

## SIGN 148 • Acute coronary syndrome

*A national clinical guideline*

*April 2016*

## KEY TO EVIDENCE STATEMENTS AND RECOMMENDATIONS

### LEVELS OF EVIDENCE

1 <sup>++</sup>	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1 <sup>+</sup>	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1 <sup>-</sup>	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2 <sup>++</sup>	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2 <sup>+</sup>	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2 <sup>-</sup>	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

### RECOMMENDATIONS

Some recommendations can be made with more certainty than others. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the 'strength' of the recommendation).

The 'strength' of a recommendation takes into account the quality (level) of the evidence. Although higher-quality evidence is more likely to be associated with strong recommendations than lower-quality evidence, a particular level of quality does not automatically lead to a particular strength of recommendation.

Other factors that are taken into account when forming recommendations include: relevance to the NHS in Scotland; applicability of published evidence to the target population; consistency of the body of evidence, and the balance of benefits and harms of the options.

**R** For '**strong**' recommendations on interventions that '**should**' be used, the guideline development group is confident that, for the vast majority of people, the intervention (or interventions) will do more good than harm. For '**strong**' recommendations on interventions that '**should not**' be used, the guideline development group is confident that, for the vast **majority** of people, the intervention (or interventions) will do more harm than good.

**R** For '**conditional**' recommendations on interventions that should be 'considered', the guideline development group is confident that the intervention will do more good than harm for most patients. The choice of intervention is therefore more likely to vary depending on a person's values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.

### GOOD-PRACTICE POINTS

✓ Recommended best practice based on the clinical experience of the guideline development group.



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Scottish Intercollegiate Guidelines Network

# Acute coronary syndrome

A national clinical guideline



April 2016

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# 1 Introduction

## 1.1 THE NEED FOR A GUIDELINE

Coronary heart disease (CHD) is the single biggest cause of death in Scotland and the rest of the UK as well as being a major cause of premature mortality (death in people aged under 75). In Scotland in 2012, CHD accounted for 16% (n=4,258) of all deaths in men and 11% (n=3,283) of all deaths in women, and 17% (n=2,015) and 9% (n=738) of premature deaths in men and women, respectively.<sup>1</sup> Myocardial infarction (MI), which together with unstable angina comprise acute coronary syndrome (ACS), accounted for more than half of all deaths from CHD in Scotland in 2013/14 (50.5% in men; 56% in women), with a third of these being in people under 75 years of age (44% in men and 21% in women).<sup>2</sup>

The age-sex standardised incidence of MI in Scotland in 2013/14 was 235.6/100,000 (307.8 in men and 163.3 in women), equating to 11,350 new cases of MI, 60% of them in men and 57% of them in people under 75 years of age. The incidence of MI in women under 75 years of age was less than half the corresponding rate in men.<sup>2</sup>

Thirty-day survival after a first emergency admission is very high, 93% for MI and 99% for unstable angina,<sup>2</sup> although longer-term prognosis remains poor for some subgroups of patients (*see section 1.2.3*).

### 1.1.1 UPDATING THE EVIDENCE

This guideline updates SIGN 93, first published in February 2007, and updated in February 2013, to reflect the most recent evidence.

Where no new evidence was identified to support an update, text and recommendations are reproduced verbatim from SIGN 93. The original supporting evidence was not reappraised by the current guideline development group.

## 1.2 REMIT OF THE GUIDELINE

### 1.2.1 OVERALL OBJECTIVES

This guideline provides recommendations for the management of patients with an ACS within the first 12 hours and up to hospital discharge. With the exception of dual antiplatelet therapy with aspirin and P2Y<sub>12</sub>-receptor antagonists (*see section 8.1.2*), this guideline does not make recommendations for long-term treatment following discharge from hospital. This guideline does not make recommendations for prehospital management, for example by ambulance service personnel, but refers to prehospital management where appropriate (*for example, see section 4*). The guideline does not address the management of undifferentiated chest pain or acute heart failure although the treatment of hypoxia and cardiogenic shock in patients with ACS is considered in section 9.

### 1.2.2 DEFINITION OF ACUTE CORONARY SYNDROME

Acute coronary syndrome encompasses a spectrum of unstable coronary artery disease from unstable angina to transmural myocardial infarction. All have a common aetiology in the formation of thrombus on an inflamed and complicated atheromatous plaque. The principles behind the presentation, investigation and management of these are similar with important distinctions depending on the category of acute coronary syndrome.

The definition of ACS depends on the specific characteristics of each element of the triad of clinical presentation, electrocardiographic changes and biochemical cardiac markers. ACS may occur in the absence of electrocardiographic changes or elevations in biochemical markers, when the diagnosis is supported by the presence of prior-documented coronary artery disease or subsequent confirmatory investigations.<sup>3</sup>

The immediate management of a patient with ACS is determined by the characteristics of the presenting electrocardiogram and, in particular, the presence or absence of ST-segment elevation. In combination with

the clinical presentation (see section 3), an ST-segment-elevation ACS is defined by the presence of  $\geq 1$  mm ST elevation in at least two adjacent limb leads,  $\geq 2$  mm ST elevation in at least two contiguous precordial leads, or new-onset bundle branch block. In the absence of ST-segment elevation (non-ST-segment-elevation acute coronary syndrome), patients are initially managed without emergency reperfusion therapy.

The main diagnostic categories of ACS, unstable angina and MI are defined by the serum or plasma concentration of cardiac troponin.<sup>4</sup> This SIGN guideline focuses on unstable angina and spontaneous type 1 MI. The management of other forms of MI, especially type 2 MI, cannot necessarily be extrapolated from this evidence base (see Table 1). In some patients with type 2 MI, treatments for ACS may be harmful.

Table 1: The universal classification of myocardial infarction<sup>4</sup>

<b>Type 1: Spontaneous myocardial infarction</b>
Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, 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. The patient may have underlying severe coronary artery disease (CAD) but on occasion non-obstructive or no CAD.
<b>Type 2: Myocardial infarction secondary to an ischaemic imbalance</b>
In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, eg coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anaemia, respiratory failure, hypotension, and hypertension with or without left ventricular hypertrophy (LVH).
<b>Type 3: Myocardial infarction resulting in death when biomarker values are unavailable</b>
Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic electrocardiograph (ECG) changes or new left bundle branch block (LBBB), but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.
<b>Type 4a: Myocardial infarction related to percutaneous coronary intervention</b>
Myocardial infarction associated with percutaneous coronary intervention (PCI) is arbitrarily defined by elevation of cardiac troponin values $> 5 \times 99^{\text{th}}$ percentile upper reference limit (URL) in patients with normal baseline values ( $\leq 99^{\text{th}}$ percentile URL) or a rise of cardiac troponin values $> 20\%$ if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia, or (ii) new ischaemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no-flow or embolisation, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
<b>Type 4b: Myocardial infarction related to stent thrombosis</b>
Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarkers values with at least one value above the $99^{\text{th}}$ percentile URL.
<b>Type 5: Myocardial infarction related to coronary artery bypass grafting</b>
Myocardial infarction associated with coronary artery bypass grafting (CABG) is arbitrarily defined by elevation of cardiac biomarker values $> 10 \times 99^{\text{th}}$ percentile URL in patients with normal baseline cardiac troponin values ( $\leq 99^{\text{th}}$ percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

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### 1.2.3 PROGNOSIS IN ACUTE CORONARY SYNDROME

In those admitted with presumed ACS, 36% will ultimately be diagnosed with MI during their index admission.<sup>5</sup> The 30-day and 6-month mortality for patients with ACS is higher in those with ST-segment deviation or



elevations in serum troponin concentrations.<sup>6,7</sup> Patients with ACS continue to have poor outcomes,<sup>8</sup> although between 2004 and 2013 overall age-sex standardised mortality rates for MI have almost halved from 164.5 to 84.1/100,000 of the population in Scotland. Amongst those aged 75 and over, mortality rates have fallen from 1,248.6/100,000 in 2004 to 646.5/100,000 population in 2013.<sup>2</sup> Rates of death associated with MI have fallen more slowly in women than in men, which has led to cardiovascular disease (CVD) remaining the leading cause of death in women, but not men in 2014.<sup>1,2</sup>

#### 1.2.4 TARGET USERS OF THE GUIDELINE

Effective diagnosis and immediate management of ACS requires co-ordination of a wide variety of services and healthcare professionals including cardiologists, ambulance services, acute and emergency medicine specialists and laboratory services. Recommendations for postdischarge treatment, in particular, will also be of interest to general practitioners and other healthcare professionals in primary care as well as patients, carers, voluntary organisations and policy makers.

#### 1.2.5 SUMMARY OF UPDATES TO THE GUIDELINE, BY SECTION

1.1	The need for a guideline	Updated
1.2.1	Overall objectives	Minor update
1.2.2	Definition of ACS	Updated
1.2.3	Prognosis in ACS	Updated
2	Key recommendations	New
3.1	Clinical presentation and immediate assessment	Minor update
3.2	Biochemical diagnosis in ACS	Updated
4	Initial management	Updated
4.4.1	Aspirin	Updated
4.4.2	Combination aspirin and P2Y <sub>12</sub> -receptor antagonist therapy	Updated
4.5.5	Overview and recommendations	New
4.7	Glycaemic control	Updated
5.1	Choice of reperfusion therapy	Minor update
5.1.1	Transfer of patients to interventional centres	Minor update
5.1.2	Intracoronary stenting	Minor update
5.1.3	Thrombectomy	New
5.2	Thrombolytic therapy	Updated
5.2.2	Contraindications to thrombolysis	Minor update
5.2.3	Choice of thrombolytic agent	Updated
5.4	'Rescue' PCI	Updated
5.5	Multivessel PCI	New
6.1.1	Risk stratification scores	Minor update
7.1.2	Invasive investigation – ST-segment-elevation ACS	Minor update
7.2	Access routes for PCI	New
7.3	Glycoprotein IIb/IIIa receptor antagonists	Updated
7.4	CABG	New
8.1.2	Dual antiplatelet therapy	Updated
8.2.1	Rivaroxaban, apixaban and dabigatran	New
9.3	Intra-aortic balloon counterpulsation	Updated
10	Provision of information	Updated
11	Implementing the guideline	Updated

### 1.2.6 PATIENT VERSION

A patient version of this guideline is available from the SIGN website, [www.sign.ac.uk](http://www.sign.ac.uk)

## 1.3 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

### 1.3.1 INFLUENCE OF FINANCIAL AND OTHER INTERESTS

It has been recognised that financial interests in, or close working relationships with, pharmaceutical companies may have an influence on the interpretation of evidence from clinical studies.

It is not possible to completely eliminate any possible bias from this source, nor even to quantify the degree of bias with any certainty. SIGN requires that all those involved in the work of guideline development should declare all financial interests, whether direct or indirect, annually for as long as they are actively working with the organisation. By being explicit about the influences to which contributors are subjected, SIGN acknowledges the risk of bias and makes it possible for guideline users or reviewers to assess for themselves how likely it is that the conclusions and guideline recommendations are based on a biased interpretation of the evidence.

Signed copies are retained by the SIGN Executive and a register of interests is available in the supporting material section for this guideline at [www.sign.ac.uk](http://www.sign.ac.uk)

### 1.3.2 PRESCRIBING OF LICENSED MEDICINES OUTWITH THEIR MARKETING AUTHORISATION

Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation (MA) also known as product licence. This is known as 'off-label' use.

Medicines may be prescribed 'off label' in the following circumstances:

- for an indication not specified within the marketing authorisation
- for administration via a different route
- for administration of a different dose
- for a different patient population.

An unlicensed medicine is a medicine which does not have MA for medicinal use in humans.

Generally 'off-label' prescribing of medicines becomes necessary if the clinical need cannot be met by licensed medicines within the marketing authorisation. Such use should be supported by appropriate evidence and experience.<sup>9</sup>

"Prescribing medicines outside the conditions of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility and potential liability".<sup>9</sup>

The General Medical Council recommends that when prescribing a medicine 'off label', doctors should:

- be satisfied that such use would better serve the patient's needs than an authorised alternative (if one exists)
- be satisfied that there is sufficient evidence/experience of using the medicines to show its safety and efficacy, seeking the necessary information from appropriate sources
- record in the patient's clinical notes the medicine prescribed and, when not following common practice, the reasons for the choice
- take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring the effects of the medicine.

Non-medical prescribers should ensure that they are familiar with the legislative framework and their own professional prescribing standards.

Prior to any prescribing, the licensing status of a medication should be checked in the summary of product characteristics ([www.medicines.org.uk](http://www.medicines.org.uk)). The prescriber must be competent, operate within the professional code of ethics of their statutory bodies and the prescribing practices of their employers.<sup>10</sup>

### 1.3.3 HEALTH TECHNOLOGY ASSESSMENT ADVICE FOR NHSSCOTLAND

Specialist teams within Healthcare Improvement Scotland issue a range of advice that focuses on the safe and effective use of medicines and technologies in NHSScotland.

The Scottish Medicines Consortium (SMC) provides advice to NHS boards and their Area Drug and Therapeutics Committees about the status of all newly-licensed medicines and new indications for established products. NHSScotland should take account of this advice and ensure that medicines accepted for use are made available to meet clinical need where appropriate.

In addition, Healthcare Improvement Scotland reviews Multiple Technology Appraisals (MTAs) produced by the National Institute for Health and Care Excellence (NICE) and provides advice about their applicability in NHSScotland. If Healthcare Improvement Scotland advises that MTA guidance is applicable in Scotland, NHSScotland should take account of this and ensure that recommended medicines and treatment are made available to meet clinical need where appropriate.

On publication NICE MTAs deemed valid for NHSScotland supersede extant SMC advice as they are generally underpinned by a larger and more recent evidence base.

SMC advice and NICE MTA guidance relevant to this guideline are summarised in section 11.4.

## 2 Key recommendations

The following recommendations were highlighted by the guideline development group as the key clinical recommendations that should be prioritised for implementation.

### 2.1 PRESENTATION, ASSESSMENT AND DIAGNOSIS

**R** In patients with suspected acute coronary syndrome, measurement of cardiac troponin at presentation and at three hours after presentation with a high-sensitivity assay should be considered as an alternative to serial measurement over 10–12 hours with a standard troponin assay to rule out myocardial infarction.

### 2.2 INITIAL MANAGEMENT

**R** In the presence of ischaemic electrocardiographic changes or elevation of cardiac troponin, patients with an acute coronary syndrome should be treated immediately with both aspirin (300 mg loading dose) and ticagrelor (180 mg loading dose).

### 2.3 REPERFUSION THERAPY FOR ST-SEGMENT-ELEVATION ACUTE CORONARY SYNDROME

**R** Patients with an ST-segment-elevation acute coronary syndrome should be treated immediately with primary percutaneous coronary intervention.

**R** When primary percutaneous coronary intervention cannot be provided within 120 minutes of ECG diagnosis, patients with an ST-segment-elevation acute coronary syndrome should receive immediate (prehospital or admission) thrombolytic therapy.

### 2.4 EARLY PHARMACOLOGICAL INTERVENTION

**R** Patients with acute coronary syndrome should receive dual antiplatelet therapy for six months. Longer durations may be used where the risks of atherothrombotic events outweigh the risk of bleeding. Shorter durations may be used where the risks of bleeding outweigh the risk of atherothrombotic events.

## 3 Presentation, assessment and diagnosis

### 3.1 CLINICAL PRESENTATION AND IMMEDIATE ASSESSMENT

A high-quality systematic review of 21 studies examined the usefulness of 16 different clinical signs and symptoms in the diagnosis of ACS.<sup>11</sup> Taken in isolation, no single sign or symptom was discriminatory. A further systematic review found that symptom characteristics were also unhelpful as prognostic factors.<sup>12</sup> The American Heart Association/American College of Cardiology guidelines recommend that clinical risk factors should be considered together when assessing the likelihood of myocardial ischaemia relating to ACS. These include increasing age, sex, family history of coronary heart disease, prior history of ischaemic heart disease and peripheral vascular disease, diabetes mellitus and renal impairment. High-risk features include worsening angina, prolonged pain (>20 minutes), pulmonary oedema (Killip class  $\geq 2$ ), hypotension and arrhythmias.<sup>13</sup>

1++  
4

The diagnosis and management of a patient with suspected ACS requires a detailed clinical assessment and the recording of a 12-lead electrocardiogram. Many treatments, especially for ST-segment-elevation ACS, are critically time dependent and the immediate clinical assessment of all patients with a suspected ACS is essential.<sup>13-15</sup>

4

The indications for reperfusion therapy (*see section 5*) are based primarily upon the meta-analysis of the Fibrinolytic Therapy Trialists' Collaboration (FTTC) group.<sup>16</sup> They reported that the electrocardiographic predictors of mortality benefit from fibrinolytic therapy were the presence of ST-segment elevation or new onset bundle branch block (*see section 1.2.2*). The FTTC group did not distinguish between left and right bundle branch block although several guidelines and trials specifically stipulate left bundle branch block only.<sup>13</sup> Registry data of acute MI show that right bundle branch block is as common as, and has a higher mortality than, left bundle branch block.<sup>17</sup> The majority of patients presenting with acute MI and right bundle branch block have associated ST-segment elevation. It is unknown whether patients with acute MI presenting with right bundle branch block in the absence of ST-segment elevation will derive benefit from reperfusion therapy.

1++

No specific evidence was identified on when to record serial electrocardiograms or on which patients they should be carried out.

**R** Patients with suspected acute coronary syndrome should be assessed immediately by an appropriate healthcare professional and a 12-lead electrocardiogram should be performed.

✓ Repeat 12-lead electrocardiograms should be performed if there is diagnostic uncertainty or a change in the clinical status of the patient, and at hospital discharge.

✓ Patients with persisting bundle branch block or ST-segment change should be given a copy of their electrocardiogram to assist their future clinical management should they re-present with a suspected acute coronary syndrome.

Continuous ST-segment monitoring, additional-lead monitoring and vector cardiography appear to yield valuable long-term prognostic information, but their role in the assessment and diagnosis of ACS has yet to be established.<sup>18-27</sup>

3

### 3.1.1 SELF MEDICATION IN PATIENTS WITH CORONARY ARTERY DISEASE

In patients with known coronary heart disease, self medication with glyceryl trinitrate provides rapid symptom relief of anginal pain, but its effect lasts for less than 60 minutes.<sup>28,29</sup> The British Heart Foundation (BHF) has published advice for self management of angina in patients with a known diagnosis of CHD.<sup>30</sup>

- ✓ When experiencing symptoms typical of angina, patients with known coronary heart disease should be advised:
- to stop what they are doing and sit down and rest
  - to take their glyceryl trinitrate spray and tablets. The pain should ease within a few minutes – if it doesn't, take a second dose
  - if the pain does not ease within a few minutes after a second dose, call 999 immediately.

### 3.2 BIOCHEMICAL DIAGNOSIS IN ACS

The diagnosis of MI relies on the measurement of serum or plasma cardiac troponin as defined in the third universal definition of myocardial infarction.<sup>31</sup> Myocardial infarction is diagnosed in patients with a rise and/or fall in cardiac troponin concentration where at least one value is above the 99<sup>th</sup> centile URL and with at least one of the following: symptoms of myocardial ischaemia; new or presumed new significant ST-segment or T-wave changes or new left bundle branch block; development of pathological Q waves; imaging evidence of loss of viable myocardium or new regional wall motion abnormality; identification of an intracoronary thrombus by angiography or autopsy. This definition describes five types of MI depending on the presentation and clinical context (*see Table 1*). It also describes 'myocardial injury' where cardiac troponin concentrations are elevated in the absence of changes on the electrocardiogram or symptoms of myocardial ischaemia.

Measurement of cardiac troponin concentration should not be relied upon in isolation.<sup>32</sup> For example, patients with unstable angina and a troponin concentration within the reference range at 12 hours are at risk of future cardiovascular events (30-day risk of death up to 4–5%).<sup>33,34</sup> The introduction of more sensitive cardiac troponin assays and lower thresholds for the diagnosis of MI has, however, markedly reduced the diagnosis of unstable angina in Scotland from 9,896 per annum in 2000/2001 to 1,823 per annum in 2014/2015.<sup>35</sup> Conversely, an elevated troponin concentration cannot diagnose MI in isolation.

Cardiac troponin is measured on presentation to guide the initial management and treatment of patients with suspected ACS, and again 10–12 hours after the onset of symptoms to coincide with the peak in plasma troponin concentrations.<sup>36</sup> Although this minimises the risk of missing a small myocardial infarct, it requires the majority of patients to be admitted to hospital for serial testing. Use of a high-sensitivity cardiac troponin assay permits the use of lower diagnostic thresholds than standard troponin assays, and allows earlier testing that may reduce unnecessary hospital admissions, waiting times for test results and associated anxiety in patients and carers.<sup>37</sup> Early rule-out protocols typically involve serial cardiac troponin measurements on presentation and three hours later.<sup>38</sup>

High-sensitivity cardiac troponin assays appear to improve the diagnostic accuracy for MI, although there is insufficient evidence to suggest that they will improve patient outcomes.<sup>39</sup> Four systematic reviews were identified that assessed the two high-sensitivity assays (Abbott ARCHITECT high-sensitivity cardiac troponin I and Roche Elecsys high-sensitivity troponin T) currently approved for clinical use within the European Union.<sup>37,40-42</sup> These two high-sensitivity assays have comparable sensitivity and specificity for MI.

Diagnostic thresholds depend on the characteristics of the reference population and differ for different assays. High-sensitivity cardiac troponin assays have identified differences between sexes with the 99<sup>th</sup> centile URL being two-fold higher in men than women.<sup>43</sup> One study reported that use of a high-sensitivity troponin I assay with sex-specific diagnostic thresholds increased the diagnosis of MI in women (from 11–22%) but had little effect in men. Use of these assays could, therefore, lead to more effective identification of women at high risk of reinfarction and death.<sup>39</sup>

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High-sensitivity troponin test strategies are cost effective relative to standard troponin testing in patients presenting to the Emergency Department with suspected ACS who had no major comorbidities requiring hospitalisation, as they are less expensive and more effective than standard testing.<sup>40</sup> This analysis is based on economic modelling that assumes high-sensitivity troponin testing will detect additional patients who would benefit from treatment for myocardial infarction who would have been missed by standard troponin testing.

Elevated troponin concentrations can occur in patients without ACS (myocardial injury) and are associated with adverse outcomes in many clinical scenarios including patients with congestive heart failure, sepsis, acute pulmonary embolism and chronic renal failure.<sup>44,45</sup> High-sensitivity assays will increase the number of patients identified with myocardial injury who do not have ACS and this may lead to inappropriate, unnecessary and potentially harmful treatments and investigations for coronary disease in patients with other illnesses.

The optimal timing of testing, diagnostic thresholds and pathways and the effect of high-sensitivity assays on patient outcomes are all uncertain due to the rapidly-evolving nature of the evidence in this field,

- R** | **In patients with suspected acute coronary syndrome, serum troponin concentration should be measured at presentation to guide appropriate management and treatment.**
- R** | **Serum troponin concentration should be measured 12 hours from the onset of symptoms to establish a diagnosis of myocardial infarction.**
- R** | **In patients with suspected acute coronary syndrome, measurement of cardiac troponin at presentation and at three hours after presentation with a high-sensitivity assay should be considered as an alternative to serial measurement over 10–12 hours with a standard troponin assay to rule out myocardial infarction.**
- R** | **Sex-specific thresholds of cardiac troponin should be used for the diagnosis of myocardial infarction in men and women.**
- ✓ | Further troponin measurements may be necessary in patients who present within three hours of the onset of chest pain.
- ✓ | When considering a diagnosis of ACS, serum troponin concentrations should not be interpreted in isolation but with regard to the clinical presentation of the patient.
- ✓ | Troponin point-of-care testing assays currently licensed in the UK are equivalent in sensitivity to 12-hour laboratory-based standard troponin assays.

## 4 Initial management

This section provides recommendations regarding the management of patients within the first 12 hours of acute coronary syndrome.

Patients with suspected ACS who are attended by ambulance paramedics and/or ambulance technicians will be assessed in the prehospital environment and receive treatment prior to admission to hospital. Within a reperfusion care pathway this may include administration of dual antiplatelet therapy in accordance with Association of Ambulance Chief Executives UK Ambulance Services Clinical Practice Guidelines 2013 or thrombolysis (*see section 5.2*).<sup>46</sup>

Prehospital treatment of patients with suspected ACS from ambulance paramedics and/or technicians reduces delays in treatment and improves outcomes for patients.<sup>47</sup> Effective communication pathways between ambulance personnel and hospital staff (with transmission of 12-lead ECG data) enhance care delivery with decision support.<sup>48</sup> This ensures an agreed care plan is followed which may include direct admission to the cardiac catheterisation laboratory for primary PCI.

### 4.1 SERVICE DELIVERY

Retrospective studies suggest that patients are more likely to receive appropriate evidence-based therapies when treated by cardiology specialists than by general internal physicians.<sup>49-51</sup> It is unclear whether this benefit is attributable to the specialist physician in isolation or reflects the overall care and treatment of patients within a specialist cardiology service. A systematic review suggests that this increased provision of evidence-based therapy is associated with improved clinical outcomes including mortality.<sup>52</sup>

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This is increasingly relevant given the greater role of invasive coronary angiography and coronary revascularisation in the modern management of patients with acute coronary syndrome.

**R** Patients with acute coronary syndrome should be managed within a specialist cardiology service.

### 4.2 CARDIAC MONITORING

Ventricular fibrillation and pulseless ventricular tachycardia are common in patients with ACS. Prompt defibrillation and cardioversion are effective and life saving (*see the SIGN guideline on management of cardiac arrhythmias in coronary heart disease*).<sup>53</sup> Continuous cardiac rhythm monitoring facilitates prompt recognition and treatment of these forms of cardiac arrest.<sup>13-15</sup>

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**R** Patients with acute coronary syndrome should have continuous cardiac rhythm monitoring.

### 4.3 OXYGEN THERAPY

A Cochrane review found no conclusive evidence from randomised controlled trials to support the routine use of inhaled oxygen in patients with acute MI.<sup>54</sup>

There is no evidence that routine administration of oxygen to all patients with the broad spectrum of ACS improves clinical outcome or reduces infarction size.



## 4.4 ANTIPLATELET THERAPY

### 4.4.1 ASPIRIN

In comparison with placebo, aspirin halves (absolute risk reduction (RR) 5.3%, relative RR 46%) the rate of vascular events (cardiovascular death, non-fatal MI and non-fatal stroke) in patients with unstable angina and reduces it by nearly a third (absolute RR 3.8%, relative RR 30%) in those with acute MI.<sup>55</sup>

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Aspirin may have been self administered or administered by the ambulance service prior to admission. Antiplatelet therapy in individuals with pre-existing indications for anticoagulation is not specifically considered in this guideline.

### 4.4.2 COMBINATION ASPIRIN AND P2Y<sub>12</sub>-RECEPTOR ANTAGONIST THERAPY

Combination therapy with aspirin and a P2Y<sub>12</sub>-receptor antagonist improves clinical outcomes (recurrent MI and death) in patients with ACS. Improvements in death and MI may be offset by increased rates of major bleeding. The choice of P2Y<sub>12</sub>-receptor antagonist will vary for different subgroups of patients and will depend on clinical presentation.

#### *Clopidogrel*

In the CURE trial, combined aspirin (300 mg loading dose and 75–150 mg daily) and clopidogrel (300 mg loading dose and 75 mg daily) therapy was more effective than aspirin therapy alone. Combination therapy provided a further 2.1% absolute RR (20% relative RR) in the combined end point of cardiovascular death, stroke or MI in high-risk patients (electrocardiographic evidence of ischaemia or elevated cardiac markers) with non-ST-segment-elevation ACS.<sup>56</sup> This benefit was seen within 24 hours and was principally due to a reduction in MI or refractory ischaemia.<sup>56,57</sup>

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The CLARITY-TIMI 28 (clopidogrel 300 mg loading dose and 75 mg daily) and COMMIT/CCS (clopidogrel 75 mg daily) trials have demonstrated an increased patency rate of the infarct-related artery and reduced mortality when comparing combination aspirin and clopidogrel therapy with aspirin alone in patients with ST-segment-elevation ACS.<sup>58,59</sup> The reductions in the rates of death, reinfarction or stroke (0.9% absolute (RR), 9% relative RR) and rate of death alone (0.6% absolute RR, 7% relative RR) were achieved without any excess major bleeding and were predominantly seen when clopidogrel was administered within the first 12 hours.

#### *Prasugrel and ticagrelor*

Prasugrel (60 mg loading dose and 10 mg daily) and ticagrelor (180 mg loading dose and 90 mg twice daily) are more effective P2Y<sub>12</sub>-receptor antagonists than clopidogrel and evidence suggests that their use as dual therapy with aspirin improves composite clinical outcomes (cardiovascular mortality, recurrent MI and stroke) compared with dual therapy with aspirin and clopidogrel (*see Table 2*).<sup>60-70</sup>

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In 18,624 patients with ACS, ticagrelor reduced vascular death, MI and stroke in comparison to clopidogrel (1.9% absolute RR, 16% relative RR,  $p < 0.001$ ).<sup>67</sup> This benefit was seen irrespective of whether or not patients had undergone PCI. Ticagrelor also reduced all-cause mortality (1.4% absolute RR, 22% relative RR,  $p < 0.001$ ) when compared with clopidogrel.<sup>67</sup>

In 13,608 patients with ACS who were scheduled for treatment with PCI, prasugrel reduced cardiovascular death, non-fatal MI and non-fatal stroke in comparison to clopidogrel (2.2% absolute RR, 19% relative RR,  $p < 0.001$ ). However, it did not significantly reduce all-cause mortality in all patients with ACS (0.2% absolute RR, 5% relative RR,  $p = 0.64$ )<sup>69</sup> or in a subgroup of patients treated with primary PCI for ST-segment-elevation myocardial infarction (1.0% absolute RR, 24% relative RR,  $p = 0.11$ ) at 15 months follow up.<sup>71</sup> Furthermore, in a subsequent trial of 9,326 patients with ACS without ST-segment elevation who did not undergo revascularisation, prasugrel did not reduce the composite end point of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke compared with clopidogrel.<sup>64</sup>

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Stent thrombosis is reduced by both prasugrel and ticagrelor, when compared with clopidogrel.<sup>66</sup> The reduction in stent thrombosis seen with prasugrel may have been overestimated because of the trial design (administration of drug at the time of PCI) and the more rapid onset of action associated with prasugrel compared with clopidogrel.<sup>65,68,69</sup>

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Patients most at risk of stent thrombosis may be those who are also at increased risk of intracranial bleeding (for example, older patients, those with diabetes mellitus or previous MI) but there is insufficient evidence to inform decision making in these patient groups.

Table 2: Composite and all-cause mortality outcomes for patients with ACS treated with prasugrel or ticagrelor compared with clopidogrel

	Primary composite end point		All-cause mortality	
	Hazard ratio (95% CI)	ARR (%)	Hazard ratio (95% CI)	ARR (%)
<b>Ticagrelor<sup>67</sup></b> (managed with or without coronary revascularisation)	0.84 (0.77 to 0.92) p<0.001	1.9	0.78 (0.69 to 0.89) p<0.001	1.4
<b>Prasugrel<sup>69</sup></b> (scheduled for PCI)	0.81 (0.73 to 0.90) p<0.001	2.2	0.95 (0.78 to 1.16) p=0.64	0.2
<b>Prasugrel<sup>64</sup></b> (managed without coronary revascularisation)	0.96* (0.86 to 1.07) p=0.45	0.6	0.94* (0.82 to 1.08) p=0.40	0.5

ARR – absolute risk reduction, CI – confidence interval, PCI – percutaneous coronary intervention

\* data shown for all patients and not restricted to those <75 years

An increase in major bleeding has been reported with prasugrel and ticagrelor, including fatal intracranial bleeding with prasugrel.<sup>69,72</sup> Results are inconsistent with some studies reporting no increase in major bleeding with ticagrelor compared with clopidogrel,<sup>60,62,67</sup> prasugrel compared with clopidogrel,<sup>64</sup> and ticagrelor or prasugrel compared with clopidogrel.<sup>66</sup>

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Other adverse effects reported for P2Y<sub>12</sub>-receptor antagonists are transient bradycardia and dyspnoea, most marked with ticagrelor.<sup>62,63,67,73</sup>

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Studies comparing prasugrel to clopidogrel,<sup>74,75</sup> and ticagrelor to clopidogrel<sup>76-78</sup> have shown that ticagrelor (for the prevention of atherothrombotic events in adult patients with acute coronary syndrome) and prasugrel (for the prevention of atherothrombotic events in patients with ACS undergoing primary or delayed PCI) are cost-effective treatment options compared with clopidogrel.

**R** In the presence of ischaemic electrocardiographic changes or elevation of cardiac troponin, patients with an acute coronary syndrome should be treated immediately with both aspirin (300 mg loading dose) and ticagrelor (180 mg loading dose).

**R** For patients with acute coronary syndrome undergoing percutaneous coronary intervention aspirin and prasugrel (60 mg loading dose) may be considered.

**R** Patients with acute coronary syndrome should be considered for aspirin (300 mg loading dose) and clopidogrel (300 mg loading dose) where the risks (bleeding) outweigh the benefits (reduction in recurrent atherothrombotic events) of ticagrelor or prasugrel.

The optimal duration of dual antiplatelet therapy is covered in section 8.1.2

The British National Formulary (BNF) notes that ticagrelor is contraindicated in individuals with active bleeding or history of intracranial haemorrhage. It advises that ticagrelor should be discontinued seven days before elective surgery if the antiplatelet effect is not desirable. Caution is advised in patients at risk of increased bleeding from trauma, surgery, or other pathological conditions and in those with asthma or chronic obstructive pulmonary disease. Caution is also indicated in individuals with bradycardia, second- or third-degree atrioventricular block or sick sinus syndrome.<sup>9</sup>

Prasugrel is contraindicated in individuals with active bleeding or history of stroke or transient ischaemic attack. The BNF advises that prasugrel should be discontinued seven days before elective surgery if the antiplatelet effect is not desirable. Caution is advised in the elderly, patients at risk of increased bleeding from trauma, surgery, gastrointestinal bleeding or active peptic ulcer disease and in those with body weight <60 kg.<sup>9</sup>

Clopidogrel is contraindicated in individuals with active bleeding. The BNF advises that clopidogrel should be discontinued seven days before elective surgery if the antiplatelet effect is not desirable. Caution is advised in patients at risk of increased bleeding from trauma, surgery, or other pathological conditions.<sup>9</sup>

## 4.5 ANTICOAGULANT THERAPY

### 4.5.1 UNFRACTIONATED HEPARIN

#### *Non-ST-segment-elevation acute coronary syndrome*

In patients with non-ST-segment-elevation ACS, unfractionated heparin (UFH) treatment for at least 48 hours reduces the combined end point of death or MI (absolute RR 2.5%, relative RR 33%).<sup>80</sup> This is predominantly driven by a reduction in non-fatal MI.

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#### *ST-segment-elevation acute coronary syndrome*

In patients with ST-segment-elevation ACS following aspirin and thrombolysis with fibrin-specific agents, UFH reduces the rate of reinfarction (absolute RR 0.3%) and death (absolute RR 0.5%).<sup>81</sup>

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### 4.5.2 LOW MOLECULAR WEIGHT HEPARIN

#### *Non-ST-segment-elevation acute coronary syndrome*

A Cochrane review of seven randomised controlled trials (RCTs) (n=11,092) reported that low molecular weight heparin (LMWH) treatment (principally enoxaparin) reduced MI and coronary revascularisation procedure rates compared with UFH. There was no difference in mortality or major bleeding episodes. The number of patients needed to treat (NNT) with LMWH rather than UFH to prevent one MI was 125 and to prevent one extra revascularisation procedure was 50. Benefits from LMWH remain evident well beyond the duration of treatment and in the TIMI IIB trial were still evident at one year.<sup>82</sup> Extended use of LMWH beyond the inpatient stay or for more than eight days is of no value.<sup>83</sup>

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When used in combination with glycoprotein IIb/IIIa receptor antagonists, LMWH is no more efficacious than UFH but is associated with similar or fewer bleeding complications.<sup>84,85</sup>

#### *ST-segment-elevation acute coronary syndrome*

RCTs comparing LMWH with UFH in patients with ST-segment-elevation ACS show some advantages for LMWH, principally enoxaparin.<sup>85-87</sup> Meta-analysis confirms that, in patients treated with thrombolytic therapy, LMWH (enoxaparin) is associated with better outcomes (MI, absolute RR 2.3%, relative RR 41%; recurrent ischaemia, absolute RR 2.0%, relative RR 30%; death or MI, absolute RR 2.9%, relative RR 26%; and death, MI or recurrent ischaemia, absolute RR 4.8%, relative RR 28%) but no decrease in mortality when compared with UFH.<sup>88</sup> There is an increase in major bleeding particularly when using enoxaparin with alteplase or tenecteplase (1% absolute risk increase, 44% relative risk increase). This is seen predominantly in patients over 75 years of age where the dose of enoxaparin may need to be reduced.<sup>89</sup>

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These findings have been confirmed in a large RCT (ExTRACT; n=20,506) of enoxaparin given throughout hospital admission versus UFH for at least 48 hours. The primary end point of death or recurrent MI was reduced (absolute RR 2.1%, relative RR 17%) although overall mortality was unchanged. Major bleeding was

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increased at 30 days (absolute risk increase 0.7%, relative risk increase 53%). Although superior efficacy of enoxaparin was apparent by 48 hours, this trial observed a rise in event rates after UFH was discontinued suggesting that 48 hours of anticoagulation is insufficient.<sup>90</sup> 1+

#### 4.5.3 DIRECT THROMBIN INHIBITORS

A meta-analysis of 11 randomised trials has demonstrated modest superiority of direct thrombin inhibitors, such as hirudin or bivalirudin, over UFH in patients with ACS.<sup>91</sup> Although there was no effect on mortality, there was a 20% relative RR (0.7% absolute RR) in reinfarction at seven days, maintained at 30 and 180 days. In comparison with UFH, there was no excess bleeding risk, except when used in patients with ST-segment-elevation ACS having thrombolysis where the 30% relative RR in reinfarction at four days was offset by a 32% relative risk increase in moderate bleeding.<sup>92</sup> 1++

Although there have been no comparative studies between direct thrombin inhibitors and LMWH in patients with ACS, direct thrombin inhibitors appear to have a similar magnitude of benefit over UFH to that seen with LMWH.<sup>83,91</sup>

#### 4.5.4 SYNTHETIC PENTASACCHARIDES

##### *Non-ST-segment-elevation acute coronary syndrome*

In the OASIS-5 RCT (n=20,078) the synthetic pentasaccharide, fondaparinux (subcutaneous injection 2.5 mg daily), had similar clinical efficacy to enoxaparin (subcutaneous injection 1 mg/kg twice daily) but with reduced risk of major bleeding (absolute RR 1.9%; relative RR 48%). Although the primary end points (death, MI or refractory ischaemia) were similar, both short- (30 day) and long-term (180 day) mortalities were lower with fondaparinux (absolute RR 0.6 % and 0.7%; relative RR 17% and 11%, respectively).<sup>93</sup> 1++

##### *ST-segment-elevation acute coronary syndrome*

In the OASIS-6 RCT (n=12,092), intravenous bolus followed by daily subcutaneous fondaparinux injection (2.5 mg) reduced the primary end point of death or recurrent MI at 30 days (absolute RR 1.5%; relative RR 14%) compared with treatment with placebo or UFH. Death rates at all time points (9, 30 and 180 days) were reduced (30 days; absolute RR 1.1%, relative RR 13%) and the incidence of major bleeding was unaffected. These benefits were only seen in those patients not treated with primary PCI.<sup>94</sup>

Due to multiple study groups and treatment regimens, the interpretation of the OASIS-6 trial is complex. In contrast to the OASIS-5 trial, there was no direct head-to-head comparison of fondaparinux with LMWH. Moreover, nearly 50% of patients recruited did not have a clear indication for anticoagulation and were randomised to placebo or fondaparinux. The OASIS-6 trial included patients presenting up to 24 hours from symptom onset. Almost a quarter of the patients had no reperfusion therapy, and in those that did, streptokinase was the predominant (73%) thrombolytic agent. 1++

Because of the differences in inclusion criteria, study design and length of anticoagulant therapies, the OASIS-6 and ExTRACT trials do not lend themselves to direct comparison. The ExTRACT trial was limited to those patients receiving predominantly (80%) fibrin-specific thrombolytic therapy. In the subgroup of OASIS-6 who did receive thrombolytic therapy and were randomised to either fondaparinux or UFH (n=2,666), there was a reduction in death (absolute RR 3.2%, relative RR 21%) and in death or recurrent MI (absolute RR 4.1%, relative RR 23%) in those patients treated with fondaparinux. This was a modest-sized subgroup analysis and should be interpreted with caution.

#### 4.5.5 OVERVIEW AND RECOMMENDATIONS

Use of anticoagulant therapy in patients with ACS favours progressively lower molecular weight heparins and more prolonged (>48 hours) durations of therapy. The pentasaccharides appear to have the best efficacy and safety profile with a reduction in adverse bleeding events coupled with a reduction in short- to medium-term mortality. Fondaparinux is the only pentasaccharide currently available for clinical use. There is a concern that LMWH and pentasaccharides do not provide adequate anticoagulation in patients undergoing PCI.

Large-scale RCTs (OASIS-5 and OASIS-6) appear to favour the use of fondaparinux over LMWH. The apparent superiority of fondaparinux in patients with non-ST-segment-elevation ACS is based upon a single large RCT (OASIS-5) and predominantly relates to short-term reductions in bleeding risk and apparent longer-term mortality benefits.<sup>93,94</sup>

In patients with ST-segment-elevation ACS, the lack of a direct comparison between fondaparinux and LMWH, and the markedly differing inclusion criteria, make specific recommendations challenging. In the relevant clinical trials evidence suggesting superiority of fondaparinux is insufficient to recommend its use in preference to LMWH. The OASIS-6 trial was distinguished by the inclusion of patients with ST-segment-elevation ACS who did not receive reperfusion therapy. Its use in this subpopulation did confer therapeutic benefit and fondaparinux should be the agent of choice in this group.<sup>94</sup>

Three large and well-conducted RCTs (ExTRACT, OASIS-5 and OASIS-6) have demonstrated that a therapeutic strategy of 48 hours of anticoagulation is insufficient, with an increased risk of MI apparent following early cessation of therapy.<sup>90,93,94</sup>

- R** | **In the presence of ischaemic electrocardiographic changes or elevation of cardiac markers, patients with an acute coronary syndrome should be treated immediately with fondaparinux or low molecular weight heparin.**
- R** | **Patients with an ST-segment-elevation acute coronary syndrome who do not receive reperfusion therapy should be treated immediately with fondaparinux.**
- ✓ | Anticoagulant therapy should be continued for eight days, or until hospital discharge or coronary revascularisation.

## 4.6 BETA BLOCKERS

### 4.6.1 NON-ST-SEGMENT-ELEVATION ACUTE CORONARY SYNDROME

There are no large-scale RCTs of beta-blocker therapy in patients with non-ST-segment-elevation ACS. Meta-analysis of small RCTs in patients with unstable angina suggests that beta blockers reduce the rate of progression to MI by 13%.<sup>95</sup> Given their secondary preventative benefits in patients with a recent MI (*see the SIGN guideline on risk estimation and the prevention of cardiovascular disease*)<sup>96</sup> beta blockers should be the first line anti-anginal agent of choice in patients with non-ST-segment-elevation ACS.

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### 4.6.2 ST-SEGMENT-ELEVATION ACUTE CORONARY SYNDROME

The ISIS-1 trial described an early (seven day) benefit in cardiovascular mortality from intravenous beta-blocker therapy in patients with MI with a 15% relative RR (0.68% absolute RR).<sup>97</sup> This benefit appeared to be mediated through a reduction in cardiac rupture.<sup>98</sup> This trial was conducted before the widespread use of thrombolytic therapy and it is unclear how relevant these findings are in the contemporary treatment of MI.

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The COMMIT/CCS RCT of 45,852 patients with ST-segment-elevation ACS demonstrated that immediate intravenous (metoprolol 5–15 mg) followed by oral (metoprolol 50 mg four times daily for the first 24 hours followed by 200 mg controlled-release metoprolol daily thereafter) beta blockade had no effect on mortality or the coprimary end points of death, reinfarction or cardiac arrest. There was a 0.5% absolute RR in reinfarction (18% relative RR) and arrhythmic death (17% relative RR) but at the expense of an absolute risk increase of 1.1% (relative increase of 30%) in cardiogenic shock. The reduction in death from ventricular fibrillation was counterbalanced by an increase in death from cardiogenic shock. The risk of cardiogenic shock was seen within the first day of presentation and in patients presenting with hypotension or in Killip class III.<sup>99</sup>

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Previous RCTs and a meta-analysis have failed to demonstrate a mortality benefit of early beta blockade.<sup>97,100,101</sup> A subsequent meta-analysis (conducted by the COMMIT/CCS authors) of RCTs of early beta blockade in 52,645 patients with ST-segment-elevation ACS in Killip class I (no clinical evidence of heart failure) with systolic blood pressure >105 mm Hg and heart rate >65/min found that intravenous followed by oral beta blockade reduces mortality (absolute RR 0.7%, relative RR 13%), reinfarction (absolute RR 0.5%, relative RR 22%) and cardiac arrest (absolute RR 0.7%, relative RR 15%).<sup>99</sup>

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**R** In the absence of bradycardia or hypotension, patients with acute coronary syndrome in Killip class I should be considered for immediate intravenous and oral beta blockade.

#### 4.7 GLYCAEMIC CONTROL

Elevated blood glucose at hospital admission is a strong independent risk marker for patients with MI.<sup>102</sup> Two major RCTs (DIGAMI 1 and DIGAMI 2) and a smaller single-centre trial (BIOMArCS-2) have investigated the effects of insulin and glucose infusion in diabetic patients with acute MI.<sup>103-105</sup> In the DIGAMI 1 trial (n=620), intensive metabolic control, aiming for a target glucose concentration of 7.0 to 10.9 mmol/L using insulin and glucose infusion in patients with diabetes mellitus or a blood glucose >11.0 mmol/L, conferred a marked mortality benefit at one year (18.6% v 26.1%).<sup>103</sup> More aggressive targets are potentially harmful.<sup>104</sup> The subsequent DIGAMI 2 trial (n=1,253) investigated whether long-term insulin therapy should be considered in patients with type 2 diabetes mellitus and acute MI. It demonstrated that long-term insulin was of no additional benefit, although there was extensive use of insulin at discharge in all treatment groups making interpretation difficult. For patients with type 2 diabetes mellitus, insulin is not required beyond the first 24 hours unless clinically required for the management of their diabetes.<sup>105</sup>

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The BIOMArCS-2 trial of tight glycaemic control (4.7 to 6.1 mmol/L) in patients with and without diabetes (except those currently receiving insulin) with hyperglycaemia, reported no evidence of benefit from intensive insulin therapy and an increase in adverse events.<sup>104</sup>

**R** Patients with confirmed acute coronary syndrome and diabetes mellitus or marked hyperglycaemia (>11.0 mmol/L) should have immediate blood glucose control aiming for a target glucose concentration of 7.0 to 10.9 mmol/L

✓ Instituting an insulin and glucose infusion should not delay institution of time-dependent interventions such as primary PCI.



## 5 Reperfusion therapy for ST-segment-elevation acute coronary syndrome

This section provides further recommendations regarding the immediate (within the first 12 hours) management of patients with ST-segment-elevation ACS, focusing on both primary PCI and thrombolysis. Investigation and revascularisation in patients with non-ST-segment-elevation acute coronary syndrome is discussed in section 7.1.1

### 5.1 CHOICE OF REPERFUSION THERAPY

A systematic review and meta-analysis of RCT data showed that primary PCI is superior to thrombolysis for the treatment of patients with ST-segment-elevation ACS.<sup>106,107</sup> When compared with thrombolysis, primary PCI reduced short- and long-term mortality, stroke, reinfarction, recurrent ischaemia and the need for CABG surgery as well as the combined end point of death or non-fatal reinfarction (see Table 3). This benefit was consistent across all patient subgroups and was independent of the thrombolytic agent used. The greatest benefit was seen in those patients treated within 12 hours of symptom onset.<sup>106,107</sup>

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Table 3: Advantages of primary percutaneous coronary intervention over thrombolysis<sup>106</sup>

Clinical indices	Event Rate		Absolute RR	Relative RR	NNT
	Thrombolysis	PCI			
Short-term mortality (4–6 weeks)	8%	5%	3%	36%	33
Long-term mortality (6–18 months)	8%	5%	3%	38%	33
Stroke	2%	<1%	2%	64%	50
Reinfarction	8%	3%	5%	59%	20
Recurrent ischaemia	18%	7%	11%	59%	9
Death or non-fatal reinfarction	12%	7%	5%	44%	20
Need for CABG	13%	8%	5%	36%	20

**R** Patients with an ST-segment-elevation acute coronary syndrome should be treated immediately with primary percutaneous coronary intervention.

#### 5.1.1 TRANSFER OF PATIENTS TO INTERVENTIONAL CENTRES

Two randomised trials have shown that emergency transfer of patients to interventional centres for PCI can be undertaken safely.<sup>108,109</sup> Prompt transfer of patients for primary PCI was associated with a reduction in the composite end point of death, reinfarction and stroke at 30 days (absolute RR 6%, relative RR 40%;<sup>108</sup> absolute RR 7%, relative RR 45%<sup>109</sup>) when compared with thrombolysis. This benefit was primarily driven by a reduction in reinfarction (absolute RR 4.7%, relative RR 75%;<sup>108</sup> absolute RR 1.7%, relative RR 55%<sup>109</sup>). In both trials overall, there was no difference in mortality compared with thrombolysis, although, where time from symptom onset was greater than three hours, this favoured PCI.

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**R** Local protocols should be developed for the rapid treatment of patients presenting with ST-segment-elevation acute coronary syndrome. Emergency transfer of patients to interventional centres for primary percutaneous coronary intervention should be considered.

✓ Primary percutaneous coronary intervention should be delivered by the centre with the least travel time for the individual patient.

✓ All centres should participate in ongoing audit of primary PCI-related treatment delay against preferred standards.

Thrombolytic therapy is covered in section 5.2

## 5.1.2 INTRACORONARY STENTING

In a meta-analysis of nine trials (n=4,433) of PCI, intracoronary stenting reduced reinfarction (absolute RR 1.2%, relative RR 33%) and target-vessel revascularisation (absolute RR 14.4%, relative RR 52%) at 12 months when compared with isolated balloon angioplasty. These benefits did not affect short- or long-term mortality.<sup>110</sup>

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**R** Intracoronary stent implantation should be used in patients undergoing primary percutaneous coronary intervention.

## 5.1.3 THROMBECTOMY

Manual and mechanical thrombectomy can be used as adjunctive therapy during primary PCI. It has the potential to improve reperfusion with the benefit of reducing infarct size, major adverse cardiovascular events and mortality. Safety concerns include iatrogenic distal embolisation of thrombus, slow or no reflow, or coronary dissection, and increased risk of stroke at 30 days.

Early evidence of improved surrogate outcomes, implying improved perfusion and improved mortality, from two RCTs<sup>111,112</sup> and four systematic reviews/meta-analyses of small RCTs<sup>113-116</sup> has been challenged by the results of three multicentre RCTs, two of them large (n=7,244 and n=10,732), which did not demonstrate benefit from the routine use of manual thrombectomy.<sup>117-119</sup> The two large RCTs reported no differences in all-cause mortality, recurrent MI, or stent thrombosis,<sup>117</sup> or in cardiovascular death, stent thrombosis or target-vessel revascularisation,<sup>118</sup> although the latter trial reported an increase in stroke risk (0.7% v 0.3% for routine treatment). Compared with those receiving PCI alone, thrombus aspiration showed no reduction in rate of death from any cause, rehospitalisation for MI or stent thrombosis at one year.<sup>120</sup>

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1-

In specific patients with a large proximal thrombus burden, manual thrombectomy remains a reasonable adjunctive therapy.

**R** A manual thrombectomy device should not be used routinely during primary percutaneous coronary intervention.

## 5.2 THROMBOLYTIC THERAPY

When patients present with ST-segment-elevation ACS, but primary PCI is unavailable, many will benefit from immediate thrombolysis. When compared with placebo, thrombolytic therapy reduces 35-day mortality (1.9% absolute RR, 18% relative RR) in patients presenting with an ST-segment-elevation ACS.<sup>16,121</sup>

1++

## 5.2.1 TIMING OF TREATMENT

Compared with primary PCI, the benefit of thrombolysis on six-month mortality is more time dependent and is associated with a lesser degree of myocardial salvage at all time points.<sup>122,123</sup> Considered expert opinion suggests that primary PCI is the recommended reperfusion therapy over fibrinolysis if performed by an experienced team within 120 minutes of first medical contact but that the target for quality assessment should be provision of primary PCI within 90 minutes of first medical contact.<sup>124</sup>

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Since the clinical benefits of thrombolysis are time dependent with an increase of 1.6 deaths per hour of delay per 1,000 patients treated,<sup>16</sup> various strategies have been successfully employed to minimise the delay between diagnosis and initiation of thrombolysis. These include prehospital thrombolysis,<sup>13,125</sup> and thrombolysis delivered in the emergency department.<sup>126-128</sup>

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**R** When primary percutaneous coronary intervention cannot be provided within 120 minutes of ECG diagnosis, patients with an ST-segment-elevation acute coronary syndrome should receive immediate (prehospital or admission) thrombolytic therapy.



## 5.2.2 CONTRAINDICATIONS TO THROMBOLYSIS

Absolute contraindications for thrombolysis include recent haemorrhage, trauma or surgery, coma, ischaemic stroke within three months, aortic dissection, bleeding diatheses, known structural cerebrovascular lesions including neoplasms, and any prior intracerebral haemorrhage.<sup>13,14,106</sup> A full list of contraindications can be found in the BNF.<sup>9</sup> In patients who cannot receive primary PCI within 120 minutes and who are being considered for thrombolysis, approximately 40–50% of patients are deemed ineligible for thrombolytic therapy. This is most often (in 35% of ineligible patients) due to delayed presentation (>12 hours from symptom onset).<sup>129</sup> Patients ineligible because of contraindications to thrombolytic therapy (10–40%) should be considered for primary PCI.<sup>129,130</sup> Primary PCI incurs a small bleeding risk from the administration of antiplatelet and anticoagulant therapies, and some relative contraindications may be common to both reperfusion strategies.

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## 5.2.3 CHOICE OF THROMBOLYTIC AGENT

Early trials of thrombolytic therapy established the mortality benefits of both fibrin-specific (tissue plasminogen activator; alteplase) and non-fibrin-specific agents (streptokinase) in patients with acute MI. Subsequent trials directly comparing the efficacy of these two classes of thrombolytic agents demonstrated similar mortality benefits at 30–35 days postinfarction, as confirmed by systematic review and meta-analysis.<sup>121,131,132</sup>

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The imperative to reduce treatment delays and the constraints of administration in the prehospital setting favour bolus agents.

**R** ■ **Thrombolysis should be conducted with a fibrin-specific agent.**

✓ ■ A bolus fibrin-specific agent is preferred on practical grounds, particularly in the prehospital setting.

## 5.3 COST EFFECTIVENESS OF REPERFUSION THERAPIES IN ST-SEGMENT-ELEVATION ACUTE CORONARY SYNDROME

### 5.3.1 PRIMARY PCI COMPARED WITH IN-HOSPITAL THROMBOLYSIS

A systematic review of 10 studies with long-term follow up found consistent evidence of lower total costs with primary PCI compared with in-hospital thrombolysis.<sup>106</sup> These reduced costs were associated with reduced length of hospital stay through early identification and discharge of low-risk patients, and need for fewer subsequent procedures.<sup>133,134</sup> None of the studies contained resource or cost information directly relevant to the NHS.

To apply these findings to the UK, an economic model was developed using NHS costs (for the year 2003) and the clinical-effectiveness data derived by meta-analysis of effectiveness studies. In this model, primary PCI was compared with thrombolysis using reteplase. Primary PCI had a higher cost per case (approximately £550) but a gain in health status of 0.08, giving an incremental cost-effectiveness ratio of about £6,500 for each unit of health state gained.<sup>106</sup> Using streptokinase rather than reteplase increased the incremental cost-effectiveness ratio to almost £29,100 per unit of health state gained.<sup>106</sup> This economic evaluation is limited to six months follow up and does not consider the longer-term consequences of treatment with either therapy.

The analysis did not use the conventional health outcome measure of a quality adjusted life year (QALY) but rather expressed benefit as a unit of health state gained. Thus the conventional thresholds for cost per QALY cannot be applied. Rather the results suggest primary PCI could be cost effective compared with thrombolysis using reteplase but are inconclusive in respect of primary PCI compared with thrombolysis using streptokinase.

### 5.3.2 PRIMARY PCI COMPARED WITH PREHOSPITAL THROMBOLYSIS

Where there is access to a PCI centre within two hours of symptom onset, one economic evaluation<sup>135</sup> using French costs for the year 2005 and clinical data from a randomised controlled trial,<sup>136</sup> concluded that it was more cost effective to reperfuse ST-segment-elevation ACS patients by PCI than by prehospital thrombolysis. The one year primary end points for the clinical event-rates of death, non-fatal myocardial infarction, and stroke were not different after primary PCI and prehospital thrombolysis with rescue PCI, but costs were lower for primary PCI. The main reasons for the lower costs in the primary PCI arm were lower initial length of stay and a lower rate of subsequent revascularisations.

### 5.3.3 A COMPARISON OF DIFFERENT THROMBOLYTIC AGENTS

One systematic review of the clinical and cost effectiveness of different thrombolytic agents concluded that the differences in clinical outcome are so small that use of the cheapest product should be advocated.<sup>121</sup> As part of this study an economic model was developed from an NHS perspective, using the BNF list prices for thrombolytic agents for the year 2001 and excluding any differences in the cost of administration. These prices do not take into account the discounts available to different markets and geographical areas. The modelled results were highly sensitive to variations in the drug costs and the study concluded that the choice of agents should be governed by the relative prices of the drugs, assuming no difference in administration costs.

## 5.4 'RESCUE' PERCUTANEOUS CORONARY INTERVENTION

Rescue PCI is undertaken within 12 hours of thrombolysis when there is an apparent failure to reperfuse the infarct-related artery. Reperfusion is taken to have occurred when there is a >50% fall in ST-segment elevation or new onset of idioventricular rhythm.<sup>137,138</sup>

Previous guidelines recommend rescue PCI as the preferred strategy for patients who fail to reperfuse after thrombolysis.<sup>13,14</sup> Rescue PCI is of particular benefit in those with large areas of myocardium at risk, haemodynamic compromise, evidence of heart failure or electrical instability and total occlusion or minimal flow in the infarct-related artery.<sup>13</sup>

A systematic review of trials of rescue PCI against conservative therapy after failed thrombolysis confirmed a reduction in early severe heart failure (absolute RR 8%, relative RR 68%) and one-year mortality in patients with clinical myocardial infarction (absolute RR 5%, relative RR 38%).<sup>139</sup>

In the REACT trial of patients who received thrombolysis within six hours of symptom onset (n=427), rescue PCI, performed at median of 414 minutes (interquartile range 350-505) from symptom onset, was associated with a marked reduction in the composite primary end point of death, reinfarction, stroke or severe heart failure (absolute RR 15%, relative RR 53%). This was predominantly driven by a reduction in reinfarction.<sup>140</sup>

**R** Patients presenting with ST-segment-elevation acute coronary syndrome within six hours of symptom onset, who fail to reperfuse following thrombolysis, should be considered for rescue percutaneous coronary intervention.

## 5.5 MULTIVESSEL PERCUTANEOUS CORONARY INTERVENTION

Patients presenting with ST-segment-elevation ACS and multivessel disease are at higher risk of further events than patients with single-vessel disease. It is possible that treatment of all obstructive lesions may improve their outcomes. Multivessel PCI in an unstable patient is, however, more hazardous than it is in a stable patient and application of a broader inclusion policy may expose patients who are more susceptible to the risks (including cardiogenic shock in the event of acute severe ischaemia in the non-infarct territory, stent thrombosis, and contrast-induced nephropathy) of a longer, more complex procedure.

The possible treatment strategies for patients with ST-segment-elevation ACS and multivessel disease are culprit-only PCI, immediate multivessel PCI or staged multivessel PCI, with or without invasive or non-invasive assessments for ischaemia. The choice for an individual patient depends on a range of patient factors including severity and complexity of non-culprit disease and size of territory at risk of myocardial

infarction, and operational issues such as hospital and catheter laboratory availability, and operator fatigue. This combination of issues applies equally to recruitment into studies, which makes observational data particularly subject to bias, and hampers recruitment of consecutive patients to randomised trials.

A meta-analysis of four RCTs examined outcomes in patients treated either with culprit-only PCI (n=478) or multivessel PCI (either immediate or staged, n=566). During follow up (range 1–2.5 years), multivessel PCI reduced all-cause mortality (relative risk 0.57, 95% confidence interval (CI) 0.36 to 0.92, p=0.02) compared with culprit-only PCI. Risks of recurrent myocardial infarction (relative risk 0.41, 95% CI 0.23 to 0.75) and future revascularisation (relative risk 0.37, 95% CI 0.27 to 0.52) were also significantly reduced.<sup>141</sup> A further meta-analysis of seven trials (including the four included above) examined complete immediate revascularisation with either culprit-only or staged multivessel revascularisation and reported that immediate complete revascularisation reduced the odds of major coronary events by 41% (odds ratio (OR) 0.59, 95% CI 0.36 to 0.97). Complete revascularisation also reduced recurrent MI (OR 0.48, 95% CI 0.27 to 0.85) and repeat revascularisation (OR 0.51, 95% CI 0.31 to 0.84).<sup>142</sup>

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The potential for harm from multivessel PCI is documented in observational data and the populations recruited to randomised studies represent only a small minority of patients with multivessel disease and ST-segment-elevation ACS.<sup>143</sup>

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Currently there is insufficient good-quality evidence to support a recommendation for treating patients with ST-segment-elevation ACS and multivessel disease. Clinical judgement may be used to identify patients at low risk of complications from complete revascularisation.

## 6 Risk stratification and non-invasive testing

### 6.1 RISK STRATIFICATION

There is evidence that identifying higher-risk individuals following admission allows selection of patients for early investigation and intervention. Data from the TACTICS-TIMI-18 and FRISC II trials in patients with non-ST-segment-elevation ACS suggest that the short-term (6–12 months) benefits of invasive investigation were predominantly seen in those at medium to high risk.<sup>144,145</sup> Analysis of long-term (five-year) outcomes in the RITA-3 trial has also demonstrated that those patients at moderate to high risk benefit most from coronary angiography and revascularisation.<sup>146</sup> Invasive investigation with coronary angiography with a view to revascularisation appears to be appropriate for patients with one- and five-year event (death or MI) rates of >10% and >20% respectively. Patients at lower risk do not appear to benefit.<sup>146</sup>

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**R** Risk stratification using clinical scores should be conducted to identify those patients with acute coronary syndrome who are most likely to benefit from early therapeutic intervention.

#### 6.1.1 RISK STRATIFICATION SCORES

There are several clinical risk stratification scoring systems that can predict death or MI in patients with ACS: the most commonly used scores include GRACE,<sup>6,7</sup> TIMI,<sup>147,148</sup> PURSUIT,<sup>149</sup> and FRISC.<sup>144</sup> All are derived from RCT populations except GRACE which is obtained from an international 'real life' observational registry. It provides a unified scoring system for both ST-segment-elevation and non-ST-segment-elevation ACS. In prospective evaluations, the GRACE registry was the most predictive of outcome and has been validated using independent external datasets.<sup>150,151</sup> The updated GRACE 2.0 ACS Risk Calculator uses revised algorithms for predicting death or death/myocardial infarction and provides population histograms of one- and three-year risk, indicating where the individual patient's result is positioned compared with the whole ACS population in the GRACE registry. The calculator is available online at [www.gracescore.org](http://www.gracescore.org) or as a mobile app.

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✓ Greater generalisability and accuracy favours the use of the GRACE score for risk stratification in patients with acute coronary syndrome.

### 6.2 ASSESSMENT OF CARDIAC FUNCTION

A systematic review of observational studies in patients with clinical MI suggests that markers of left ventricular dysfunction and heart failure provide better prognostic information than stress testing.<sup>152</sup> This is consistent with cohort studies that suggest plasma B-type natriuretic peptide concentrations and measurements of ejection fraction provide complementary prognostic information.<sup>153,154</sup>

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2<sup>+</sup>

The selection of certain therapies, such as mineralocorticoid receptor antagonists (*see section 8.7*),<sup>155</sup> may require the assessment of left ventricular function before initiation of therapy.

**R** In patients with acute coronary syndrome, assessment of cardiac function should be conducted in order to identify those patients at high risk and to aid selection of appropriate therapeutic interventions.

### 6.3 STRESS TESTING

A systematic review of 54 observational studies incorporating 19,874 patients with clinical MI found that pre-discharge stress testing provides limited additional prognostic information to guide patient management.<sup>152</sup> All forms of non-invasive stress testing demonstrate similar sensitivities and specificities for the prediction of future cardiac events.<sup>152</sup> Although the negative predictive value is high (approximately 94%), the positive predictive value is low (<10% for cardiac death and <20% for cardiac death or MI). The sensitivity of these tests is poor ( $\leq 44\%$ ) because, unlike chronic stable angina, the underlying pathogenesis is dictated by dynamic thrombotic occlusion of the coronary artery rather than a fixed flow-limiting stenosis. Stress testing identifies less than half of those individuals who will go on to have a further adverse cardiac event. Clinical risk markers are more appropriate for the selection of patients for early investigation and intervention (*see section 6.1*).

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Predischarge stress testing may have a limited role in patients identified as low risk who would otherwise not undergo early invasive investigation.

- ✓ Predischarge stress testing should be considered in low-risk patients with acute coronary syndrome.

## 7 Invasive investigation and revascularisation

### 7.1 INVASIVE INVESTIGATION

#### 7.1.1 NON-ST-SEGMENT-ELEVATION ACUTE CORONARY SYNDROME

A meta-analysis of seven trials reported that, in comparison with a conservative approach, in the absence of inducible ischaemia, routine coronary angiography and revascularisation reduced rates of MI, severe angina and rehospitalisation although overall mortality was unchanged (5.5% v 6.0%, absolute RR 0.5%, relative RR 8%, 95% CI 9 to 23%) after a mean follow up of 17 months. The effects on mortality varied with time; with an early (in-hospital) hazard (1.8% v 1.1%, absolute risk increase 0.7%, relative risk increase 60%, 95% CI 14 to 125%) and a late (postdischarge) benefit (3.8% v 4.9%, absolute RR 1.1%, relative RR 24%, 95% CI 6 to 38%).<sup>156</sup> The meta-analysis is limited by significant heterogeneity between the seven trials and the high rate of crossover from a conservative strategy to an invasive strategy in most of the trials. This makes it difficult to determine the potential benefits of an early invasive strategy.

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Four large RCTs (n>1,000)<sup>157-161</sup> and five smaller RCTs (n=131-993)<sup>162-166</sup> compared an early invasive with a conservative strategy in patients with unstable angina and non-ST-segment-elevation ACS. There was significant heterogeneity amongst these nine trials often with high crossover rates to an invasive strategy.

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The FRISC II trial (n=2,457) had strict adherence to study randomisation (10-day revascularisation of 71% versus 9% in the conservative arm) and demonstrated a 26% relative reduction (95% CI 8 to 40%, absolute RR 3.0%) in MI and a 43% relative RR (95% CI 10 to 64%, absolute RR 1.7%) in mortality at one year.<sup>157,158</sup>

Similar benefits in MI but not mortality were seen in the TACTICS-TIMI 18 trial (n=2,220).<sup>159</sup> This trial had a high crossover rate with 51% of patients in the conservative strategy group undergoing in-hospital coronary angiography resulting in modest differences in revascularisation rates (in-hospital revascularisation of 37% with a conservative strategy versus 61% in the invasive strategy arm). This may have led to underestimation of treatment benefits.

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Both the FRISC II and TACTICS-TIMI-18 trials systematically biased the diagnosis of MI according to treatment group with those undergoing revascularisation having a higher biochemical threshold for MI than those who did not. This may have led to an overestimation of the benefits on this end point.

The RITA-3 trial (n=1,810) recruited moderate-risk patients with non-ST-segment-elevation ACS: one-year mortality was 8.3% compared with 14.1% in the FRISC II trial.<sup>160</sup> It also demonstrated a benefit of early invasive investigation and revascularisation with a 34% relative reduction (95% CI 15 to 59%, absolute RR 4.9%) in the risk of the combined primary end point of death, MI or refractory angina at four months. A halving of refractory angina primarily drove this end point. There were no differences in mortality. When using the European Society of Cardiology/American College of Cardiology definition of MI an early invasive strategy also reduced MI rates by 33% (95% CI 14 to 49%) at one year. Five-year follow-up data have confirmed that the reductions in the combined end point of death or MI are sustained.<sup>146</sup>

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The ICTUS trial (n=1,200) failed to demonstrate a significant benefit of early invasive intervention in low-risk patients with non-ST-segment-elevation ACS. There was a high rate (>50%) of coronary angiography in the conservative treatment group and the overall mortality in the trial was exceptionally low at 2.5% (compared with 14% in the FRISC trial).<sup>161</sup> The evidence suggests that a routine invasive approach is indicated only in patients at medium to high risk.

**R** Patients with non-ST-segment-elevation acute coronary syndrome at medium or high risk of early recurrent cardiovascular events should undergo early coronary angiography and revascularisation.

### 7.1.2 ST-SEGMENT-ELEVATION ACUTE CORONARY SYNDROME

Four small (n=164–500) RCTs assessed the benefit of early (within 24 hours) coronary angiography and revascularisation in patients with ST-segment-elevation ACS treated with thrombolytic therapy.<sup>167-170</sup> All trials suggest a favourable outcome with early PCI. In the largest study, the GRACIA-1 trial, the majority of patients in the intervention group underwent PCI (84%) or CABG (2%) in comparison to 20% in the conservative (ischaemia-driven) treatment arm.<sup>168</sup> At one-year follow up, the primary end point of death, MI or revascularisation was reduced (absolute RR 12%, relative RR 56%, 95% CI 30 to 72%) in the invasive treatment arm. The incorporation of coronary revascularisation into the primary end point biased the apparent benefit in favour of the intervention group. Although there was an apparent trend, the more appropriate secondary end point of death or reinfarction was not reduced (absolute RR 5%, relative RR 41%, 95% CI -5 to 67%). This was a pilot study and the apparent clinical benefits need to be established in larger definitive RCTs.

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A strategy of primary PCI or early coronary angiography is associated with a shorter median length of hospital stay<sup>80</sup> because, in conjunction with clinical risk stratification, it enables the identification of low-risk patients who can be safely discharged home early.<sup>133,135</sup>

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The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology recommend routine pre-discharge coronary angiography in patients who have received successful thrombolysis.<sup>171</sup>

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**R** | **Patients with ST-segment-elevation acute coronary syndrome treated with thrombolytic therapy should be considered for early coronary angiography and revascularisation.**

✓ | Hospitals adopting early invasive intervention for patients with acute coronary syndrome should consider the early discharge of patients at low risk of subsequent events.

### 7.2 ACCESS ROUTES FOR PERCUTANEOUS CORONARY INTERVENTION

Both femoral and radial artery access routes are used for carrying out PCI. Evidence from systematic reviews and meta-analyses comparing femoral with radial access shows that the radial access route reduces the risk of major adverse cardiovascular events and associated major bleeding.<sup>172-175</sup> One review of RCT data covering 5,055 patients showed that the radial approach was associated with reduced mortality (2.7% v 4.7%, OR 0.55, 95% CI 0.40 to 0.76) and major bleeding (1.4% v 2.9%, OR 0.51, 95% CI 0.31 to 0.85) compared with the femoral approach.<sup>173</sup> Similar results were found in a meta-analysis of data from 15 observational studies including 24,509 patients (short-term mortality 5.9% v 11.1%, OR 0.48, 95% CI 0.43 to 0.54; major bleeding 1.4% v 4.6%, OR 0.32, 95% CI 0.25 to 0.42).<sup>172</sup>

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The radial access route is associated with a reduction in the relative risk of access-site bleeding<sup>173</sup> (2.1% v 5.6%, OR 0.35, 95% CI 0.25 to 0.50) and complications (relative risk 0.31, 95% CI 0.17 to 0.58).<sup>174</sup> Stroke risk is similar between the two approaches (0.5%).<sup>173</sup>

Studies show that the procedure time is slightly longer with radial than with femoral access but that these differences are minor and of no clinical relevance.<sup>173,175</sup>

Results from a large, recent RCT of 8,404 patients with ST or non-ST-segment-elevation ACS support these results. Radial access was associated with a reduction in major adverse cardiovascular events (1.5% absolute RR, 15% relative RR) compared with femoral access. Net adverse clinical events were also lower (1.9% absolute RR, 17% RR) with radial access and this was driven by reductions in major bleeding (0.6% absolute RR, 33% relative RR) and all-cause mortality (0.6% absolute RR, 28% relative RR).<sup>176</sup>

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One study noted a preference for the radial route amongst patients undergoing subsequent procedures but no information was given about how this preference was assessed.<sup>177</sup>

**R** | **In patients with acute coronary syndrome, the radial artery should be the vascular access route of choice in patients undergoing PCI.**



### 7.3 GLYCOPROTEIN IIb/IIIa RECEPTOR ANTAGONISTS

A systematic review of 60 trials, including 48 trials in patients undergoing PCI (n=33,513) (of which 11 trials involved patients with ST-segment-elevation ACS, 7 trials involved patients with non-ST-segment-elevation ACS, 18 trials involved patients with stable angina and 12 trials included mixed populations), reported that intravenous glycoprotein IIb/IIIa receptor antagonists led to a reduction in all-cause mortality at 30 days (OR 0.79, 95% CI 0.64 to 0.97, NNT=249) but not at six months (OR 0.90, 95% CI 0.77 to 1.05), a reduction in death or non-fatal MI at 30 days (OR 0.66, 95% CI 0.60 to 0.72) and six months (OR 0.75, 95% CI 0.64 to 0.86, NNT=42), and a reduction in urgent revascularisation. Most of the benefit derived from a reduction in periprocedural MI. There was, however, a significant increase in severe bleeding (OR 1.39, 95% CI 1.21 to 1.61, number needed to harm (NNH)=125).<sup>178</sup>

The efficacy of glycoprotein IIb/IIIa receptor antagonists was less marked in patients pretreated with clopidogrel. In all the studies, patients received aspirin and clopidogrel or ticlopidine. The review precedes the current use of the more potent ticagrelor or prasugrel. In only two of the studies were drug-eluting stents used in the majority of patients.

The review included 12 studies (n=33,176) assessing the use of glycoprotein IIb/IIIa receptor antagonists in the medical management of non-ST-segment-elevation ACS. There was no significant reduction in all-cause mortality at 30 days or six months. There was a slight reduction in death or MI at 30 days (OR 0.91, 95% CI 0.85 to 0.98) and at six months (OR 0.88, 95% CI 0.81 to 0.96) but an increase in severe bleeding (OR 1.29, 95% CI 1.14 to 1.45, NNH=714).

A meta-analysis of 11 observational studies of primary PCI for patients with ST-segment-elevation ACS reported similar findings.<sup>179</sup>

Glycoprotein IIb/IIIa receptor antagonists are considered cost-effective treatment options in patients with ACS, with use of glycoprotein IIb/IIIa receptor antagonists as part of the initial management of high-risk patients with ACS being the most cost-effective strategy.<sup>180,181</sup>

**R** Glycoprotein IIb/IIIa receptor antagonists should not be given routinely in patients with acute coronary syndrome.

**R** Glycoprotein IIb/IIIa receptor antagonists should be considered at the time of PCI in patients at high risk of adverse cardiovascular events and those not adequately pretreated with dual antiplatelet therapy.

### 7.4 CORONARY ARTERY BYPASS GRAFTING SURGERY

Both CABG and PCI are treatment options for patients with obstructive coronary artery disease including patients with ACS. Treatment decisions will depend on the balance of benefit and risk in specific subgroups of patients.

In the absence of evidence solely derived from a population with unstable CAD, evidence was identified from one systematic review which included some trials which recruited mixed populations of patients with stable and unstable CAD. This review, of 13 RCTs and four meta-analyses, reported reduced rates of cardiac adverse events following CABG surgery compared with PCI in patients with unprotected left main-stem disease (ULMD), or multivessel CAD, or left ventricular dysfunction, and complex coronary disease (SYNTAX score greater than 22). In patients with diabetes and multivessel CAD (five of the 13 RCTs) long-term survival and the number of cardiac adverse events were reduced in patients receiving CABG compared with PCI.<sup>182</sup> Most of the benefit was due to a reduction in repeated coronary revascularisation procedures.

In patients with less complex coronary disease (SYNTAX score 22 or less), or in patients with a higher surgical risk, PCI should be considered.<sup>182</sup>



The rate of repeat revascularisation was generally higher following PCI than CABG, particularly in patients with multivessel CAD. Only one RCT reported rates of peri-operative stroke separately from major adverse cardiac and cerebrovascular events for patients with ULMD or multivessel CAD and in both groups, stroke rates were higher following CABG than PCI (2.7 v 0.3%, respectively, for ULMD; 2.2 v 0.6%, respectively for multivessel CAD).

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The period of convalescence and trauma of surgery, long-term outcome and avoidance of recurrent heart problems, may all influence patient acceptability. Patient preferences must be taken into account when assessing treatment options as part of a multidisciplinary team approach considering coronary disease complexity, patient comorbidities and local expertise.

Studies comparing the cost effectiveness of PCI compared with CABG suggest that PCI is unlikely to be cost effective because of the need for repeat revascularisation over time.<sup>183,184</sup>

**R** | **In patients with non-ST-segment-elevation acute coronary syndrome with disease amenable to revascularisation:**

- **coronary artery bypass graft surgery should be considered for patients with diabetes mellitus, left main-stem disease or multivessel coronary artery disease**
- **percutaneous coronary intervention should be considered for patients with a SYNTAX score of 22 or less or those with a high surgical risk.**

✓ | The selection of revascularisation strategy should be agreed in consultation with the patient and the multidisciplinary heart team taking into account patient preferences, disease complexity, comorbidities and local expertise.

## 8 Early pharmacological intervention

This section provides recommendations for the pharmacological management of ACS beyond the first 12 hours and up to hospital discharge. With the exception of P2Y<sub>12</sub>-receptor antagonists (*see section 1.2.1*), the duration of long-term therapy beyond hospital discharge was not within the remit of this guideline development group (*see the SIGN guideline on risk estimation and the prevention of cardiovascular disease*).<sup>96</sup>

### 8.1 ANTIPLATELET THERAPY

#### 8.1.1 ASPIRIN

In addition to the acute effects of aspirin (*see section 4.4*), the long-term secondary preventative benefits of aspirin are well established in patients with coronary heart disease (absolute RR 2.7%, relative RR 37%).<sup>55,185</sup>

**R** | Following acute coronary syndrome all patients should be maintained on long-term aspirin therapy.

✓ | A dose of 75 mg aspirin per day is recommended in patients with acute coronary syndrome.

#### 8.1.2 DUAL ANTIPLATELET THERAPY

##### *Acute coronary syndrome*

The major trials of dual antiplatelet therapy, clopidogrel, ticagrelor or prasugrel for ACS (*see section 4.4.2*) included patients who were treated for between three and 15 months. The CURE trial of clopidogrel versus placebo was administered for between three and 12 months (median nine months) after diagnosis of ACS.<sup>56</sup> The PLATO trial of ticagrelor versus clopidogrel was administered for between six and 12 months (median nine months) and the TRITON-TIMI<sup>38</sup> trial of prasugrel versus clopidogrel had a duration of six to 15 months (median 14.5 months). It is not possible to draw inferences about the relative benefits of shorter or longer duration of dual antiplatelet therapy from the PLATO or TRITON-TIMI<sup>38</sup> trials as neither included a placebo or 'no treatment' control group for any period during follow up.

In the CURE trial in which clopidogrel was compared with placebo (*see section 4.4.2*) the clinical benefits were predominantly seen in the first three months of therapy.<sup>57</sup> There were no differences in clinical outcome beyond three months,<sup>57</sup> although bleeding risks with clopidogrel were consistently higher.<sup>186</sup> Nonetheless, the study was not designed to assess temporal effects.

A recent large RCT comparing ticagrelor (60 or 90 mg daily) with placebo in 21,162 patients maintained on aspirin 1–3 years after MI, demonstrated a reduction in atherothrombotic events (absolute RR 1.2%), an increase in major bleeding (absolute risk increase 1.2–1.5%) but no effect on overall mortality, suggesting that durations of treatment beyond 12 months may not be beneficial.<sup>73</sup> However, no clinical trials have been published comparing duration of therapy for unselected patients with ACS.

##### *Dual antiplatelet therapy following PCI*

Three systematic reviews and meta-analyses of RCTs have compared different durations of dual antiplatelet therapy in patients undergoing PCI.<sup>187–189</sup> These analyses included trials recruiting a large proportion of patients with ACS. One meta-analysis found no difference in all-cause mortality, MI, stent thrombosis or stroke in patients receiving extended therapy. The risk of Thrombolysis in Myocardial Infarction (TIMI) major bleeding was, however, increased in patients receiving extended therapy (OR 2.64, 95% CI 1.31 to 5.30).<sup>187</sup> The median duration of therapy was 16.8 months for those receiving extended therapy compared with 6.2 months for short-term therapy.<sup>187</sup>

Two further meta-analyses, both of which included the same 10 RCTs incorporating approximately 32,000 patients compared short-term (3–6 months), 12-month and extended (>12 months) dual antiplatelet therapy in patients undergoing PCI with drug-eluting stents.<sup>188,189</sup> Both analyses reported a number of similar results and findings. Firstly, compared with short-term therapy, 12-month dual antiplatelet therapy was associated

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with a doubling in the risk of major bleeding but had no further beneficial effects on MI, stent thrombosis, cardiac death or all-cause death. Secondly, compared with 12-month therapy, extended therapy reduced recurrent MI and stent thrombosis but increased major bleeding and increased overall mortality. For mortality there was an increase in non-cardiac mortality that was not offset by a reduction in cardiac mortality. Both comparisons consistently demonstrated that shorter courses of therapy are not associated with worse outcomes. Sensitivity analyses identified no differences in these outcomes in patients with or without ACS.<sup>189</sup>

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#### *Dual antiplatelet therapy in medically-managed patients*

There is a lack of contemporary evidence for the optimal duration of dual antiplatelet therapy for patients who do not undergo PCI. Patients with ACS who do not undergo PCI usually either have minimal atheromatous disease or are frail with comorbid conditions which may be associated with an increased risk of bleeding. As such, a shorter duration of therapy is likely to be appropriate for most patients with ACS who are not undergoing early PCI.

#### *Cost effectiveness*

Treatment with 12 rather than three months of clopidogrel as an adjunct to aspirin among patients with ACS was found to be cost effective in patients at high risk of atherothrombotic events (age >70, ST depression, or diabetes) but not in patients at low risk of atherothrombotic events, even where clopidogrel is available as a generic drug.<sup>190</sup> However, the increasing use of early PCI in patients at high risk of atherothrombotic events may reduce the applicability of these findings.<sup>190</sup>

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The available evidence indicates that short-term (3–6 months) therapy with dual antiplatelet therapy is associated with either equal or lower rates of all-cause mortality compared with longer durations ( $\geq 12$  months), but approximately half the risk of major bleeding. However 12-month or extended dual antiplatelet therapy may have a role in selected patients with ACS and a high risk of recurrent atherothrombotic events but a low risk of bleeding. Similarly, shorter durations of therapy may be appropriate in patients at low risk of recurrent atherothrombotic events but high risk of bleeding. Decisions for individual patients are complicated by the fact that those factors which predict increased cardiovascular risk also predict bleeding.<sup>191</sup>

**R** Patients with acute coronary syndrome should receive dual antiplatelet therapy for six months. Longer durations may be used where the risks of atherothrombotic events outweigh the risk of bleeding. Shorter durations may be used where the risks of bleeding outweigh the risk of atherothrombotic events.

## 8.2 ANTICOAGULANT THERAPY

A meta-analysis of RCTs in patients with CHD found that, compared with 'no aspirin' control, warfarin reduces subsequent mortality and MI but is associated with an increase in major bleeding. Compared with aspirin, warfarin therapy did not reduce the combined outcome of death, MI or stroke but it increased major bleeding 2.4-fold (95% CI 1.6 to 3.6,  $p < 0.001$ ).<sup>192</sup> The combination of aspirin and oral anticoagulation, compared with aspirin alone, was only superior when the international normalised ratio (INR) target was  $\geq 2.0$ , reducing the composite event rate of death, MI and stroke by 56% (95% CI 17 to 77%,  $p = 0.01$ ) with major bleeding appearing to increase 1.9-fold (0.6 to 6.0-fold,  $p > 0.10$ ). These data suggest that for every 1,000 patients treated with warfarin plus aspirin (instead of aspirin alone) 54 vascular events would be prevented and 16 major bleeds caused.

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A meta-analysis of 10 trials incorporating 5,938 patients with ACS found that, compared with aspirin alone, warfarin (INR target  $\geq 2.0$ ) plus aspirin reduces the annual rate of MI (absolute RR, 1.9%; relative RR, 44%), ischaemic stroke (absolute RR, 0.4%; relative RR, 54%) and coronary revascularisation (absolute RR, 2.0%; relative RR, 20%).<sup>193</sup> This is associated with an increased risk of major bleeding (absolute risk increase, 0.9%; relative risk increase, 150%) and no improvement in overall mortality. The trials excluded patients who had intracoronary stent implantation and the data cannot be extrapolated to patients receiving this intervention.

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### 8.2.1 RIVAROXABAN, APIXABAN AND DABIGATRAN

A systematic review and meta-analysis of seven RCTs (n=30,866) showed that the addition of rivaroxaban, apixaban or dabigatran to dual antiplatelet therapy led to a small reduction in major adverse cardiovascular events (hazard ratio (HR) 0.87, 95% CI 0.80 to 0.95) compared with dual antiplatelet therapy (aspirin and clopidogrel) alone but more than doubled the risk of clinically-significant bleeding (HR 2.34, 95% CI 2.06 to 2.66).<sup>194</sup> This review included patients with non-ST and ST-segment-elevation ACS. Overall trial results were similar across study designs and excluded patients with increased risk of bleeding (for example thrombocytopenia) and those with ongoing anticoagulant therapy or patients in whom anticoagulant therapy was planned.

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In contrast, a recent meta-analysis of clinical trials of dabigatran versus a range of comparators (warfarin, placebo, and enoxaparin) for a range of indications (atrial fibrillation, treatment and prophylaxis of venous thromboembolic disease, ACS and MI) found that the incidence of MI was increased in patients treated with dabigatran (OR 1.34, 95% CI 1.08 to 1.65).<sup>195</sup> However, in a stratified analysis compared with any control, dabigatran significantly reduced major bleeding (OR 0.88, 95% CI 0.79 to 0.99) and all-cause mortality (OR 0.89, 95% CI 0.80 to 1.00).

Information on outcomes for patients with specific comorbidities is not available and it is not, therefore, possible to know whether the net benefits or harms would be greater or smaller for specific patterns of comorbidity. There are currently no identified factors which could be used to stratify patients into those likely or unlikely to benefit from novel anticoagulant therapy.

No published cost-effectiveness studies comparing the addition of rivaroxaban, apixaban or dabigatran to dual antiplatelet therapy alone were found.

**R** Patients with acute coronary syndrome should not be offered rivaroxaban, apixaban or dabigatran in addition to dual antiplatelet therapy.

### 8.3 STATIN THERAPY

The primary<sup>196,197</sup> and secondary<sup>198-201</sup> preventative benefits of statin therapy are well established (*see the SIGN guideline on risk estimation and the prevention of cardiovascular disease*).<sup>96</sup> The initial major RCTs excluded patients in the early postinfarction period (first 4–6 months) and it was unclear whether early statin therapy was safe or beneficial.

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Observational studies have suggested that early statin therapy (within 24 hours) is associated with major benefits although these studies are open to patient selection bias and are likely to overestimate the benefits of therapy.<sup>202-204</sup> Two large RCTs have reported modest benefits after four months of statin therapy when started early (within one to five days of admission or symptoms) after an ACS event (absolute RR 2.6%, relative RR 16%) in primary end point of death, reinfarction, resuscitated cardiac arrest or rehospitalisation for ischaemia.<sup>205,206</sup> Meta-analysis confirms that early statin therapy is safe but short-term (four months) benefits are limited to the prevention of recurrent ischaemia rather than mortality.<sup>207</sup>

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**R** Patients with acute coronary syndrome should be started on long-term statin therapy prior to hospital discharge.

## 8.4 BETA-BLOCKER AND ANTIANGINAL THERAPY

### 8.4.1 BETA-BLOCKER THERAPY

#### *Acute coronary syndrome without myocardial infarction*

There are only a small number of randomised controlled trials assessing beta-blocker therapy in patients with unstable angina (see section 4.6). Meta-analysis of these trials suggests a reduction in progression to MI.<sup>95</sup> The benefits of short- and long-term beta-blocker therapy for patients with unstable angina are based upon extrapolated evidence from the proven secondary preventative benefits in patients with clinical MI or left ventricular failure (see SIGN guideline 147 on management of chronic heart failure),<sup>208</sup> and the reduction of symptomatic angina in patients with stable angina.<sup>209,210</sup>

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#### *Acute coronary syndrome with myocardial infarction*

A meta-analysis of 25 long-term RCTs involving over 20,000 patients on long-term beta-blocker therapy after MI showed a 23% relative risk reduction in total mortality and a 32% relative risk reduction in sudden death.<sup>101</sup>

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#### *Clinical myocardial infarction with left ventricular failure*

The CAPRICORN trial (n=1,959) in patients with low ejection fraction (<0.40) following MI showed that delayed (3–14 days) and cautious uptitration (over 4–6 weeks postinfarction) of carvedilol resulted in a 3% absolute RR (23% relative RR) in all-cause mortality compared with placebo. Although immediate beta-blocker therapy should be avoided in patients with acute pulmonary oedema and acute left ventricular failure, subsequent cautious introduction of beta blockade is associated with major benefits.<sup>211</sup>

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**R** Patients with acute coronary syndrome should be maintained on long-term beta-blocker therapy.

### 8.4.2 NITRATES AND CALICUM CHANNEL BLOCKERS

In the ISIS-4 trial of over 58,000 patients, oral nitrates for four weeks did not reduce five-week mortality.<sup>212</sup> Similar results were obtained in the GISSI-3 trial of 20,000 patients who received intravenous nitroglycerin followed by transdermal nitroglycerin or standard therapy for six weeks.<sup>213</sup>

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✓ Nitrates should be used in patients with acute coronary syndrome to relieve cardiac pain due to continuing myocardial ischaemia or to treat acute heart failure.

Two trials of the effect of rate-limiting calcium channel blocking drugs (verapamil, diltiazem) on mortality and reinfarction in patients following MI have not demonstrated benefit. Post hoc subgroup analysis indicated that these drugs were of marginal benefit in patients with normal left ventricular function.<sup>214,215</sup> There was insufficient evidence to recommend the routine use of rate-limiting calcium channel blockers following ACS.

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## 8.5 ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

### 8.5.1 UNSTABLE ANGINA

The HOPE study of 9,297 high-risk patients with vascular disease in the absence of documented heart failure found that ramipril reduced all-cause mortality, MI, and stroke. These beneficial effects appeared to be independent of the associated reductions in blood pressure and were particularly marked in patients with diabetes mellitus.<sup>216</sup>

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These findings have been confirmed in the EUROPA trial of 13,655 patients with stable coronary heart disease.<sup>217</sup> Perindopril 8 mg daily led to a 20% relative RR in the likelihood of cardiovascular death, MI or cardiac arrest: 50 patients needed to be treated for four years to avoid one event. The PEACE trial contrasts with the HOPE and EUROPA trials in that it did not demonstrate a benefit from trandolipril in 8,290 patients with stable coronary heart disease.<sup>218</sup>

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The event rate in this trial was much lower than the rate in the treatment arms of both the HOPE and EUROPA trials.<sup>216,217</sup> Given that patients with an ACS have a higher event rate than patients in the EUROPA and HOPE trials, it seems justifiable to extrapolate the evidence to recommend that angiotensin-converting enzyme (ACE) inhibitor therapy should be given to all patients with an ACS irrespective of the presence of heart failure or left ventricular dysfunction.

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**R** Patients with unstable angina should be commenced on long-term angiotensin-converting enzyme inhibitor therapy.

#### 8.5.2 ACUTE CORONARY SYNDROME WITH MYOCARDIAL INFARCTION OR LEFT VENTRICULAR FAILURE

The major morbidity and mortality benefits of ACE inhibitor therapy have been widely established in patients with heart failure or with left ventricular dysfunction following MI.<sup>219,220</sup>

Meta-analysis of almost 100,000 patients receiving therapy with a converting enzyme inhibitor within 36 hours of acute MI and continued for at least four weeks, confirmed that ACE inhibitors reduce mortality and that most of the benefits appeared to occur during the first few days, when mortality was highest. Patients at higher risk appeared to gain a greater absolute benefit.<sup>219</sup>

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**R** Patients with myocardial infarction should be commenced on long-term angiotensin-converting enzyme inhibitor therapy within the first 36 hours.

#### 8.6 ANGIOTENSIN RECEPTOR BLOCKERS

ACE inhibitor drugs have significant side effects and are not well tolerated by up to a third of patients.<sup>216,217</sup> Angiotensin receptor blockers (ARBs) are better tolerated and provide a suitable alternative.<sup>221</sup> The VALIANT trial has demonstrated non-inferiority of valsartan (160 mg twice daily) to captopril in patients who have sustained a recent MI complicated by heart failure or left ventricular systolic dysfunction.<sup>222</sup> Not all head-to-head comparisons have consistently demonstrated non-inferiority to ACE inhibition (OPTIMAAL trial).<sup>221</sup> Trials in patients with chronic heart failure also demonstrate that ARBs are a suitable alternative in patients intolerant of ACE inhibitors<sup>223-225</sup> (see SIGN guideline 147 on management of chronic heart failure).<sup>208</sup>

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**R** Patients with myocardial infarction complicated by left ventricular dysfunction or heart failure should be commenced on long-term angiotensin receptor blocker therapy if they are intolerant of angiotensin-converting enzyme inhibitor therapy.

No trials have been identified that assess the use of a combination of an ACE inhibitor with an ARB in patients with acute coronary syndrome.

#### 8.7 MINERALOCORTICOID RECEPTOR ANTAGONISTS

In an RCT, eplerenone (25–50 mg) was started within 3–14 days of infarction and continued for at least 16 months.<sup>226,227</sup> Patients were required to have an ejection fraction of <40% and either clinical signs of heart failure or have diabetes mellitus. The majority of patients received concomitant aspirin, beta-blocker and ACE inhibitor therapy. Eplerenone treatment resulted in a 2.3% absolute RR (14% relative RR) in all-cause mortality as well as similar reductions in the combined primary end point of all-cause mortality and hospitalisation.

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**R** Patients with myocardial infarction complicated by left ventricular dysfunction (ejection fraction <40%) in the presence of either clinical features of heart failure or diabetes mellitus should be commenced on long-term eplerenone therapy.

## 9 Treatment of hypoxia and cardiogenic shock

The management and treatment of acute arrhythmias and chronic heart failure are considered in the SIGN guideline on cardiac arrhythmias in coronary heart disease and SIGN guideline 147 on management of chronic heart failure.<sup>53,208</sup>

### 9.1 NON-INVASIVE VENTILATION

Non-invasive ventilation may improve short-term outcomes in patients with acute cardiogenic pulmonary oedema. The majority of studies compare continuous positive airway pressure (CPAP) against standard oxygen therapy and consistently report that non-invasive ventilation more rapidly improves symptoms and short-term physiological parameters, and also reduces the need for intubation and invasive ventilation.<sup>228-234</sup> There is no definitive evidence that CPAP reduces mortality although a systematic review and summary of the pooled data have found improved mortality in patients treated with CPAP.<sup>235,236</sup> A meta-analysis of 15 small-scale trials has suggested that non-invasive ventilation reduces mortality (absolute RR 9%, relative RR 45%) and the need for intubation (absolute RR 18%, relative RR 57%).<sup>237</sup> This evidence is not definitive because of study heterogeneity and the small patient numbers recruited to each individual trial.

The symptomatic and physiological benefits of non-invasive ventilation are predominantly seen early (one hour) and are similar to standard oxygen therapy by six hours following treatment.<sup>236</sup>

**R** Patients with acute coronary syndrome complicated by acute cardiogenic pulmonary oedema and hypoxia should be considered for non-invasive positive airway pressure ventilation.

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### 9.2 INTRAVASCULAR VOLUME LOADING AND INOTROPIC THERAPY

There are no large RCTs of inotropic therapy or intravascular volume loading in patients with cardiogenic shock secondary to ACS.

The majority of patients with ventricular dysfunction and haemodynamic compromise following ACS demonstrate evidence of elevated cardiac filling pressures and preload, and intravascular volume loading is not indicated. In cases of right ventricular infarction or complex clinical scenarios involving multiple pathologies, such as concomitant sepsis, intravascular volume loading should be considered to ensure adequate cardiac filling pressures and preload, particularly before instituting inotropic therapy.<sup>13</sup>

There are small studies examining the effects of different inotropic agents on surrogate measures, such as filling pressures and cardiac output, but not on clinical outcomes. One meta-regression analysis of 21 studies involving 632 patients with severe heart failure found that there was no convincing evidence of symptomatic improvement associated with inotropic therapy.<sup>238</sup> In this analysis, most studies excluded patients with ACS and mandated adequate cardiac filling pressures.

In the absence of clinical trial evidence, considered expert opinion is that the use of intravascular volume loading and inotropic therapy is of benefit in patients with hypotension and cardiogenic shock. This is based on clinical experience of efficacy and on surrogate haemodynamic measures.<sup>13</sup>

**R** In the absence of clinical evidence of volume overload, patients with acute coronary syndrome complicated by hypotension and cardiogenic shock should be considered for intravascular volume loading.

**R** In the presence of clinical evidence of volume overload, patients with acute coronary syndrome complicated by hypotension and cardiogenic shock should be considered for inotropic therapy.

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### 9.3 INTRA-AORTIC BALLOON COUNTERPULSATION

Intra-aortic balloon pump counterpulsation is commonly used as a means of supporting patients undergoing surgical revascularisation in the acute cardiology setting. Early suggestions of the beneficial haemodynamic effects of intra-aortic balloon pumps (IABP) have not been translated into improvements in survival. IABP use also carries risks of vascular injury, peripheral limb ischemia and local or systemic infection although the SHOCK-II trial showed no differences in these safety outcomes.<sup>239</sup> | 1+

A meta-analysis of 16 studies including 11,778 patients with MI in the presence or absence of cardiogenic shock reported no difference in in-hospital mortality between patients receiving IABP and those not receiving IABP.<sup>240</sup> Rates of reinfarction and recurrent ischaemia were the same in both groups but IABP increased the risk of moderate and major bleeding (relative risk 1.71, 95% CI 1.03 to 2.85; relative risk 4.01, 95% CI 2.66 to 6.06, respectively). | 2-

A meta-analysis based on six RCTs and 190 patients with acute MI and cardiogenic shock provided no evidence to support the use of IABP in this patient group.<sup>241</sup> | 1++

A large RCT (n=598) of IABP in patients with acute MI complicated by cardiogenic shock with planned early revascularisation reported no benefit of IABP on in-hospital mortality (39.7% IABP v 41.3% controls).<sup>242</sup> At follow up, there were no differences in one-year mortality (52% IABP v 51% controls), rates of reinfarction, recurrent revascularisation or stroke.<sup>239</sup> | 1+

A meta-analysis of 17 studies, including 4 RCTs and 13 observational studies (n=14,186) comparing IABP with no IABP in patients with acute MI complicated by cardiogenic shock showed no difference in in-hospital mortality within the no-reperfusion subgroup but a decrease in in-hospital mortality among patients also receiving thrombolytic therapy (relative risk 0.77) and an increase in in-hospital mortality in patients receiving PCI (relative risk 1.18).<sup>243</sup> | 2-

**R** | **Routine use of intra-aortic balloon counterpulsation is not recommended in patients with acute coronary syndrome and cardiogenic shock.**

### 9.4 CORONARY REVASCULARISATION

Two small RCTs suggest an early revascularisation strategy may be of benefit in patients with acute MI complicated by cardiogenic shock due to left ventricular failure.<sup>244,245</sup> Both trials were unable to recruit the prespecified study population: the SMASH trial (n=55)<sup>245</sup> did not reach a definitive conclusion but reported findings consistent with the SHOCK trial. The SHOCK trial (n=302) showed a benefit of early revascularisation on long-term (6–12 month; 20% relative RR) but not early (30-day) mortality particularly in younger (<75 years) male patients with a prior MI.<sup>246</sup> Benefit was most marked in those patients randomised to revascularisation within six hours following onset of MI. These findings are consistent with other observational data.<sup>247</sup> | 1+  
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**R** | **Patients presenting with cardiogenic shock due to left ventricular failure within six hours of acute myocardial infarction should be considered for immediate coronary revascularisation.**

### 9.5 CARDIAC SURGERY

Cohort studies suggest that early (within the first 24–48 hours) corrective surgery is beneficial in patients with mechanical complications of acute MI.<sup>246,248,249</sup> There is concern over selection bias in that patients with less comorbidity and better overall prognosis would be more likely to undergo corrective surgery. | 2-

In the absence of evidence from RCTs, the recommendation is based on considered expert opinion that prompt surgical repair of mechanical defects is indicated. | 4

**R** | **Patients with mechanical complications of acute myocardial infarction (ventricular septal, free wall or papillary muscle rupture) should be considered for corrective surgery within 24–48 hours.**



## 10 Provision of information

This section reflects the issues likely to be of most concern to patients and their carers. These points are provided for use by health professionals when discussing ACS with patients and carers and in guiding the production of locally produced information materials.

### 10.1 EARLY PSYCHOSOCIAL INTERVENTIONS

This section provides recommendations for psychosocial interventions started in the early assessment and intervention stages of the cardiac rehabilitation care pathway (primarily the first 72 hours).

There is evidence that early identification of, and intervention in, those most at risk of psychological distress can reduce psychological distress, hospital readmission rates and anxiety and depression scores at one year.<sup>250</sup> Physicians' and nurses' subjective judgements of patient anxiety are not as accurate as measurements of anxiety on validated scales.<sup>13</sup> Standardised screening tools, such as the Hospital Anxiety and Depression Scale, are useful in psychological assessment. It is particularly important to screen for depression in the early postevent phase.<sup>251</sup> The experiences and needs of patients with CHD and depression are diverse and include psychosocial issues involving interpersonal and health/control losses.<sup>252</sup>

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False beliefs about cardiac illness can cause related negative emotions (denial, fear, anger) affecting treatment compliance and rehabilitation.<sup>251</sup> Interventions correcting cardiac misconceptions improve patient knowledge and reduce stress (both immediately and at one year follow up) for both patient and partner or family.<sup>253-255</sup> Psychosocial intervention also improves functional outcome by reducing anginal symptoms, and helping recovery and return to work.<sup>254</sup>

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**R** Patients with acute coronary syndrome should be offered early psychosocial assessment and individualised psychosocial intervention with an emphasis on identifying and addressing health beliefs and cardiac misconceptions.

✓ Psychosocial intervention forms part of the formal cardiac rehabilitation programme and should be viewed as a continuous process throughout the patient care pathway.

### 10.2 INFORMATION NEEDS OF PATIENTS

Understanding the information needs of people with ACS and their carers and families is important so that appropriate information is given in an appropriate way at the appropriate time. A questionnaire survey, developed by patient and lay representatives on the guideline development group, of patients and carers with experience of cardiac disease showed that different information is required at different stages of the patient's journey and that the requirements of individual patients may be very different. For example, whereas some want to learn as much as possible about their condition, as soon as possible, so they feel engaged with all that is happening, others may be less involved. There may be a preference for verbal or written information. The survey identified key themes, namely that information and advice should be:

- timely
- consistent
- involve partners/relatives/carers when appropriate and with consent of the patient
- delivered with a sensitive approach by all healthcare professionals.

#### 10.2.1 CHECKLIST FOR PROVISION OF INFORMATION

This section gives examples of the information patients/carers may find helpful at the key stages of the patient journey. The checklist was designed by members of the guideline development group based on their experience, their understanding of the evidence base, and the results of a questionnaire survey of patients and carers with experience of cardiac disease (see section 10.2). In developing the checklist, consideration was given to what patients and carers valued. The checklist is neither exhaustive nor exclusive.

<b>Initial presentation and admission</b>
<ul style="list-style-type: none"> <li>• First responders, paramedics and GPs involved in the patient's care should have a sympathetic, understanding and reassuring approach to the patient and their relatives/carers who may be anxious or fearful.</li> <li>• The final decision regarding admission should be made by the healthcare professional in consultation with the patient.</li> <li>• Healthcare professionals should explain any procedures/tests they are carrying out and answer patient/carer's questions in as simple language as possible.</li> <li>• Explain to the patient how to distinguish between cardiac and non-cardiac pain, eg indigestion, anxiety etc.</li> <li>• Some patients require very little information and to be reassured they are 'in safe hands' but others may wish more detail.</li> </ul>
<b>Assessment and investigation</b>
<ul style="list-style-type: none"> <li>• Ensure patients are kept informed about which tests will be performed, when they are likely to be carried out and what the results mean.</li> <li>• Identify the knowledge, understanding and readiness to learn of patients and their relatives so that information can be tailored appropriately using clear, concise jargon-free language.</li> <li>• Listen carefully to the needs and priorities of patients and carers.</li> <li>• Ensure the patient is aware of what they should report to the nurse/doctor during their hospital stay, for example, specific symptoms.</li> </ul>
<b>Diagnosis</b>
<ul style="list-style-type: none"> <li>• Provide time and support to patients and carers when the diagnosis is explained and discussed, including explanation of uncertainties around diagnostic status.</li> <li>• Give written information to patients and carers, for example, BHF or CHSS patient information booklets (<i>see section 10.3</i>) or SIGN patient booklets to allow absorption at their preferred pace.</li> <li>• Where the diagnosis of ACS is excluded, the patient should be reassured and given clear guidance on when to seek help in the future.</li> </ul>
<b>Treatment</b>
<ul style="list-style-type: none"> <li>• Explain different types of treatment including risks and benefits of recommended tests, medications and treatment and provide written information as appropriate.</li> <li>• Encourage patients and their families to discuss their questions and concerns and provide regular updates on progress.</li> <li>• Ensure consistent and appropriate information is given to patients and carers.</li> </ul>
<b>Discharge/follow up/cardiac rehabilitation</b>
<ul style="list-style-type: none"> <li>• Explain to the patient that an individual assessment for a tailored programme of interventions by a cardiac rehabilitation team will be arranged and encourage engagement.</li> <li>• Advise the patient of ways to improve their lifestyle to enhance recovery and avoid recurrence of ACS.</li> <li>• Ensure patients and families are provided with written information, telephone helplines (for example, BHF, CHSS or a local helpline) and signposted to support groups and helpful websites where appropriate (<i>see section 10.3</i>).</li> <li>• Explain that patients commonly feel quite 'low', anxious, vulnerable or emotional when returning home. Explain how and where to find support.</li> <li>• Ensure the patient and relative/carer have an understanding of all the essential information required about ACS and have obtained clear instructions (for example regarding exercise, diet, smoking cessation, alcohol consumption, resuming sexual activity, driving, return to work and follow-up appointments) prior to leaving hospital.</li> </ul>

## 10.3 SOURCES OF FURTHER INFORMATION

### **NHS inform**

Caledonia House, Fifty Pitches Road, Cardonald Park, Glasgow, G51 4EB

Tel: 0800 22 44 88 (8am–10pm)

[www.nhsinform.co.uk](http://www.nhsinform.co.uk) • Email: [nhs.inform@nhs24.scot.nhs.uk](mailto:nhs.inform@nhs24.scot.nhs.uk)

NHS Inform provides national health and care information service for Scotland.

NHS inform A-Z articles: [www.nhsinform.co.uk/health-library/subjects/heart-and-circulation-disorders/](http://www.nhsinform.co.uk/health-library/subjects/heart-and-circulation-disorders/)

### **The Heart Zone**

[www.nhsinform.co.uk/heart/](http://www.nhsinform.co.uk/heart/)

The Heart Zone, which has been developed on Scotland's national health information website, NHS inform, provides a range of information and resources to support the self-management of short- and long-term heart disease, as well as on a range of inherited and congenital heart conditions.

### **British Heart Foundation**

Ocean Point 1, 94 Ocean Drive, Edinburgh, EH6 6JH

Tel: 020 7554 0000 • Heart Helpline: 0300 330 3311

[www.bhf.org.uk](http://www.bhf.org.uk) • Email: [bhfhi@bhf.org.uk](mailto:bhfhi@bhf.org.uk)

The BHF is a national heart charity and the largest independent funder of cardiovascular research in the UK. It provides vital support, information and care for patients and their carers and provides forums to listen to, engage and influence both patients and key stakeholders.

### **Chest Heart & Stroke Scotland**

Third Floor, Rosebery House, 9 Haymarket Terrace, Edinburgh, EH12

Tel: 0131 225 6963 • Advice Line Nurses: 0808 801 0899 (9.30am–4pm, Mon–Fri)

[www.chss.org.uk](http://www.chss.org.uk) • Email: [admin@chss.org.uk](mailto:admin@chss.org.uk)

The Scottish health charity set up to improve the quality of life for people in Scotland affected by chest, heart and stroke illness, through medical research, influencing public policy, advice and information and support in the community.

### **Local support groups and telephone helplines**

Tel: 0800 22 44 88 (8am–10pm)

[www.nhsinform.co.uk/support-services](http://www.nhsinform.co.uk/support-services)

Local groups can be found by visiting the Support Service Directory on the NHS inform website.

## 10.3.1 ADDITIONAL WEBSITES

### **Action on Depression**

21–23 Hill Street, Edinburgh, EH2 3JP

[www.actionondepression.org](http://www.actionondepression.org) • Email: [admin@actionondepression.org](mailto:admin@actionondepression.org)

This website highlights local support and raises awareness about low mood and depression.

### **Active Scotland**

[www.activescotland.org.uk](http://www.activescotland.org.uk)

This website provides information and ideas on a range of indoor and outdoor activities in Scotland on land, water and in the air.

### **Blood Pressure UK**

Wolfson Institute of Preventive Medicine, Charterhouse Square, London, EC1M 6BQ

Tel: 020 7882 6218

[www.bloodpressureuk.org/home](http://www.bloodpressureuk.org/home) • Email: [help@bloodpressureuk.org](mailto:help@bloodpressureuk.org)

A UK charity dedicated to lowering the nation's blood pressure to prevent disability and death from stroke and heart disease.

### **Breathing Space**

Tel: 0800 83 85 87 (Weekdays: Mon–Thur 6pm–2am. Weekend: Friday 6pm to Monday 6am)

[www.breathingspace.scot](http://www.breathingspace.scot)

Breathing Space is a free, confidential phone and web-based service for any individual who is experiencing low mood or depression, or who is unusually worried and in need of someone to talk to.

### **Diabetes UK**

Careline Scotland, The Venlaw, 349 Bath Street, Glasgow, G2 4AA

Tel: (Careline Scotland) 0141 212 8710

[www.diabetes.org.uk](http://www.diabetes.org.uk) • Email: [careline.scotland@diabetes.org.uk](mailto:careline.scotland@diabetes.org.uk)

Diabetes UK provides information, advice and support to help people with diabetes manage the condition well, and brings people together for support when it's needed most.

### **Drink Smarter**

[drinksmarter.org](http://drinksmarter.org)

A national charity working to reduce the harm caused by alcohol, find information on easy ways to cut back and sensible drinking.

### **Eat Better Feel Better**

[www.eatbetterfeelbetter.co.uk](http://www.eatbetterfeelbetter.co.uk)

This website provides recipes for healthier and cheaper meals and information on improving cooking skills.

### **UK Government information**

[www.gov.uk/heart-attacks-and-driving](http://www.gov.uk/heart-attacks-and-driving)

Information relating to regulations about driving after having experienced a heart attack.

### **Scottish Association for Mental Health**

[www.samh.org.uk](http://www.samh.org.uk)

The Scottish Association for Mental Health is Scotland's leading mental health charity. It provides community-based services for people with mental health problems, carries out policy and campaigning work and is building five national programmes designed to address wider societal needs for information, resources and services.

### **Smokeline**

Caledonia House, Fifty Pitches Road, Cardonald Park, Glasgow, G51 4EB

Tel: 0800 84 84 84 (8am–10pm)

[www.canstopsmoking.com](http://www.canstopsmoking.com) • Email: [smokeline@nhs24.scot.nhs.uk](mailto:smokeline@nhs24.scot.nhs.uk)

Scotland's national stop smoking helpline; open every day from 8am–10pm

# 11 Implementing the guideline

This section provides advice on the resource implications associated with implementing the key clinical recommendations, and advice on audit as a tool to aid implementation.

## 11.1 IMPLEMENTATION STRATEGY

Implementation of national clinical guidelines is the responsibility of each NHS board and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

Implementation of this guideline will be encouraged and supported by SIGN. The implementation strategy for this guideline encompasses the following tools and activities.

## 11.2 RESOURCE IMPLICATIONS OF KEY RECOMMENDATIONS

No recommendations are considered likely to reach the £5 million threshold which warrants full cost-impact analysis.

## 11.3 AUDITING CURRENT PRACTICE

A first step in implementing a clinical practice guideline is to gain an understanding of current clinical practice. Audit tools designed around guideline recommendations can assist in this process. Audit tools should be comprehensive but not time consuming to use. Successful implementation and audit of guideline recommendations requires good communication between staff and multidisciplinary team working.

The guideline development group has identified the following as key points to audit to assist with the implementation of this guideline:

- the proportion of people with a diagnosis of ACS who are managed within a specialised cardiology service
- the proportion of people with ACS and ischaemic electrocardiographic changes and/or elevated cardiac troponin levels who receive immediate aspirin and a P2Y<sub>12</sub>-receptor antagonist
- the proportion of people with ACS and ischaemic electrocardiographic changes and/or elevated cardiac troponin levels who receive immediate anticoagulant therapy
- the proportion of people with ST-segment-elevation ACS receiving reperfusion therapy
- the proportion of people with ST-segment-elevation ACS receiving primary PCI within 120 minutes of ECG diagnosis
- the proportion of people with ACS with recorded risk stratification using clinical scoring systems
- the proportion of people with ACS who receive assessment of cardiac function
- the proportion of people with non-ST-segment ACS who are at medium or high risk of early recurrent cardiovascular events who receive early coronary angiography and revascularisation
- the proportion of people with ACS undergoing PCI via the radial artery
- the proportion of patients with ACS who receive at least six months dual antiplatelet therapy
- the proportion of patients with ACS who receive long-term statin therapy
- the proportion of patients with ACS who receive long-term ACE-inhibitor or ARB therapy
- the proportion of patients with MI complicated by LVSD with either heart failure or diabetes mellitus who receive long-term eplerenone therapy
- the proportion of patients with ACS who receive long-term beta-blocker therapy
- the proportion of patients with ACS who are offered early psychosocial assessment and intervention.

#### 11.4 ADDITIONAL ADVICE TO NHSSCOTLAND FROM THE SCOTTISH MEDICINES CONSORTIUM

On 9 May 2011 SMC advised that following a full submission:

ticagrelor film-coated tablets (Brilique®) are accepted for use within NHSScotland, coadministered with aspirin, for the prevention of atherothrombotic events in adult patients with acute coronary syndromes (unstable angina, non-ST-segment-elevation myocardial infarction or ST-segment-elevation myocardial infarction); including patients managed medically, and those who are managed with PCI or CABG.

As dual therapy with aspirin, ticagrelor demonstrated a significant reduction in ischaemic events compared with another antiplatelet drug without significantly increasing the incidence of study-defined major bleeding.

Alternative treatments are available at a lower drug acquisition cost.

SMC advice for prasugrel (September 2009) was superseded by NICE TA317 in July 2014 which now provides the extant advice to NHSScotland. Prasugrel 10 mg in combination with aspirin is recommended as an option for preventing atherothrombotic events in adults with acute coronary syndrome having primary or delayed PCI.

## 12 The evidence base

### 12.1 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Evidence and Information Scientist. Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. The year range covered was 2005–2014. Internet searches were carried out on various websites including the US National Guidelines Clearinghouse. The main searches were supplemented by material identified by individual members of the development group. Each of the selected papers was evaluated by two members of the group using standard SIGN methodological checklists before conclusions were considered as evidence.

#### 12.1.1 LITERATURE SEARCH FOR PATIENT ISSUES

At the start of the guideline development process, a SIGN Evidence and Information Scientist conducted a literature search for qualitative and quantitative studies that addressed patient issues of relevance to the management of patients with acute coronary syndrome. Databases searched include Medline, Embase, Cinahl and PsycINFO, and the results were summarised by the SIGN Patient Involvement Officer and presented to the guideline development group.

#### 12.1.2 LITERATURE SEARCH FOR COST EFFECTIVENESS

The guideline development group identified key questions with potential cost-effectiveness implications where it was judged particularly important to gain an understanding of the additional costs and benefits of different treatment strategies, based on the following criteria:

- treatments which may have a significant resource impact
- opportunities for significant disinvestment or resource release
- the potential need for significant service redesign
- cost-effectiveness evidence could aid implementation of a recommendation.

A systematic literature search for economic evidence for these questions was conducted using Medline, Embase, NHS Economic Evaluation Database (NEED) and Health Economics Evaluation Database (HEED), covering the years 2010–2014. Papers were selected and evaluated by a Health Economist, and considered for clinical relevance by guideline group members.

Interventions are considered to be cost effective if they fall below the commonly-accepted UK threshold of £20,000 per QALY.

The key questions are listed in Annex 1.

### 12.2 RECOMMENDATIONS FOR RESEARCH

The guideline development group was not able to identify sufficient evidence to answer all of the key questions asked in this guideline (*see Annex 1*). The following areas for further research have been identified:

- Do centres adopting early rule-out strategies with high-sensitivity troponin have improved or worse outcomes compared with those not adopting this approach?
- What are the underlying biological causes and the clinical implications of elevated troponin concentrations in patients without ACS or with type 2 MI?
- How effective are high-sensitivity assays in important subgroups of patients including older patients and those with renal or heart failure?
- What is the optimal antiplatelet regimen in patients with ACS who have prior indications for anticoagulation?

- How should clinicians assess if more potent, and more expensive, P2Y<sub>12</sub>-receptor antagonists can be justified in higher-risk patients who may also be those at higher risk of intracranial bleeding?
- What is the optimal duration of dual antiplatelet therapy with aspirin and a P2Y<sub>12</sub>-receptor antagonist after ACS?
- What are the effects of ticagrelor and prasugrel on long-term survival?
- Are there patients at increased baseline risk of major cardiovascular events in whom the increased risk of bleeding associated with the addition of rivaroxaban, apixaban or dabigatran to dual antiplatelet therapy is outweighed by the possible reduction in major adverse cardiovascular events?
- What is the clinical effectiveness, safety and cost effectiveness of glycoprotein IIb/IIIa inhibitors in patients with ACS pretreated with ticagrelor?
- What is the clinical effectiveness and safety of upstream glycoprotein IIb/IIIa inhibitors in patients with high-risk non-ST-segment-elevation MI or ST-segment-elevation MI being transferred to regional PCI centres?
- Which patients with ACS gain most from complete revascularisation and which are at greatest risk from prolonged procedures?
- Does manual thrombectomy compared with usual care improve outcomes in patients with ST-segment-elevation MI undergoing primary PCI with a large thrombus burden?
- In patients with ACS, what is the optimal duration of dual antiplatelet therapy in patients undergoing early PCI and stenting?
- What is the optimal duration of dual antiplatelet therapy for specific drug-eluting stents?
- What is the clinical effectiveness of percutaneous left ventricular assist devices in patients with ACS and cardiogenic shock?
- In post-MI patients at very high risk of ventricular tachycardia/fibrillation, what is the clinical and cost effectiveness of wearable cardioverter defibrillators as a bridge to implantable devices?
- What is the clinical effectiveness of intra-aortic balloon counterpulsation in patients with ACS and cardiogenic shock who are younger, have left main-stem disease or who have an out-of-hospital cardiac arrest?

### 12.3 REVIEW AND UPDATING

This guideline was issued in 2016 and will be considered for review in three years. The review history, and any updates to the guideline in the interim period, will be noted in the review report, which is available in the supporting material section for this guideline on the SIGN website: [www.sign.ac.uk](http://www.sign.ac.uk)

Comments on new evidence that would update this guideline are welcome and should be sent to the SIGN Executive, Gyle Square, 1 South Gyle Crescent, Edinburgh, EH12 9EB (email: [sign@sign.ac.uk](mailto:sign@sign.ac.uk)).



# 13 Development of the guideline

## 13.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of Healthcare Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising healthcare professionals using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in 'SIGN 50: A Guideline Developer's Handbook', available at [www.sign.ac.uk](http://www.sign.ac.uk)

This guideline was developed according to the 2015 edition of SIGN 50.

## 13.2 THE GUIDELINE DEVELOPMENT GROUP

Professor David Newby (Chair)	<i>British Heart Foundation Professor of Cardiology, University of Edinburgh</i>
Mrs Helen Anderson	<i>Lay representative, Arbroath</i>
Mr Norman Anderson	<i>Lay representative, Arbroath</i>
Mr Graham Bell	<i>Lay representative, Penicuik</i>
Mr Geoff Berg	<i>Cardiac Surgeon, Golden Jubilee National Hospital, Glasgow</i>
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Ms Naomi Fearn	<i>Health Services Researcher, Healthcare Improvement Scotland</i>
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Mrs Emma Riches	<i>Health Services Researcher, Healthcare Improvement Scotland</i>
Dr Duncan Scott	<i>Consultant Physician and Associate Director of Medical Education, Raigmore Hospital, Inverness</i>
Dr Carolyn Sleith	<i>Evidence and Information Scientist, SIGN</i>
Ms Pernille Sorensen	<i>Senior Cardiac Pharmacist, South Glasgow University Hospitals</i>
Dr Rebecca Wheeler	<i>General Practitioner, Arbroath, and Clinical Lead, Angus Cardiovascular Clinical Working Group</i>

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest. A register of interests is available in the supporting material section for this guideline at [www.sign.ac.uk](http://www.sign.ac.uk)

Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive. All members of the SIGN Executive make yearly declarations of interests. A register of interests is available on the contacts page of the SIGN website [www.sign.ac.uk](http://www.sign.ac.uk)

Euan Bremner	<i>Project Officer</i>
Lesley Forsyth	<i>Events Co-ordinator</i>
Karen Graham	<i>Patient Involvement Officer</i>
Karen King	<i>Distribution and Office Co-ordinator</i>
Stuart Neville	<i>Publications Designer</i>
Gaynor Rattray	<i>Guideline Co-ordinator</i>

### 13.2.1 ACKNOWLEDGEMENTS

SIGN would like to acknowledge the guideline development group responsible for the development of SIGN 93: Acute Coronary Syndromes, on which this guideline is based and the guideline development group responsible for the updated version of SIGN 93 published in February 2013. SIGN would also like to acknowledge the following individuals who contributed during the early stages of guideline development.

Ms Beatrice Cant	<i>Programme Manager, SIGN</i>
Mr Gordon Thomson	<i>Lead Clinical Pharmacist, Urgent Care and Medicine, Ninewells Hospital, Dundee</i>

### 13.3 THE STEERING GROUP

A steering group comprising the chairs of the six SIGN CHD guidelines and other invited experts was established to oversee the progress of the guideline development. This group met regularly throughout the development of the guidelines.

Professor Sir Lewis Ritchie, OBE (Chair)	<i>Mackenzie Professor and Head of Department, Department of General Practice and Primary Care, University of Aberdeen</i>
Mrs Corinne Booth	<i>Senior Health Economist, Healthcare Improvement Scotland</i>
Mr James Cant	<i>Director, British Heart Foundation Scotland</i>
Dr Derek Connelly	<i>Consultant Cardiologist, Golden Jubilee Hospital, Glasgow</i>
Dr Nick Cruden	<i>Interventional Cardiologist, Royal Infirmary of Edinburgh</i>
Mr Steve McGlynn	<i>Principal Pharmacist, Department of Pharmaceutical Sciences, Strathclyde Institute for Biomedical Sciences, Glasgow</i>
Dr Susan Myles	<i>Lead Health Economist, Healthcare Improvement Scotland</i>
Professor David Newby	<i>British Heart Foundation Professor of Cardiology, University of Edinburgh</i>
Dr Morag Osborne	<i>Counsultant Clinical Psychologist, Southern General Hospital, Glasgow</i>
Professor Naveed Sattar	<i>Professor of Metabolic Medicine, Institute of Cardiovascular and Medical Sciences, University of Glasgow</i>
Mr Gordon Snedden	<i>Lay representative, Forfar</i>
Professor Allan Struthers	<i>Professor of Cardiovascular Medicine and Therapeutics, Ninewells Hospital and Medical School, Dundee</i>
Dr Iain Todd	<i>Consultant in Cardiovascular Rehabilitation, Astley Ainslie Hospital, Edinburgh</i>

## 13.4 CONSULTATION AND PEER REVIEW

### 13.4.1 PUBLIC CONSULTATION

The draft guideline was available on the SIGN website for a month to allow all interested parties to comment. All contributors made declarations of interest and further details of these are available on request from the SIGN Executive.

### 13.4.2 SPECIALIST REVIEW

This guideline was also reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline.

SIGN is very grateful to all of these experts for their contribution to the guideline.

Mr Gordon Adamson	<i>Specialist Clinical Pharmacist, Cardiac Services, Golden Jubilee National Hospital, Glasgow</i>
Dr Alan Begg	<i>General Practitioner, Townhead Practice Montrose and Honorary Senior Lecturer, University of Dundee</i>
Professor Colin Berry	<i>Consultant Cardiologist, Golden Jubilee National Hospital, Glasgow</i>
Dr Nicholas Boon	<i>Retired Consultant Cardiologist, Edinburgh</i>
Dr Russell Duncan	<i>Consultant, Emergency Department, Ninewells Hospital, Dundee</i>
Dr David Hogg	<i>GP Principal, Arran Medical Group, Isle of Arran</i>
Ms Eleanor MacDonald	<i>Lay Reviewer, Orkney</i>
Dr Julie Ronald	<i>Consultant in Emergency Medicine, Emergency Department, Ninewells Hospital, Dundee</i>
Mr Dennis Sandeman	<i>Cardiology Nurse Consultant, Victoria Hospital, Kirkcaldy</i>
Professor Adam Timmis	<i>Professor of Clinical Cardiology, Bart's Heart Centre, London</i>
Professor Olivia Wu	<i>Professor in Health Technology Assessment, University of Glasgow</i>

The guideline group addresses every comment made by an external reviewer, and must justify any disagreement with the reviewers' comments. A report of the peer review comments and responses is available in the supporting material section for this guideline on the SIGN website. All expert referees made declarations of interest and further details of these are available on request from the SIGN Executive.

### 13.4.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows. All members of SIGN Council make yearly declarations of interest. A register of interests is available on the SIGN Council Membership page of the SIGN website [www.sign.ac.uk](http://www.sign.ac.uk)

Dr Jenny Bennison	<i>Vice Chair of SIGN; Co-Editor</i>
Dr Roberta James	<i>SIGN Programme Lead; Co-Editor</i>
Dr Daniel Beckett	<i>Royal College of Physicians of Edinburgh</i>
Dr Karen MacPherson	<i>Lead Health Services Researcher, Healthcare Improvement Scotland</i>
Mr Alan Timmins	<i>Royal Pharmaceutical Society</i>

## Abbreviations

<b>ACE</b>	angiotensin converting enzyme
<b>ACS</b>	acute coronary syndrome
<b>ARB</b>	angiotensin receptor blockers
<b>ARR</b>	absolute risk reduction
<b>BHF</b>	British Heart Foundation
<b>BIOMArCS</b>	the Biomarker study to identify the acute risk of a coronary syndrome
<b>BNF</b>	British National Formulary
<b>CAD</b>	coronary artery disease
<b>CABG</b>	coronary artery bypass graft
<b>CAPRICORN</b>	Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction trial
<b>CHD</b>	coronary heart disease
<b>CI</b>	confidence intervals
<b>CLARITY-TIMI</b>	Clopidogrel as Adjunctive Reperfusion Therapy - Thrombolysis in Myocardial Infarction trial
<b>COMMIT/CCS</b>	Clopidogrel and Metoprolol in Myocardial Infarction Trial/Chinese Cardiac Study
<b>CPAP</b>	continuous positive airway pressure
<b>CURE</b>	Clopidogrel in Unstable Angina to Prevent Recurrent Events trial
<b>CVD</b>	cardiovascular disease
<b>DIGAMI</b>	Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction trial
<b>ECG</b>	electrocardiograph
<b>EUROPA</b>	European trial on reduction of cardiac events with perindopril in patients with stable coronary artery disease
<b>ExTRACT</b>	The Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment trial
<b>FRISC</b>	Fragmin and Fast Revascularization during Instability in Coronary Artery Disease trial
<b>FTTC</b>	Fibrinolytic Therapy Trialists' Collaboration
<b>GISSI</b>	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto trial
<b>GRACIA</b>	Grupo de Análisis de la Cardiopatía Isquémica Aguda
<b>HEED</b>	Health Economics Evaluation Database
<b>HOPE</b>	Heart Outcomes Prevention Evaluation
<b>HR</b>	hazard ratio
<b>IABP</b>	intra-aortic balloon pump
<b>ICTUS</b>	Invasive versus Conservative Treatment in Unstable Coronary Syndromes trial
<b>INR</b>	international normalised ratio
<b>ISIS</b>	International Study of Infant Survival
<b>iv</b>	intravenous administration
<b>LBBB</b>	left bundle branch block
<b>LMWH</b>	low molecular weight heparin

<b>LVH</b>	left ventricular hypertrophy
<b>MA</b>	marketing authorisation
<b>MI</b>	myocardial infarction
<b>MTA</b>	multiple technology appraisal
<b>NEED</b>	NHS Economic Evaluation Database
<b>NICE</b>	National Institute for Health and Care Excellence
<b>NNH</b>	number needed to harm
<b>NNT</b>	number needed to treat
<b>OASIS</b>	Organization for the Assessment of Strategies for Ischemic Syndromes
<b>OPTIMAAL</b>	Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan
<b>OR</b>	odds ratio
<b>PCI</b>	percutaneous coronary intervention
<b>PEACE</b>	Prevention of Events with Angiotensin Converting Enzyme Inhibition
<b>PLATO</b>	the study of Platelet Inhibition and Patient Outcomes
<b>po</b>	oral administration
<b>PURSUIT</b>	the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy trial
<b>QALY</b>	quality adjusted life year
<b>RCT</b>	randomised controlled trial
<b>REACT</b>	the Rescue Angioplasty versus Conservative Treatment or Repeat Thrombolysis trial
<b>RITA</b>	Randomized Intervention Treatment of Angina trial
<b>RR</b>	risk reduction
<b>sc</b>	subcutaneous administration
<b>SIGN</b>	Scottish Intercollegiate Guidelines Network
<b>SMASH</b>	the Swiss Multicentre trial of Angioplasty for Shock
<b>SMC</b>	Scottish Medicines Consortium
<b>ST-segment</b>	portion of the electrocardiographic tracing that can indicate ischaemia
<b>SYNTAX score</b>	An assessment of overall coronary lesion complexity, with higher scores representing more complex coronary disease (a low score is defined as $\leq 22$ , an intermediate score as 23–32, and a high score as $\geq 33$ )
<b>TACTICS-TIMI</b>	Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction trial
<b>TIMI</b>	Thrombolysis in Myocardial Infarction
<b>TRITON-TIMI</b>	Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction
<b>UFH</b>	unfractionated heparin
<b>ULMD</b>	unprotected left main-stem disease
<b>URL</b>	upper reference limit
<b>VALIANT</b>	Valsartan in Acute Myocardial Infarction

# Annex 1

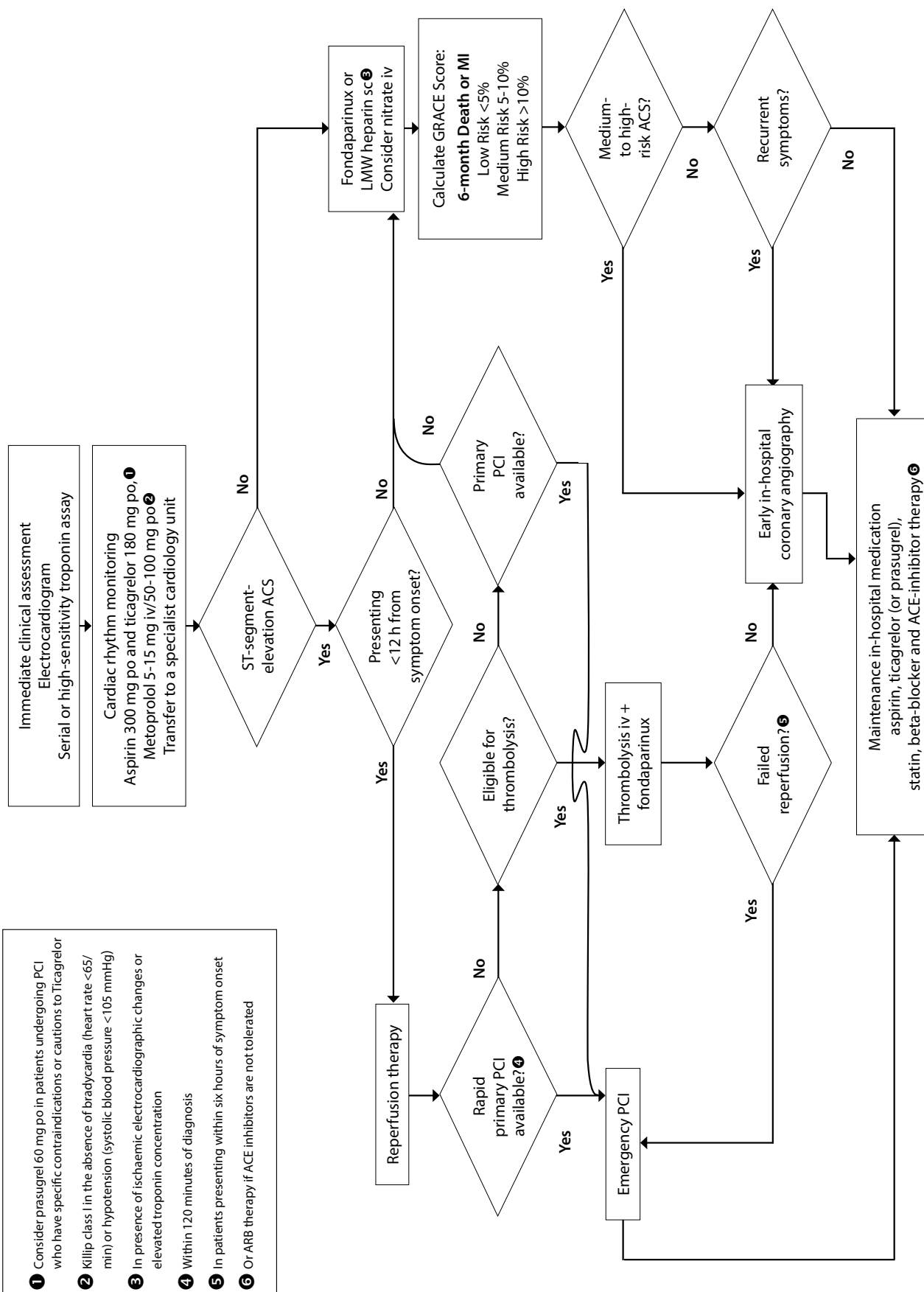
## Key questions addressed in this update

This guideline is based on a series of structured key questions that define the target population, the intervention, diagnostic test, or exposure under investigation, the comparison(s) used and the outcomes used to measure efficacy, effectiveness, or risk. These questions form the basis of the systematic literature search.

Guideline section	Key question	
3.2	1	What is the clinical and cost effectiveness of serial measurement of plasma troponin concentration using a high-sensitivity assay within four hours of presentation compared with serial troponin measurement over 10–12 hours for the exclusion of acute myocardial infarction?
4.4.2	2	What is the clinical and cost effectiveness of prasugrel or ticagrelor compared with clopidogrel in patients with acute coronary syndrome?
4.7	3	What is the clinical effectiveness of intensive insulin therapy in patients with acute coronary syndrome and hyperglycaemia (>11 mmol/L)?
5.1.3	7	What is the clinical effectiveness of thrombectomy in patients with ST-segment-elevation myocardial infarction?
5.5	6	What is the clinical and cost effectiveness of multivessel compared with culprit-only primary percutaneous coronary intervention in patients with ST-segment-elevation myocardial infarction and multivessel coronary disease?
7.2	5	Which is the preferred arterial access route in patients with acute coronary syndrome undergoing coronary angiography with a view to percutaneous coronary intervention?
7.3	4	What is the clinical and cost effectiveness of glycoprotein IIb/IIIa receptor antagonists in patients with acute coronary syndrome?
7.4	8	What is the clinical and cost effectiveness of multivessel percutaneous coronary intervention compared with coronary artery bypass grafting surgery in patients with non-ST-segment-elevation acute coronary syndrome?
8.1.2	9	What is the optimal duration (clinical and cost effectiveness) of dual antiplatelet therapy in patients with acute coronary syndrome?
8.2.1	10	What is the clinical and cost effectiveness of rivaroxaban or apixaban or dabigatran in addition to dual antiplatelet therapy in patients with acute coronary syndrome?
9.3	11	What is the clinical effectiveness of intra-aortic balloon counterpulsation in patients with acute coronary syndrome and cardiogenic shock?

## Annex 2

### Summary of management of acute coronary syndrome





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