patients aged >80 years have been enrolled in trials, limiting the quality of evidence in the very elderly [145,146]. Elderly patients should be considered for an invasive strategy after careful evaluation of potential harms and

benefits, estimated life expectancy, co-morbidity burden, quality of life, frailty, and patient values and preferences.

4.3.1.3. Patients With Diabetes. Patients with diabetes are at increased risk of future fatal and non-fatal cardiac events following NSTEACS. Studies to date have been too small to evaluate effects of a routine invasive strategy, although there is potential for benefit given the high prevalence of multivessel CAD and benefits associated with CABG over PCI in such patients.

4.3.1.4. Patients With Chronic Kidney Disease (CKD). There are limited data regarding relative harms and benefits of a routine invasive strategy among patients with moderate to severe CKD despite their increased risk of death and recurrent cardiac events. Adequate pre-hydration with normal saline and minimal volumes of low- or iso-osmolar contrast media are recommended when employing an invasive strategy. The evidence for use of N-acetyl cysteine is heterogeneous and therefore precludes definitive recommendations.

4.3.1.5. Patients With Heart Failure. Reduced left ventricular systolic function in patients with NSTEACs is associated with an increase in late mortality, recurrent MI and re-hospitalisation. No randomised trials have assessed effects of a routine invasive strategy in such patients, although trials of CABG in patients with heart failure outside the context of ACS have shown modest benefit [147].

4.3.1.6. Rural and Remote Patients. Decisions regarding transfer of patients to PCI-capable facilities for urgent angiography in the absence of recurrent ischaemia should be based on estimated individualised risks for future events, need for other non-invasive services and informed patient preferences.

4.3.1.7. Invasive Management for Type 2 MI (refer to 3.1.3, and to Table 7). 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 which provoked the Type 2 MI.

4.3.2. Optimal Timing of Invasive Management for Patients Undergoing Invasive Strategy

(a) Recommendation: 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), an immediate invasive strategy is recommended (i.e. within two hours of admission). (NHMRC Level of Evidence (LOE): IIC; GRADE strength of recommendation: Strong).

(b) Recommendation: 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) an early invasive strategy is recommended (i.e. within 24 hours of admission), (NHMRC Level of Evidence (LOE): IC, GRADE strength of recommendation: Weak)

(c) Recommendation: 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), an invasive strategy is recommended (i.e. within 72 hours of admission). (NHMRC Level of Evidence (LOE): IIC, GRADE strength of recommendation: Weak)

Rationale: In the most comprehensive meta-analysis examining optimal timing of angiography among NSTEACS patients in whom use of invasive management had been decided, (5,370 patients within seven randomised trials; 77,499 patients within four observational studies), early or delayed intervention was defined as treatment within, or beyond, approximately 20 hours of presentation [148,149]. Overall, there was no reduction in mortality, recurrent MI or major bleeding events. Only one study (TIMACS) had sufficient power to assess the subgroup interaction (n=961) between timing of intervention and baseline patient ischaemic risk. It found a reduction in death, MI and stroke at six months associated with early (within 24 hours) versus delayed (median time 50 hours) intervention (13.9% vs. 21.0%, p = 0.005) among patients with a GRACE risk score >140 [150], with no increase in major bleeding.

Benefits and harms: Routine use of an early (within 24 hours) invasive strategy in all patients with NSTEACS, in the absence of considering individual risk, is unlikely to reduce mortality, recurrent MI or bleeding. On the basis of current data, there is little or no clinical harm or benefit associated with the use of a routine invasive strategy within 24 hours of presentation in patients who do not demonstrate very high or high-risk criteria.

Resources and other considerations: The current recommendations assume appropriate initiation of adjunctive pharmacotherapies. The cost-effectiveness of an invasive approach in patients with co-morbidities or in rural or remote settings has not been adequately delineated. Nevertheless, early angiography is associated with reduced hospital length of stay.

Practice Advice

4.3.2.1. Very High-Risk Patients. In patients, in whom the decision has been made to pursue invasive management, urgent access to coronary angiography (within two hours), which may require inter-hospital transfer, is recommended.

4.3.2.2. High-Risk Patients (see Table 10). Such patients should undergo early invasive intervention (within 24 hours).

4.3.2.3. Intermediate-Risk Patients. The risk of recurrent MI or cardiac death among patients with ischaemia on provocative testing remains low over the short term (i.e. within 30 days). This risk is influenced by the extent of LV ischaemia, with an ischaemic burden affecting >10% of the left ventricle being defined as a critical threshold. Consideration of the timing of inpatient (within 72 hours) versus outpatient angiography should consider this ischaemic burden in addition to other clinical and logistical factors.

5. Pharmacotherapy of Acute Coronary Syndromes

5.1. Acute Anti-Ischaemic Therapies

Within the acute management of patients with ongoing ischaemia, oxygen therapy, nitrates, beta blockers and opioid analgesia may have a role in offering short-term symptom relief. These therapies have not been shown to reduce the incidence of recurrent MI or death and therefore should not be considered as an alternative to early invasive management among patients where revascularisation is considered clinically appropriate. In the absence of adequate data documenting an impact on clinical outcomes, discussion of these agents is offered as practice advice.

Practice Advice

5.1.1.1. Oxygen Supplementation: Refer to Section 2.3.1.1.

5.1.1.2. Nitrates. By providing vasodilatation and lowering blood pressure, either sublingual, transdermal or IV nitrates are effective in controlling the symptoms of ischaemia. Intravenous administration is more effective but requires closer blood pressure monitoring. These agents are contraindicated in patients who have recently taken type 5 phosphodiesterase inhibitors due to the risk of profound hypotension.

5.1.1.3. Beta Blockers. Through the inhibition of catecholamine effects, beta blockers reduce ischaemia by decreasing myocardial oxygen demand. Evidence of benefit in reducing mortality with these agents is observed within large-scale meta-analyses of studies pre-dating current revascularisation and pharmacologic practices. A more recent meta-analysis [151] which stratified studies by reperfusion/revascularisation practice has suggested relative reductions in mortality of 14% in the pre-reperfusion era (incident rate ratio [IRR] 0.86, 95% CI 0.79-0.94) but not in the current era (IRR 0.98, 95% CI 0.92-1.05), interaction p-value: 0.02. Within contemporary trials, beta blockers are associated with a significant reduction in recurrent MI (IRR 0.72, 95% CI 0.62-0.83) and angina (IRR 0.80, 95% CI 0.65-0.98), but a significant increase in heart failure (IRR 1.10, 95% CI 1.05-1.16) and cardiogenic shock (IRR 1.29, 95% CI 1.18-1.40). Caution in using beta blockers should be exercised when LV function is known to be low or there is evidence of haemodynamic compromise, conduction abnormalities or inferior infarction.

5.1.1.4. Opioid Analgesia. Among patients with ongoing chest pain despite other anti-ischaemic therapies, the use of opioid analgesia (e.g. morphine, or fentanyl [not pethidine]) may be considered. However, the potential for these agents to slow gastric emptying and delay the absorption of other oral ACS therapies, in particular oral $P2Y_{12}$ inhibitors, should be considered when planning peri-procedural antiplatelet therapies.

5.2. Antiplatelet Therapy

Several parenteral and oral antiplatelet therapies have well established efficacy in patients with ACS. However, evidence continues to evolve regarding the optimal timing of initiation in association with invasive management, which combinations of agents are best for specific patients, and their effects when used concurrently with anticoagulants.

5.2.1. Aspirin

Recommendation: 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. (NHMRC Level of Evidence (LOE): IA; GRADE strength of recommendation: Strong).

Rationale: Aspirin is an inhibitor of the cycloxygenase pathway, and inhibits the collagen activation of platelets by thromboxane A_2. Its use is supported by a large collaborative meta-analysis of 15 randomised trials conducted before 1997 involving 19,302 patients [152]. Compared with placebo, aspirin reduces risk of serious vascular events (vascular death, MI and stroke) with an OR of 0.70 (95% CI 0.64-0.77). The risk of haemorrhagic stroke is increased while that of ischaemic stroke decreased, giving an overall reduction in all-stroke risk (OR 0.62, 95% CI 0.33-0.91). More recently, high-dose aspirin was compared with low-dose aspirin among 26,086 patients which showed no significant difference in ischaemic or bleeding events between groups [153]. The incremental effect of aspirin among patients treated with potent $P2Y_{12}$ inhibition is not known and is currently under investigation.

Benefits and harms: Based on contemporary event rates, aspirin is estimated to reduce the incidence of death or recurrent MI and stroke at 12 months by 5 percentage points (NNTB 21) without a discernible increase in bleeding. These effect estimates predate co-administration of contemporary antiplatelet therapy.

Resources and other considerations: Considering the favourable harm-benefit profile, ease of administration and very low cost, aspirin use should be included in all management protocols for ACS, including those for pre-hospital care.

Practice Advice

5.2.1.1. High-Risk Patients. While definitive data are lacking, the absolute benefits for aspirin are likely to be greater among patients at high risk for recurrent ischaemic events such as the elderly, diabetic patients and those with renal impairment. Enteric-coated aspirin preparations and concurrent prescription of proton-pump inhibitors (PPI) should be considered in patients at increased risk of upper gastrointestinal bleeding, especially when aspirin is prescribed in combination with other antiplatelet agents and anticoagulants. The use of enteric-coated preparations should be avoided at the time of emergency presentations due to delayed gastrointestinal (GI) absorption.

5.2.2. $P2Y_{12}$ Inhibition

Recommendation: 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 per day) is recommended in addition to aspirin (ticagrelor or prasugrel preferred: See practice advice). (NHMRC Level of Evidence (LOE): IA; GRADE strength of recommendation: Strong).

Rationale: Platelet inhibition through the antagonism of the $P2Y_{12}$ receptor has a key role in reducing recurrent ischaemic events across the spectrum of ACS patients. While the efficacy of clopidogrel (300 mg oral bolus and 75 mg daily) plus aspirin (i.e. dual antiplatelet therapy [DAPT]) over aspirin alone in ACS patients is now well established, newer more potent $P2Y_{12}$ inhibitors with superior efficacy are currently available [154] [155]. Among ACS patients undergoing PCI, prasugrel (60 mg oral bolus and 10 mg daily) was more effective than standard dose clopidogrel when added to aspirin, for reducing the composite endpoint of death, recurrent MI and stroke, but was associated with an increase in bleeding events, especially among patients requiring CABG. In patients over 75 years age or of low body weight (<60 kg) or prior cerebrovascular disease, prasugrel was associated with more harm than benefit when compared with clopiodgrel. Among intermediate- to very-high-risk ACS patients subjected to either an invasive or conservative strategy, ticagrelor (180 mg oral bolus and 90 mg twice daily) was more efficacious than clopidogrel in reducing ischaemic events among patients treated with concurrent aspirin [156]. Within this study, a small absolute, but statistically significant reduction of cardiovascular mortality was also observed, although at the expense of increased non-CABG related bleeding risk.

Summary of the $P2Y_{12}$ trials demonstrates that, compared with placebo, clopidogrel is associated with a relative reduction in death, recurrent MI or stroke (OR 0.80, 95% CI 0.72-0.90, p<0.001), and a relative increase in major bleeding (OR 1.38, 95% CI 1.13-1.67) [154]. When compared with clopidogrel, prasugrel is associated with a relative reduction in death, recurrent MI or stroke by 12 months (OR 0.81, 95% CI 0.73-0.91), and a relative increase in major bleeding (OR 1.32, 95% CI 1.03-1.68) [157]. Further, when compared with clopidogrel, ticagrelor is associated with a relative reduction in death, recurrent MI or stroke (OR 0.84, 95% CI 0.77-0.92), and a relative increase in major bleeding (OR 1.25, 95% CI 1.03-1.53) [156] when using similar definitions.

Benefits and harms: The addition of ticagrelor to aspirin among ACS patients undergoing PCI is expected to reduce the absolute rate of death, recurrent MI or stroke over 12 months by 5.3% (NNTB 19) but increase the absolute rate of in-hospital major bleeding events by 1% (NNTH 100). Adding prasugrel to aspirin among ACS patients undergoing PCI is expected to reduce the absolute rate of death, recurrent MI or stroke over 12 months by 5.7% (NNTB 18) but increase the absolute rate of in-hospital major bleeding events by 1.2% (NNTH 86). The addition of clopidogrel to aspirin is expected to reduce the rate of death, recurrent MI and stroke by 3.2 percentage points over 12 months (NNTB 31), but increase in-hospital major bleeding by 0.5 percentage points (NNTH 183).

Resources and other considerations: The incremental cost effectiveness of use of the newer $P2Y_{12}$ agents in place of clopidogrel has not been evaluated.

Practice Advice

5.2.2.1. Choice Between $P2Y_{12}$ Inhibitors. Given superior efficacy ticagrelor and prasugrel are the preferred first line $P2Y_{12}$ inhibitors. Use of ticagrelor is advised among a broad spectrum of ACS patients with STEMI or NSTEACS who are at intermediate to high risk of an ischaemic event in the absence of atrioventricular (AV) conduction disorders (second and third degree AV block) and asthma/chronic obstructive pulmonary disease (COPD). Prasugrel may be considered in patients who have not received a $P2Y_{12}$ antagonist in whom PCI is planned, but should not be used for patients >75 years of age, of low body weight (< 60 kg), or with a history of transient ischaemic attacks (TIAs) or stroke disease. Use of either prasugrel or ticagrelor, rather than clopidogrel is also recommended in patients with recurrent events on clopidogrel or who have experienced stent thrombosis. Clopidogrel is recommended for patients who cannot receive ticagrelor or prasugrel, as an adjunctive agent with fibrinolyisis or for those requiring oral anticoagulation. (Refer to relevant prescriber information documentation).

5.2.2.2. Timing of $P2Y_{12}$ Initiation. In a trial of the optimal timing of initiation for $P2Y_{12}$ inhibition in association with PCI), earlier 'pre-treatment' with prasugrel 30 mg at the time of diagnosis (before angiography) compared to 60 mg at the time of PCI following angiography did not reduce ischaemic events, but did increase bleeding events, especially in those requiring CABG [158]. A lack of treatment efficacy was also seen with pre-hospital initiation of ticagrelor compared with initiation in the catheterisation laboratory in STEMI patients [159]. Based on these limited data:

- Ticagrelor or clopidogrel should be commenced soon after diagnosis but due consideration should be given to ischaemic and bleeding risk, the likelihood of needing CABG (more likely in patients with extensive ECG changes, ongoing ischaemia or haemodynamic instability) and the delay to angiography.
- Prasugrel should be commenced immediately following diagnosis among patients undergoing primary PCI for STEMI, or after the coronary anatomy is known among those undergoing urgent PCI. Initiation of prasugrel prior to coronary angiography outside the context of primary PCI is not recommended.

5.2.2.3. Duration of $P2Y_{12}$ Inhibition in DAPT. Based on the initial $P2Y_{12}$ inhibitor trials, the standard duration of DAPT has been 12 months following the index event. However, more recent studies and a meta-analysis of prolonged therapy focussing on patients with prior MI demonstrated a relative reduction in cardiovascular death (RR 0.85, 95% CI 0.74-0.98), and recurrent MI (RR 0.70, 95% CI 0.55-0.88), but with an increase in bleeding events (RR 1.73, 95%

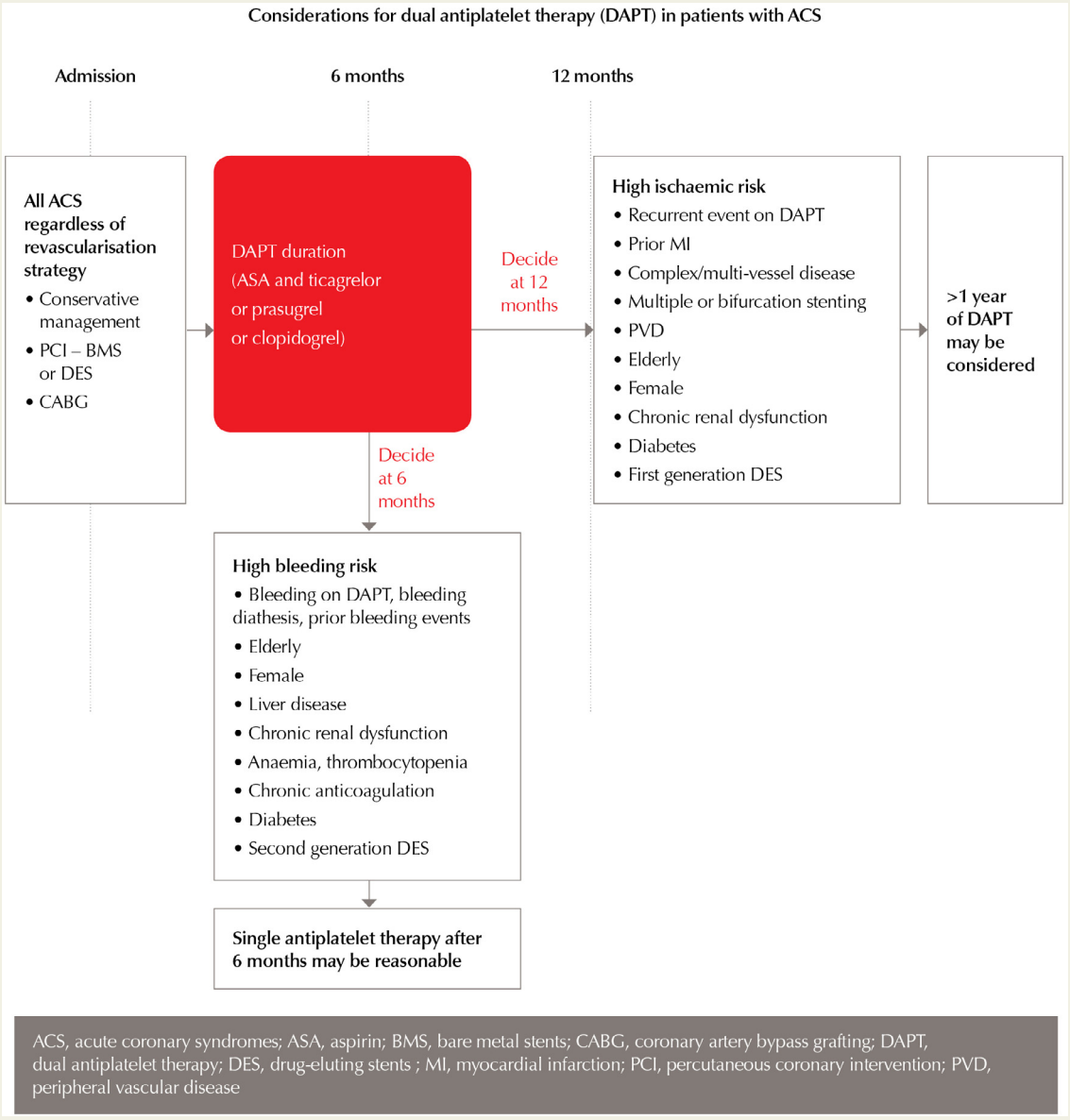

Figure 5 Considerations for dual antiplatelet therapy (DAPT) in patients with ACS [163].

CI 1.19-2.50) and no reduction in non-cardiovascular death or overall mortality. The risk of recurrent ischaemic events must be carefully weighed against the risk of bleeding events using risk scoring methods (e.g. possible tools include the DAPT Score) [160]. Extending $P2Y_{12}$ inhibition up to three years with either clopidogrel and ticagrelor [161] may be considered in patients at high-risk of recurrent ischaemic events with low bleeding risk. (Note: troponin-positive ACS identifies patients at increased risk and therefore likely to receive greater benefit in trials of prolonged DAPT following both bare metal stents (BMS) and drug eluting stents (DES)[162].) Conversely, among patients with a high bleeding risk and low risk for recurrent ischaemic events, a shorter duration of treatment (e.g. six months) may be considered. Based on the most recent systematic review of all trials and meta-analyses performed up to the time of release of these guidelines [163], Figure 5 provides guidance in regards to a comprehensive evaluation of ischaemic and bleeding risk in deciding duration of DAPT following PCI using DES.

5.2.2.4. Discontinuation of $P2Y_{12}$ Inhibition Prior to Cardiac and Non-Cardiac Surgery. The increased risk of ischaemic events and stent thrombosis should be weighed against the reduced risk of bleeding events when considering discontinuation of $P2Y_{12}$ inhibition in individual patients. Discussion between physician and surgeon should be undertaken. If these agents are to be discontinued, ticagrelor and clopidogrel should be suspended for five days, and prasugrel for seven days prior to surgery. Platelet function testing may

shorten this time interval. These agents should be recommenced as soon as feasible after the surgery.

5.2.2.5. $P2Y_{12}$ Dosing Among Patients With CKD. Dose adjustment of the $P2Y_{12}$ inhibitors for patients with stage 4 or less CKD is not required. In stage 5 CKD, ticagrelor and prasugrel are not recommended.

5.2.2.6. Genetic or Platelet Function Testing for Clopidogrel. While differences in platelet inhibition achieved by clopidogrel has been observed with various genetic polymorphisms, in association with higher rates of ischaemic events, using genetic testing to guide the dosing of clopidogrel or choice of $P2Y_{12}$ inhibitor has not been adequately examined and cannot be recommended. Similarly, reduced responsiveness to clopidogrel based on platelet function assays has been correlated with an increased recurrent ischaemic event rate, but trials of platelet function testing to guide clopidogrel dosing or choice of $P2Y_{12}$ inhibitor have not demonstrated improved outcomes and routine use of platelet function testing is not recommended.

5.2.2.7. Combination of $P2Y_{12}$ Inhibition with Long-Term Anticoagulation. Among patients with an indication for oral anticoagulation (OAC), a careful assessment of thrombotic and bleeding risks is required using CHA_2DS_2VASC and HAS-BLED scores respectively. The following advice is based on consensus opinion.

Acute management: For patients treated with either vitamin K antagonists (VKAs) or non-VKA oral anticoagulants (NOACs), indication and timing of angiography should be determined as described in Section 4.3. In patients at very high risk of recurrent ischaemic events, patients should proceed to angiography without interruption of VKA or NOAC, with radial access preferred. The initiation of $P2Y_{12}$ inhibition prior to angiography is not recommended. Low-dose intraprocedural heparin (e.g. 2000 units) is suggested in patients treated with NOACs regardless of timing of the last dose. For patients not at very high risk of recurrent ischaemic events, delay (refer to Section 4.3.2.3 and 5.3.1.4) in providing invasive management may allow for suspension of oral anticoagulation resulting in some return of coagulation function. Note, newer generation drug eluting stents appear to be associated with a lower rate of stent thrombosis and may be preferred when planning the duration of combination antiplatelet and OAC therapy.

Long-term management: In patients with a strong long-term indication for anticoagulation (i.e. mechanical heart valves, atrial fibrillation [AF] with CHA_2DS_2VASC score $\geq$2), the anticoagulant should be continued at a reduced dose (i.e. VKA, Target INR 2.0-2.5, apixaban 2.5 mg BD, rivaroxaban 15 mg daily, dabigatran 110 mg daily) and clopidogrel used, rather than ticagrelor or prasugrel.

The evidence base for triple therapy (TT) comprising aspirin, $P2Y_{12}$ inhibitor (DAPT) plus oral anticoagulant (OAC) following PCI is still evolving. In the most recent systematic review published just prior to release of these guidelines which analysed three prospective controlled trials and five non-randomised observational cohort studies comparing OAC and single antiplatelet agents with TT (OAC and DAPT) [164], there were no differences between the two groups in all-cause or cardiovascular mortality, stroke, and major bleeding, although TT was associated with significantly lower rates of MI. However, there was considerable heterogeneity between studies and analysis restricted to the controlled trials alone suggested a tendency towards fewer deaths and strokes among those assigned to OAC and single antiplatelet agents.

Given this uncertainty in the current evidence base, the duration of triple therapy should be determined by the bleeding risk.

- For patients with a HAS-BLED score <3, consider 3-6 months of triple therapy and then aspirin or clopidogrel with OAC up to 12 months.
- For patients with a HAS-BLED score $\geq$3, consider 1 month of triple therapy and then aspirin or clopidogrel with OAC up to 12 months.
- Patients with AF at low thromboembolic risk (CHA_2DS_2-VASC score =1) should be managed with dual antiplatelet therapy for 12 months, beyond which OAC may be considered.
- Routine concurrent use of a proton pump inhibitor should be considered for the duration of triple therapy.

5.2.3. Glycoprotein IIb/IIIa Inhibition

Recommendation: 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. (NHMRC Level of Evidence (LOE): IB; GRADE strength of recommendation: Strong).

Rationale: The glycoprotein IIb/IIIa inhibitors are either recombinant antibody (abciximab) or small molecule (tirofiban and eptifibatide) antagonists of platelet aggregation. Studies of intravenous (IV) glycoprotein IIb/IIIa inhibition in combination with heparin among ACS patients undergoing either invasive or conservative management were conducted in an era prior to the routine use of $P2Y_{12}$ inhibition. A meta-analysis of glycoprotein IIb/IIIa inhibition in ACS demonstrated a relative reduction in death or MI (OR 0.77, 95% CI 0.65–0.92) among patients undergoing PCI, but with an increase in major bleeding (OR 1.41, 95% CI 1.03-1.93) [165]. Collectively, these studies demonstrated reduced rates of death or recurrent MI, moreso among those with elevated biomarkers and undergoing PCI [166]. Two studies examined abciximab or tirofiban upstream among patients planned for primary PCI for STEMI, and showed marginal benefits [167] [168]. A study of abciximab among patients already treated with aspirin and clopiodgrel demonstrated benefit in those with troponin elevation [169]. While sub-group analyses have observed similar efficacy for prasugrel and ticagrelor over clopidogrel, regardless of concurrent use of glycoprotein IIb/IIIa inhibitors,

studies that compare the combination of glycoprotein IIa/IIIa and $P2Y_{12}$ inhibitors with either alone have not been conducted.

Benefits and harms: Using IV glycoprotein IIb/IIIa inhibition among ACS patients undergoing PCI is expected to reduce the 30-day absolute rate of death, recurrent MI by 2.6% (NNTB 38) but increase absolute rate of major bleeding events by 1.3% (NNTH 74). However, these estimates may overstate reduction in ischaemic risk in association with substantial uncertainty around bleeding risk due to the practice of upstream use in past clinical trials and lack of data pertaining to contemporary practice. These agents should be reserved for patients with high ischaemic risk or with thrombotic complications during PCI.

Resources and other considerations: The incremental cost-effectiveness of routine use of glycoprotein IIb/IIIa inhibitors within contemporary practice has not been evaluated.

Practice advice

5.2.3.1. Timing of Glycoprotein IIb/IIIa Inhibition Initiation. Compared to use during PCI, early 'upstream' initiation at the time of diagnosis (i.e. prior to the cath-lab) is associated with increased bleeding events without significant reduction in ischaemic events. Upstream initiation may be of benefit among patients with ongoing ischaemia, especially if there is anticipated delay in obtaining angiography.

5.2.3.2. Glycoprotein IIb/IIIa Inhibition in Patients with CKD. Dose adjustment of eptifibatide is recommended in patients with CKD stage 3, and is not recommended in CKD stage 4 and 5. Adjustment of tirofiban infusion (but not the bolus) is required in CKD stage 4 and this agent is not recommended in stage 5. No dose adjustment of abcixmab is required in CKD stage 3-5, but individual bleeding risk needs careful consideration.

5.2.3.3. Thrombocytopaenia and High Bleeding Risk. Glycoprotein IIb/IIIa inhibition is not recommended in patients with thrombocytopaenia (platelet count <100,000/mL) and should be suspended immediately if platelet count falls below this level or drops by 50% or more from baseline on monitoring of platelet counts. Platelet transfusions should only be considered for active bleeding. Intravenous glycoprotein IIb/IIIa inhibition should not be used among patients with active bleeding or receiving oral anticoagulants.

5.3. Anticoagulant Therapy

5.3.1. Heparin and Enoxaparin

Recommendation: Either enoxaparin or unfractionated heparin (UFH) is recommended in patients with ACS at intermediate to high risk of ischaemic events. (NHMRC Level of Evidence (LOE): IA; GRADE strength of recommendation: Strong).

Rationale: UFH is an indirect thrombin inhibitor while enoxaparin is a low molecular weight heparin that principally inhibits factor Xa.

Enoxaparin or UFH Versus Placebo: Early studies demonstrated the benefit of UFH among ACS patients treated with aspirin but with a rebound in ischaemic events following its cessation. Subsequently, prolonged enoxaparin (five days) was shown to be superior to UFH (two days) for preventing death or recurrent MI among conservatively managed patients. Meta-analysis of trials of NSTEACS patients largely managed conservatively suggests that low molecular weight heparin (LMWH) or UFH reduces recurrent MI (OR 0.40, 95% CI 0.25-0.63), and death or MI (OR 0.61, 95% CI 0.47-0.82), without a significant reduction in mortality. Major and minor bleeding were increased (RR 2.05, 95% CI 0.91-4.60 and RR 6.80, 95% CI 1.23-37.49 respectively).[170].

Enoxaparin Versus UFH: Enoxaparin versus UFH in primary PCI was not associated with a reduction in death or MI in a randomised comparison of 910 patients. However, a meta-analysis including both randomised studies and observational studies comparing enoxaparin versus UFH across the spectrum of patients undergoing PCI (i.e. primary PCI for STEMI, urgent PCI and elective PCI) has reported a relative reduction in mortality associated with enoxaparin (RR 0.66 [95% CI 0.57-0.76]) with this effect seen when used with primary PCI for STEMI [171]. This meta-analysis reported lower major bleeding event rates with enoxaparin. Among fibrinolytic-treated STEMI patients, prolonged enoxaparin (eight days) has also been shown to be superior to UFH (two days) for the prevention of death or recurrent MI.

Benefits and harms: In conservatively managed patients, enoxaparin or UFH reduces absolute rates of death or MI at 30 days by 4.3% (NNTB 23) but with a 1.5% absolute increase in major bleeding events (NNTH 65). Among patients managed with an invasive strategy, enoxaparin reduces absolute rates of death or MI within 30 days by 4.0% (NNTB 25) with a 1% absolute increase in major bleeding events when compared with no therapy (NNTH 105).

Practice advice

5.3.1.1. Choice Between Indirect Thrombin Inhibitors. Enoxaparin may be preferred over UFH as it does not require activated partial thromboplastin time (aPTT) monitoring and is simpler to administer. Swapping between enoxaparin and UFH has been shown to increase bleeding risk and is not recommended.

5.3.1.2. Standard Dosing. Among NSTEACS and STEMI patients not receiving fibrinolysis, the standard recommended dose of enoxaparin is 1 mg/kg subcutaneous (SC) BD. Among these patients, the recommended dosing of UFH is 60–70 units/kg IV (max 4000 units) and initial infusion 12–15 units/kg/hr (max 800 units/h) with target aPTT 1.5–2.5 x control.

5.3.1.3. Patients Receiving Fibrinolysis for STEMI. Enoxaparin with a 30 mg IV bolus (<75 years) and then 1 mg/kg SC BD is recommended in fibrinolytic-treated patients. For those ≥75 years of age the dose should be 0.75 mg/kg SC BD with no IV bolus. See dose reduction in CKD (5.3.1.5) [28,129].

5.3.1.4. Additional Dosing During PCI. In patients proceeding to PCI, those receiving UFH should receive an additional bolus (70–100 IU/kg or 50–70 IU/kg if concomitant glycoprotein IIb/IIIa inhibition IV) prior to the procedure. Dosing should consider the use of UFH prior to the procedure and guidance by activated clotting time (ACT) monitoring is advised. Patients receiving enoxaparin do not require additional dosing if the last dose was <8 hours prior to the procedure. For doses given 8–12 hours or >12 hours prior, an additional bolus of 0.3 mg/kg and 0.5–0.75 mg/kg IV respectively is recommended. For patients undergoing primary PCI, the enoxaparin dose of 0.5 mg/kg IV bolus has been studied in a small randomised comparison and was not superior to heparin. Crossing over between these agents (i.e. using enoxaparin during PCI among patients with prior UFH use or using UFH during PCI in patients treated with enoxaparin) is not recommended. UFH or enoxaparin post-PCI is not required in patients with successful revascularisation and no other indication for anticoagulation.

5.3.1.5. Enoxaparin in Patients With CKD. Enoxaparin should be dosed as 1 mg/kg daily in patients with CKD stage 4, and is not recommended in CKD stage 5. No dose reduction of UFH is required.

5.3.1.6. Enoxaparin or UFH in Patients Already Receiving Warfarin or NOACs

- Patients undergoing angiography: In patients receiving warfarin with an INR value >2.5, do not administer intra-procedural UFH or enoxaparin prior to angiography.
- Patients undergoing PCI: The safety of PCI in patients receiving NOACs without additional parenteral anticoagulation is unknown. In intermediate risk patients at low stroke risk receiving NOACs (AF with CHA_2DS_2VASC-score <4) these agents, given their relatively short half-life, may be suspended 24 hours prior to the procedure and standard intra-procedural anticoagulation initiated (refer to Section 5.3.1.2). Alternatively, additional low-dose enoxaparin (0.5 mg/kg) or UFH (60 units/kg), regardless of the last timing of administration of NOAC, can be considered. Ideally, oral anticoagulants should not be ceased in patients with atrial fibrillation and high CHA_2DS_2VASC-score (>4), mechanical heart valves, or recurrent venous thromboembolism.

5.3.2. Intravenous Direct Thrombin Inhibition

Recommendation: Bivalirudin (0.75 mg/kg IV with 1.75 mg/kg/hr 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. (NHMRC Level of Evidence (LOE): IIB; GRADE strength of recommendation: Weak).

Rationale: The direct thrombin inhibitors antagonise the actions of thrombin independent of antithrombin. In the context of primary PCI for STEMI, bolus and infusion of bivalirudin has been compared to UFH (with various rates of glycoprotein IIb/IIIa inhibitor use) in four moderate sized RCTs, totalling ~10,000 patients [172–175]. Overall bivalirudin reduced bleeding events but was associated with an increase in very early stent thrombosis, although overall ischaemic event rates were similar. Of these, a recent single centre trial with a high rate of radial access showed an increase in both ischaemic and bleeding event rates with bivalirudin as compared to UFH [175], although infusion of bivalirudin was ceased at the end of the PCI procedure rather than continued for two hours or more post-PCI which is currently recommended.

Collectively, meta-analysis of clinical trials of NSTEACS patients indicate bivalirudin is associated with a relative reduction in bleeding events (RR 0·53, 95% CI 0·47–0·61) but a trend towards increased ischaemic events, in particular stent thrombosis compared with heparin and glycoprotein IIb/IIIa inhibition [176]. Reductions in bleeding events are not apparent when compared with UFH or enoxaparin alone. A small increase in risk of early stent thrombosis has also been consistently observed. No adequately powered studies have compared bivalirudin with contemporary doses of UFH or enoxaparin (i.e. without glycoprotein IIb/IIIa inhibition) or among patients treated with prasugrel or ticagrelor.

Benefits and harms: Use of bivalirudin in ACS patients undergoing PCI is expected to reduce absolute in-hospital major bleeding event rates by 0.7% (NNTB 152) compared with heparin and glycoprotein IIb/IIIa inhibition. Greater reductions in bleeding events are likely among patients at high bleeding risk (i.e. advanced age, female gender, low body weight (<60 kg), anaemia, renal impairment, large calibre femoral access, thrombocytopaenia, known history of bleeding, use of multiple concurrent antithrombotic therapies).

Resources and other considerations: The cost-effectiveness of bivalirudin versus UFH has not been studied.

Practice advice

5.3.2.1. Dose Reduction in CKD. In CKD stage 4 and stage 5, no reduction in the bolus dose is required but infusions should be reduced to 1.0 mg/kg/hr and 0.25 mg/kg/hr, respectively.

5.3.2.2. Risk Assessment. In the context of routine assessment of ischaemic and bleeding risk, as well as the risk of stent thrombosis, bivalirudin may be preferred among patients undergoing PCI with low risk of ischaemic events and high bleeding risk.

5.4. Duration of Cardiac Monitoring

No studies have prospectively evaluated the optimal duration of monitoring among patients with suspected or confirmed ACS. Clinical assessment for the risk of life-threatening arrhythmia should be individualised based on factors known to be associated with increased risk (e.g. clinically significant arrhythmias, ongoing discomfort, failed reperfusion, haemodynamic compromise, LV ejection

fraction <40%, known stenoses of major coronary vessels, complications of PCI [side branch occlusion or distal embolisation]). The following practice advice based on the clinical status of the patient is suggested.

Practice advice

5.4.1.1 Patients with suspected ACS and unstable angina in whom symptoms have resolved, initial ECGs shows no ischaemic changes (including the absence of LBBB), and initial troponin value is within normal reference range do not require continuous ECG monitoring. Recurrent symptoms should prompt re-evaluation (refer to Section 2.5.1.6).

5.4.1.2 Patients with MI at low risk of arrhythmias (i.e. absence of risk characteristics described above) should be monitored for 24 hours or until successful revascularisation has occurred (whichever comes later).

5.4.1.3 Patients with characteristics associated with an increased risk of arrhythmias (e.g, QT prolongation (including drug-related) and prior ventricular arrhythmias) should be monitored for >24 hours.

6. Discharge Management and Secondary Prevention

Secondary prevention strategies are critically important for reducing the occurrence of new vascular events in patients surviving to discharge from hospital with a confirmed diagnosis of ACS. These strategies comprise the adoption by patients of healthy behaviours (e.g. quitting smoking, being physically active, eating healthily), intensive risk factor modification (e.g. controlling hypertension, managing diabetes mellitus) and adherence to proven cardioprotective medications (e.g. aspirin, another antiplatelet drug, statin, beta-blockers, angiotensin co-enzyme inhibitors/angiotensin receptor blockers). In addition, strategies to avoid the precipitants of ACS (medications and vaccinations) should be considered. Finally, referral to secondary prevention or rehabilitation services and the provision of a chest pain management plan are important in providing comprehensive care among patients recovering from an ACS event and transitioning to the chronic self-management of CAD.

6.1. Late and Post-Hospital Pharmacotherapy

6.1.1. Long-term Antiplatelet Therapy: Refer to section 5.2.1 and 5.2.2

Recommendations:

(a) Aspirin (100–150 mg/day) should be continued indefinitely unless it is not tolerated or an indication for anticoagulation becomes apparent. (NHMRC LOE IA, GRADE strength of recommendation: Strong).

(b) Clopidogrel should be prescribed if aspirin is contraindicated or not tolerated. (NHMRC LOE IA, GRADE strength of recommendation: Strong).

(c) 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. (NHMRC LOE IA, GRADE strength of recommendation: Strong).

(d) Consider continuation of dual-antiplatelet therapy beyond 12 months if ischaemic risks outweighs the bleeding risk of $P2Y_{12}$ inhibitor therapy; conversely consider discontinuation if bleeding risk outweighs ischaemic risks. (NHMRC LOE IIC, GRADE strength of recommendation: Weak).

Practice advice

6.1.1.1 Extending $P2Y_{12}$ inhibition up to 3 years with either clopidogrel or ticagrelor may be considered in patients at high risk of recurrent ischaemic events (e.g. particularly those receiving coronary stents or suffering ischaemic events while on aspirin) with low bleeding risk.

6.1.1.2 Consider using appropriate objective measures or risk scoring to assist in weighing future ischaemic risk and bleeding risk, as described in Section 3.2.

6.1.2. Statins

Recommendation: Initiate and continue indefinitely, the highest tolerated dose of HMG-CoA reductase inhibitors (Statins) for a patient following hospitalisation with ACS unless contraindicated or there is a history of intolerance. (NHMRC LOE IA, GRADE strength of recommendation: Strong).

Rationale: Statin therapy is effective in reducing low-density lipoprotein-cholesterol (LDL-C), reduces arterial inflammation, stabilises the lipid core, and helps to regress atherosclerotic plaque. Long-term statin therapy lowers the annual risk of major vascular event by about 20% for every 1mmol/L reduction in LDL cholesterol [177]. A meta-analysis of individual participant data from 22 trials of statin therapy versus controls (n=134,537) and five trials of high versus lower dose statins (n=39,612) reported the relative reduction in non-fatal MI, ischaemic stroke, and all-cause death per 1.0 mmol/L reduction in LDL as: 0.74 (95% CI 0.71-0.77), 0.79 (95% CI 0.74-0.85) and 0.91 (95% CI 0.88-0.93), respectively. In the subset of people with pre-existing vascular disease (n=64,443) the composite endpoint of MI, stroke, coronary revascularisation or vascular death was reduced by 20% for every 1.0 mmol/L reduction in LDL (RR 0.80 [95% CI 0.77-0.82]). Another meta-analysis of eight studies involving 13,208 patients with ACS found initiation of statin therapy before or after PCI led to 35 fewer MACE at 12 months per 1,000 treated [178]. Of note, many of the trials cited predated contemporary coronary revascularisation. High-dose statins versus no- or low-dose statins reduced the combined endpoint of death, recurrent MI and stroke (OR 0.52, 95% CI 0.37-0.73). There was non-significant reduction in MI (OR 0.81, 95% CI 0.65-1.01; P = 0.06). The benefit of fewer deaths, MI and strokes occurs within the first 6 months after ACS.

Benefits and harms: Statins are estimated to reduce the absolute 2-year vascular event rate by at least 1.1% (NNTB 93) in patients with established CAD. There is no evidence that reduction of LDL cholesterol with a statin increases cancer incidence, cancer mortality, or other non-vascular mortality.

Resources and other considerations: Referral to an accredited practising dietitian to assist with following a healthy eating pattern to improve blood cholesterol levels should be considered.

Practice advice

6.1.2.1. Timing of Initiation. Initiate statin therapy early during the ACS admission, irrespective of baseline LDL-C level. Lower intensity statin therapy should be used for those at greater risk of side effects such as myositis on the basis of otherwise unexplained chronically elevated creatine kinase levels. Recheck total and LDL cholesterol level (at approximately 3 months) and adjust statin therapy according to whether levels are at target values.

6.1.2.2. 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 LDL cholesterol level $\leq$1.8 mmol/L is suggested in the first instance.

6.1.2.3. Premature Coronary Artery Disease. While a confirmed ACS event represents an opportunity for lifestyle counselling aimed at the patient's family, events among younger patients (i.e. <50 years of age in males and <60 years of age in females) warrant the consideration of genetic predisposing factors such as familial hypercholesterolaemia, which, if confirmed on cascade screening, may lead to initiation of statins among family members.

6.1.2.4. Statin Intolerance. Given the substantial evidence base demonstrating the benefits of statins among patients with ACS, reported statin intolerance should be carefully reexamined. Some patients (up to 70%) reporting statin intolerance may tolerate reduced dose regimens or more hydrophilic agents [179].

6.1.2.5. Sub-optimal LDL. Among patients with suboptimal LDL cholesterol levels or who are statin intolerant, ezetimibe 10 mg daily should be considered [180].

6.1.3. Beta-blockers

Recommendation: Initiate treatment with vasodilatory beta-blockers in patients with reduced LV systolic function (LV ejection fraction [EF] ≤40%) unless contraindicated. (NHMRC LOE IIA, GRADE strength of recommendation: Strong).

Rationale: The evidence supporting use of beta-blockers is stronger among patients with reduced LV function following ACS. Importantly, the vasodilatory beta-blockers (e.g. carvedilol, bisoprolol, nebivolol and metoprolol succinate) reduce peripheral vascular resistance while maintaining or improving cardiac output, stroke volume and left ventricular function. They may also limit infarct size [181,182]. Beta-blocker therapy appears to reduce mortality in patients after MI [183–185], although many of the relevant trials predate current reperfusion, revascularisation, dual antiplatelet and statin practice [181,182]. A meta-analysis of 31 long-term (6-48 months) trials randomising 24,184 patients post MI to either beta-blockers or placebo, in addition to background aspirin and lipid-lowering therapy, found a 23% reduction in all-cause mortality, but no reduction in recurrent MI. When the results were stratified according to use of reperfusion or revascularisation, the benefit of beta-blockers was diminished [185] (Refer to section 5.1.1.3). However, evidence of benefit for vasodilatory beta-blockers was stronger among patients with reduced LV function following ACS. The quality of past evidence for routine beta-blocker use was strong but is no longer applicable to current practice.

Benefits and harms: With long-term care, beta-blocker therapy is estimated, on the basis of only moderate quality evidence, to lower the risk of death by 23% [186], with a NNTB of 42 for 2 years to avoid one death among patients with reduced LV function. Within current practice, the incremental benefit of beta-blockers is not well established and likely to be marginal among patients with successful revascularisation, preserved LV function, no ongoing angina or residual ischaemia. The adverse effects of beta-blocker therapy include bradycardia, hypotension, bronchospasm, fatigue, reduced libido, depression, new onset diabetes and the additional medication burden.

Practice advice

6.1.3.1 The applicability of trial evidence for long-term post MI beta-blocker therapy within contemporary practice is unclear given the widespread use of reperfusion and thrombolytic therapy, statins and renin-angiotensin-aldosterone system antagonists. Most of the data suggests a reduction in total mortality, re-infarction and sudden cardiac death in the first 3 years of beta-blocker use, particularly in patients with LV systolic dysfunction. Most of the benefit occurs within the first year of acute MI, with benefit beyond one year being less evident. Overall, low-risk asymptomatic patients or those with preserved LV ejection fraction benefit the least from beta-blocker therapy which could be ceased at 12 months. Beta-blockers continue to have a role in the medical management of stable angina.

6.1.4. Renin-angiotensin Antagonists

Recommendation: Initiate and continue angiotensin converting enzyme (ACE) inhibitors (or angiotensin receptor blockers [ARBs]) in patients with evidence of heart failure, LV systolic dysfunction, diabetes, anterior MI or co-existent hypertension. (NHMRC LOE IA, GRADE strength of recommendation: Strong).

Rationale: The purpose of renin-angiotensin antagonists post ACS is for cardioprotection. Survival following MI with or without evidence of LV systolic dysfunction or heart failure is improved by the use of ACE inhibitors [187,188], attributed to their ability to limit infarct size and reduce ventricular remodeling. The combined findings of three large trials [188] showed long-term use of ACE inhibitors significantly reduced all-cause mortality (7.8 *vs* 8.9%, p=0.0004), cardiovascular mortality (4.3 *vs* 5.2%, p=0.0002), non-fatal MI (5.3 *vs* 6.4%, p=0.0001), stroke (2.2 *vs* 2.8%, p=0.0004), heart failure (2.1 *vs* 2.7%, p=0.0007) and composite of cardiovascular mortality, non-fatal MI, or stroke (10.7% vs 12.8%, p<0.0001). Overall, ACE-inhibition is associated with a reduction in cardiovascular mortality (OR 0.82; 95% CI 0.76–0.88; p<0.0001), non-fatal MI and stroke in the context of long-term secondary prevention.

Benefits and harms: Benefits of ACE inhibitors were noted in patients taking beta-blockers, lipid-lowering agents, and antiplatelet therapy, individually or together. ACE-inhibition is expected to reduce absolute rates of major vascular events by 2.1% (NNTB 48) over 4-5 years, though this benefit is less striking among those patients with none of the listed concurrent indications. Adverse effects associated with ACE inhibitors include falls, dizziness, hypotension, hyperkalaemia, fatigue, acute kidney injury, cough and angio-oedema.

Practice advice

6.1.4.1. ACE-I vs ARB. An angiotensin receptor blocker (ARB) is an alternative to ACE inhibitors in those intolerant to such treatment, with evidence suggesting similar levels of benefit in patients with ACS and no heart failure.

6.1.4.2. Treatment of Hypertension. the primary goal of renin-angiotensin antagonism post ACS is cardiac protection. For patients with concurrent hypertension, ACE inhibitors and ARBs are indicated as first-line agents and current blood-pressure management and targets are provided in the Heart Foundation hypertension guidelines [189].

6.2. Secondary Prevention

6.2.1. Establishing a Secondary Prevention Plan and Referral to Cardiac Rehabilitation

Recommendation: Attendance at cardiac rehabilitation or undertaking a structured secondary prevention service is recommended for all patients hospitalised with ACS. (NHMRC LOE IA, GRADE strength of recommendation: Strong).

Rationale: A key component of establishing effective secondary prevention services within individuals with ACS is teaching self-management of chronic CAD, adopting healthy behaviours including regular exercise, controlling biomedical indices and adhering to cardioprotective medicines [190]. Light-to-moderate exercise (increased breathing while able to sustain a conversation) is preferred to vigorous exercise (e.g. puff and pant and unable to sustain a conversation), which has been known to trigger a cardiovascular event, particularly in people who are habitually sedentary. Among individuals with established CAD, the estimated rates for non-fatal and fatal cardiovascular events are 1 per 115,000 patient-hours and 1 per 750,000 patient hours of supervised exercise respectively [191]. Exercise-induced cardiac events are negligible in comparison to the day-to-day risk associated with being sedentary. Communication practices around the time of patient discharge, and during attendance to cardiac rehabilitation represents distinct critical times for imparting the necessary information for patients to acquire the capacity for both self-care and life-long prevention.

Earlier systematic reviews of all RCTs comparing usual medical care to either cardiac rehabilitation or structured secondary prevention in people with CAD favoured the intervention group for all-cause mortality at 1 and 3 years, particularly in those post-MI. The recent systematic review of 63 studies randomising 14,486 patients to either exercise-based cardiac rehabilitation or usual care with a median follow-up of 12 months showed falls in cardiovascular mortality and hospital admissions (RRs 0.74, 95% CI 0.64-0.86 and 0.82, 95% CI 0.70-0.96 respectively) [192]. There was no significant effect on all-cause mortality (RR 0.96, 95% CI 0.88-1.04), MI (RR 0.90, 0.79-1.04), PCI (RR 0.85, 95% CI 0.70-1.04) and CABG (RR 0.96, 95% CI 0.80-1.16). These benefits appeared to be consistent across patient categories (including those at-risk) and intervention types (comprehensive and exercise only) and independent of setting (centre-based, home or combined) and publication date (pre-1995, post-1995). An earlier meta-analysis of 63 randomised trials (n=21,295 patients with coronary disease) encompassing a variety of secondary prevention formats, components and settings reported a risk ratio of 0.85 (95% CI 0.77-0.94) for all-cause mortality over 24 months [193]. These findings included ACS patients who were stented, surgically revascularised or treated medically.

*Benefits and harms:*Among patients who attend and complete a secondary prevention program, the absolute risk of cardiovascular death, MI and stroke at 12 months is reduced by approximately 4.5% (NNTB 22) in patients recovering from ACS [192].

Resources and other considerations: Large metropolitan centres who care for significant numbers of ACS patients and are appropriately staffed and resourced will likely provide combinations of comprehensive facility and home-based cardiac rehabilitation programs for both individuals and groups. However, many ACS survivors may prefer home-based, individualised coaching services mediated by telephone or programs offered in community or primary-care settings, all of which are more convenient and accessible [194]. These various formats can be supplemented with multimedia educational resources such as manuals, DVDs and text message [190,195–198]. Contemporary cost-effectiveness analyses of different approaches to counseling and cardiac rehabilitation/secondary prevention services for patients after ACS are required.

Practice advice

6.2.1.1. Discharge Processes. While robust evidence supporting the implementation of specific local practices at the time of discharge are not available, the format and content of secondary prevention and self-care instruction is likely to be important. Furthermore, ensuring the provision of advice in a culturally and linguistically appropriate manner, with particular consideration among Aboriginal and Torres Strait Islander patients and CALD groups, is likely to be an important aspect of communication. A comprehensive, individualised and consistently delivered process for ensuring ACS patients receive the required secondary prevention information at the time of discharge is recommended.

Components of advice: During the ACS admission and, where appropriate, initiate lifestyle counselling on smoking cessation, ambulatory exercise and healthy eating. This advice should be clearly documented in the discharge communication to the patient, their companion(s) and all treating health professionals.

Chest pain management plan: Prior to discharge with a diagnosis of ACS, patients should receive an angina symptom management plan which entails guidance on the use of prescribed medicines to manage acute worsening or new unstable angina symptoms, and when and how (i.e. call ambulance rather than self-drive) to present to EDs for acute care. A copy of their latest ECG should also be provided to the patient.

6.2.1.2. Individualisation of Cardiac Rehabilitation/secondary Prevention Service Referral. A wide variety of prevention programs improve health outcomes in patients with coronary disease. Following discharge from hospital patients with ACS and where appropriate their companion(s) should be referred to an individualised preventive intervention according to personal preference, values and the available resources. Services can be hospital-based, in primary care, the local community or in the home.

7. System Considerations, Measures of Performance and Clinical Standards

Audits in Australia suggest unexplained variations in the management of ACS patients which do not accord with contemporary guideline recommendations. The intensity of care that patients receive is often inversely related to their underlying disease risk (and hence likelihood of benefit) [117], and patients with certain co-morbidities are less likely to receive evidence-based care despite the absence of contra-indications [199]. Adherence to ACS guidelines has been correlated with improvements in patient outcomes, including reduced mortality. Furthermore, an ACS Clinical Care Standards and accompanying indicator specification have recently been developed by the Australian Commission for Safety and Quality in Health Care (ACSQHC) [1]. This standard focusses on aspects of chest pain and ACS care more frequently associated with unwarranted variation, and which potentially have the greatest impact on patient outcomes. Mechanisms enabling health services in the collection of some of this data, including the National Quality Use of Medicines Indicators, have been developed and validated. It is recognised that consistently providing care as described in the Clinical Care Standard and ensuring guideline-concordant care will require the development of local protocols and pathways, combined with specific health service design characteristics that ensure consistent and timely access to individualised diagnostic expertise and therapeutic interventions. (Refer to ''Resource and other considerations'' in Sections 2.1.3, 2.4.1.3, 3.2.1, 4.1.2.3, 4.2.1.2, and 6.2.1).

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. Potentially useful quality and outcome indicators for patients presenting with suspected and confirmed ACS include:

1. Time from presentation to first ECG in patients presenting with suspected ACS;
2. Proportion and appropriate identification of suspected ACS patients managed under a Suspected ACS-AP;
3. Rate of 30-day death and MI among patients managed under a Suspected ACS-AP;
4. Door-to-device time among patients with STEMI undergoing primary PCI;
5. Door-to-needle time among patients with STEMI undergoing fibrinolysis;
6. Proportion of high-risk NSTEACS patients in whom the options for invasive management versus conservative management have been discussed;
7. Proportion of ACS patients who receive a prescription of aspirin and a $P2Y_{12}$ inhibitor at the time of discharge;
8. Proportion of ACS patients who receive a prescription of a statin at the time of discharge;
9. Proportion of ACS patients who receive a prescription of an ACE-inhibitor or ARB at the time of discharge;
10. Proportion of ACS patients who receive personalised lifestyle (diet, exercise, cessation of smoking) advice at the time of discharge;
11. Proportion of ACS patients who receive a personalised chest pain action plan;
12. Proportion of ACS patients who receive a referral to a cardiac rehabilitation or secondary prevention program;
13. The 30-day mortality rate among patients with confirmed ACS;
14. The 30-day rate of new or recurrent MI among patients with confirmed ACS;
15. The 12-month mortality rate among patients with confirmed ACS.

8. Areas for Further Research

- Randomised comparisons of very short (0 and 1 hour) ACS rule-out pathways using high-sensitivity troponin assays compared with standard care.
- The role of other biomarkers in patients with possible AMI, including heart-type fatty acid-binding protein (hFABP) and copeptin, where sensitive and highly sensitive troponin assays are available.
- Defining patients who do not need further objective testing for symptomatic ischaemia or anatomically significant CAD.
- Appropriate length of stay for MI.
- The efficacy in terms of bleeding events and ischaemic events of single antiplatelet therapy with newer $P2Y_{12}$ inhibitors, compared with dual antiplatelet therapy following ACS.
- Optimal combinations of antiplatelet therapies and long-term anticoagulation for patients at various degrees of risk for recurrent ischaemic and bleeding events.
- The cost-effectiveness of current and emerging approaches to secondary prevention programs.
- The fidelity of specific performance measures in chest pain assessment and ACS care and their correlation with late clinical and patient reported outcomes.

9. ACS Therapies Currently not Approved in Australia

9.1. Rivaroxaban

Rivaroxaban, an oral factor Xa inhibitor is approved (15 mg or 20 mg orally daily) for use among patients with non-valvular atrial fibrillation. Among patients with ACS *without known atrial fibrillation*, 2.5 mg and 5 mg twice daily dosing has been studied in addition to dual antiplatelet therapy for a duration of 13–31 months. Both doses were associated with reductions in cardiovascular death, recurrent MI and stroke, with the 2.5 mg dose reducing cardiovascular mortality (2.7% vs 4.1%, p=0.002) and all-cause mortality (2.9% vs 4.5%, p=0.002). However, rivaroxaban increased the rate of non-CABG related major bleeding (2.1% vs 0.6%, P<0.001) and intracerebral haemorrhage (0.6% vs 0.2%, P=0.009). Use of rivaroxaban in these doses in addition to dual anti platelet therapy will require careful clinical assessment of ischaemic and bleeding risk. This agent is not currently approved for use for this indication and at these doses in Australia.

9.2. Cangrelor

Cangrelor is an intravenous agent with immediate onset, short-acting (duration 1–2 hours) reversible $P2Y_{12}$ inhibitor which has been shown in meta-analysis of several PCI trials involving patients with ACS to reduce periprocedural MI with only modest increase in bleeding events, particularly among patients not initially loaded with clopidogrel (note: in STEMI, absorption of the oral $P2Y_{12}$ inhibitors is slowed and platelet inhibition may be delayed by several hours). Compared with clopidogrel initiated at the time of PCI, cangrelor is associated with a relative reduction in death, recurrent MI, urgent revascularisation and stent thrombosis by 48 hours of 13% (OR 0.87, 95% CI 0.78-0.99, p=0.007), and a relative increase in major bleeding of 38% (OR 1.38 95% CI 1.03-1.85, p=0.029). This agent may have a role as a periprocedural antiplatelet therapy in patients not adequately loaded with oral $P2Y_{12}$ inhibition.

9.3. Fondaparinux

Fondaparinux is a synthetic pentasaccharide parenteral selective factor Xa inhibitor that binds reversibly and non-covalently to antithrombin with high affinity, thereby preventing thrombin generation. In NSTEACS, the recommended dose is 2.5 mg daily subcutaneously. Large-scale clinical trials have demonstrated non-inferiority of this agent when compared with enoxaparin, with substantial benefits in terms of reduced bleeding events. However, when used among patients undergoing early invasive management, supplemental heparin is required to prevent catheter thrombosis. This agent is not currently approved for use in Australia for patients with ACS and no future application is anticipated. Therefore, no formal recommendation regarding the use of this agent is provided.

9.4. Vorapaxar

Vorapaxar is an orally active PAR-1 inhibitor of the thrombin receptor activating peptide (TRAP), thereby inhibiting platelet aggregation. A secondary prevention study of 26,449 patients with MI, stroke and peripheral vascular disease, randomisation to vorapaxar was associated with a lower rate of cardiovascular death, MI and stroke over three years (vorapaxar 9.3% vs placebo 10.5%, HR 0.87; 95% CI 0.80-0.94, p<0.001). However clinically significant bleeding events, including intracerebral haemorrhage, occurred with greater frequency than the reduction in ischaemic events (vorapaxar 15.8% vs. placebo 11.1%, HR 1.46; 95% CI 1.36-1.57, p<0.001). This agent is not currently approved for use in Australia.

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Acknowledgement of Contribution to the Development of the Heart Foundation/CSANZ ACS Guideline 2016

We acknowledge the following for their contribution to the development of the NHFA/CSANZ: Australian clinical guidelines for the management of acute coronary syndromes 2016:

Professor David Brieger (NSW)
Ms Karen Sanders (Vic)
Associate Professor David Sullivan (NSW)
Dr Ross White (NSW)
Mr Andrew Newcomb (Vic)
Professor Richard (Rick) Harper (Vic)
Professor Yusuf Nagree (WA)
Mr Lachlan Parker (Qld)
Professor Harvey White (NZ)
Ms Sue Sanderson (Tas)
Associate Professor Clara Chow (NSW)
Mr Ross Proctor (NSW)
Ms Jinty Wilson (Vic)
Professor Anne-Maree Kelly (Vic)
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Suggested citation: National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand. Australian clinical guidelines for the management of acute coronary syndromes 2016. Heart, Lung and Circulation, 25 (2016) pp 895–951.

Appendix 1: Consultation and Endorsing Organisations

Cardiac Clinical Networks across Australia were consulted on the scope determination.
Potential endorsing organisations were approached for representation within working groups.
NHFA/CSANZ Australian Clinical Guidelines for the Management of Acute Coronary Syndromes 2016 has been endorsed by the following organisations:

- Australasian College for Emergency Medicine (ACEM)
- Australian Cardiovascular Health and Rehabilitation Association (ACRA)
- Royal College of Pathologists of Australasia (RCPA)
- Internal Medicine Society of Australia and New Zealand (IMSANZ)
- The Australasian Cardiovascular Nursing College (ACNC)
- Council of Remote Area Nurses of Australia (CRANA)
- Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS)
- Australian Commission on Safety and Quality in Health Care (ACSQHC)

Appendix 2: Online Register of Conflicts of Interest

Available at: https://heartfoundation.org.au/for-professionals/clinical-information/acute-coronary-syndromes.

Appendix 3: Clinical Questions for NHFA/CSANZ ACS Guideline Update Literature Review

Clinical Questions for NHFA/CSANZ ACS Guideline Update Literature Review

Clinical Question: Chest Pain

1. In adult patients presenting to the Emergency Department (ED) with chest pain what evidence exists regarding clinical approaches for risk stratification pathways/protocols (e.g. TIMI score, GRACE score, HEART score, ADAPT, modified ADAPT, ASPECT, EDACS-ADP, NHFA Risk Stratification or MACS rule) to optimise outcomes of safety (risk for 30-day events of death, acute myocardial infarction (AMI), or revascularisation), length of stay, and cost effectiveness not included in the current National Heart Foundation (NHF) guideline recommendations for assessment of possible acute coronary syndrome (ACS)?

a) Secondary safety endpoint: 30-day events for arrhythmia, heart failure, and readmission

Clinical Question: Chest Pain

2. In adult patients presenting to ED with suspected ACS, what are the time- and assay-dependent performance characteristics of biomarkers in diagnosing acute myocardial infarction (AMI)?

a) How do these performance characteristics vary according to:

i. Assay type (Troponin – I (TnI) or Troponin T (TnT)), sensitive or highly-sensitive assays, point of care or laboratory assays?

ii. Timing (on admission, 2 hours, 4 hours, 6 hours, 12 hours after admission or after symptom onset)?

Clinical Question: Chest Pain

3. In adult patients presenting to ED with suspected ACS and in whom AMI has been ruled out:

a) which subsequent test (Exercise Stress Test (EST), Stress Echocardiography (ECHO), nuclear medicine testing, CT Coronary Angiogram (CTCA), Magnetic Resonance Imaging (MRI)) is most accurate and cost-effective in detecting symptomatic coronary ischaemia?

b) when should the test be performed (e.g. within 72 hours, within 30 days)? Are there different time frames for different risk cohorts?

c) Are there subgroups in whom further testing is unnecessary?

Clinical Question: Secondary Prevention

4. In hospitalised adults with ACS (by STEMI, NSTEMI, Unstable Angina (UA)) what is the evidence that prescription of multiple/cumulative cardio-protective medicines (including: aspirin, other antiplatelet agent, statin, beta-blocker, angiotensin converting enzyme inhibitor/angiotensin receptor blocker) (including order) prior to discharge from hospital compared to single or no medicines improves the composite endpoint of all-cause and cardiac mortality, myocardial infarction and stroke by 12 months or longer?

Clinical Question: Secondary Prevention

5. In hospitalised adults with ACS (by STEMI, NSTEMI, UA) what is the evidence that documented referral to secondary prevention (e.g. post-hospital cardiac rehabilitation), receipt of lifestyle counselling on smoking cessation, exercise, healthy eating and angina symptom management advice compared to no referral and no counselling improves health related quality of life and the composite endpoint of all-cause mortality, myocardial infarction and stroke at 12 months?

Clinical Question: Secondary Prevention

6. In hospitalised adults with ACS (by STEMI, NSTEMI, UA) what is the evidence that documented receipt of optimal secondary prevention (including lifestyle counselling, referral to secondary prevention service) and cumulative (>1) cardio-protective medicines prior to discharge from hospital compared to no counselling or referral to secondary prevention service and single or no medicines is cost-effective beyond 12 months?

Clinical Question: NSTEACS

7. In adult patients with NSTEACS, does a routine invasive approach of coronary angiography and possible revascularization in all patients confer greater net clinical benefit (reduction in rates of major cardiac events weighed against rates of bleeding events) than an initial ischaemia guided approach?

How does this net benefit vary according to:

1) results of biomarkers

2) clinical co-morbidities and

3) overall patient risk using current stratification tools?

Clinical Question: NSTEACS

8. Among adults with NSTEACS undergoing planned invasive management, what is the optimal timing for performing coronary angiography and possible revascularization in order to reduce the risk of recurrent MI or death when considering patient risk characteristics and the specific time categories below?:

- Emergent (STEMI like)

- same day (i.e. call in the laboratory if necessary/arrange urgent transfer if at a non-cath-lab hospital)

- within 24 hours (i.e. can leave overnight, but do over weekend)

- within 48 hours

- during admission.

Clinical Question: NSTEACS

9. In adult patients with NSTEACS, which antithrombotic drug combination, including $P2Y_{12}$ inhibitors, confer greatest net benefit (reduced rates of cardiac events vs rates of bleeding events) during hospital admission and by 12 months?

a) How does this benefit vary according to patient subgroups (invasive versus conservative management, increased need for cardiac surgery or non-cardiac surgery, age >70 years, atrial fibrillation, renal impairment [eGFR <30; <45; <60])?

Clinical Question: STEMI

10. Among patients presenting with STEMI, comparing delay to percutaneous coronary intervention (First Medical Contact (FMC) to first device) with delay to fibrinolysis (FMC to needle), what is the maximum acceptable time delay to percutaneous coronary intervention (PCI) after which fibrinolysis is associated with a lower rate of 30-day or 1 year mortality, and is the 'tolerable' time delay different for those with onset to FMC <120 min compared to FMC >120 min?*

a) Does the rate and timing of angiography/angioplasty during the initial hospitalisation in STEMI patients, who successfully and unsuccessfully received fibrinolytic therapy, affect this conclusion?

**First Medical Contact (FMC) includes a paramedic or nurse who can administer fibrinolysis*

Clinical Question: STEMI

11. For adult patients with STEMI, what system-based strategies (e.g. protocols, clinical support networks, community education programs) have been associated with a higher proportion of patients receiving timely reperfusion, with consideration for fibrinolysis and primary PCI collectively and separately, and do such systems alter 30-day or 1 year mortality?

Clinical Question: STEMI

12. For adult patients with STEMI undergoing reperfusion treatments, what combination of antithrombin and antiplatelet therapies result in the best net clinical benefit over 30-days or 1 year (i.e. lowest rate of major adverse cardiac events of death, MI, and stroke, weighed against bleeding events), a) with primary PCI and b) with fibrinolytic therapy?

Appendix 4: NHMRC Guideline Development Methodology [13]

See Tables A1–A3.

Table A1 NHMRC level of evidence

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, among consecutive persons with a defined clinical presentation	A prospective cohort study	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised 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, among non-consecutive persons with a defined clinical presentation	All or none	All or none	A pseudorandomised 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	A retrospective cohort study		A comparative study with concurrent controls: ▪ Non-randomised, experimental trial ▪ Cohort study ▪ Case-control study

Table A1. (Continued).

Level	Intervention	Diagnostic Accuracy	Prognosis	Aetiology	Screening Intervention
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

Table A2 NHMRC body of evidence matrix

Component	A: Excellent	B: Good	C: Satisfactory	D: Poor
Evidence	One or more level I trials with a low risk of bias or several level II trials with low risk of bias	One or two level II trials with a low risk of bias or a systematic review/several level III trials with a low risk of bias	One or two level III trials with a low risk of bias or a level I or II trials with a moderate risk of bias	Level IV trials, or level 1 to III trials/systematic reviews with a high risk of bias
Consistency	All trials consistent	Most trials consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical Impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population/s in evidence summary are the same as the target population for the guideline	Population/s in evidence summary are similar to the target population for the guideline	Population/s in evidence summary differ to target population for the guideline but is clinically sensible to apply to target population	Population/s in evidence summary differ to target population and hard to judge whether it is sensible to generalise to target population
Applicability	Directly applicable to Australian heart care	Applicable to Australian heart care context with few caveats	Probably applicable to Australian heart care context with some caveats	Not applicable to Australian heart care context

Table A3 NHMRC grades of recommendation

Grade of Recommendation	Description
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

Appendix 5: GRADE Methodology for Recommendations [12]

Strength of recommendation using GRADE Methodology

Within GRADE methodology there are two strengths of recommendation: Strong or Weak/conditional. The direction and strength of each recommendation is determined on the basis of four key factors: level of confidence in effect estimates (as determined by quality of evidence), balance between benefits and harms, uncertainty or variability in patients' values and preferences, and resource considerations.

The strength of the recommendation is defined by the following principles [213]:

GRADE METHODOLOGY	
Strong recommendation	High or moderate confidence in effect estimates AND Benefits clearly outweigh the harms or vice versa AND All or almost all fully informed patients will make the same choice AND Benefits of the intervention are clearly justified in all or almost all circumstances of resource allocation
Weak recommendation	Low or very low confidence in effect estimates OR Balance between benefits and harms is close OR Variability or uncertainty in what fully informed patients may choose OR Benefits of the intervention may not be justified in some circumstances of resource allocation

Abbreviations and Acronyms

ABS	Australian Bureau of Statistics
ACE	Angiotensin converting enzyme
ADP	Accelerated diagnostic protocol
ADAPT	2-Hour Accelerated Diagnostic Protocol to Assess Patients with Chest Pain Symptoms Using Contemporary Troponins as the Only Biomarker
AIHW	Australian Institute of Health and Welfare
ARB	Angiotensin receptor blockers
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
Suspected ACS-AP	Suspected acute coronary syndrome assessment protocol
CSANZ	Cardiac Society of Australia and New Zealand
ECG	Electrocardiogram
EDACS	Emergency Department Assessment of Chest pain Score
ED	Emergency department
FFE	Freedom from event
GRACE	Global Registry of Acute Coronary Events
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard ratios
HEART	History, electrocardiogram, age, risk factors, troponin
IABP	Intra-aortic balloon pump
LR	Likelihood ratio
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
NACPR	North American Chest Pain Rule
NHFA	National Heart Foundation of Australia
NNTB	Number needed to benefit
NNTH	Number needed to harm

NPV	Negative predictive values
NSTEACS	Non-ST elevation acute coronary syndromes
OR	Odds ratio
PCI	Percutaneous coronary intervention
POC	Point-of-care
PPV	Positive predictive value
RR	Relative risk
NPV	Negative predictive value
STEMI	ST elevation myocardial infarction
TIMI	Thrombolysis in myocardial infarction
UA	Unstable angina

Heart, Lung and Circulation (2017) **26,** 1117
1443-9506/04/$36.00
http://dx.doi.org/10.1016/j.hlc.2017.08.004

CORRIGENDUM

Corrigendum to 'National Heart Foundation of Australia & Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Management of Acute Coronary Syndromes 2016' Heart Lung and Circulation volume 25, (2016) 898 - 952

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Please note that on p.929 in 5.2.2.7, paragraph 3, the dose of dabigatran should read as BD rather than daily. We regret any inconvenience that this may have caused

DOI of original article: http://dx.doi.org/10.1016/j.hlc.2016.06.789